Alberta STE Report

First and Second Trimester Prenatal Screening for Trisomies 13, 18, and 21 and Open Neural Tube Defects

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Alberta STE Report: Policy-driven Health Technology Assessment reports that include an analysis of the social and system demographics, technological effectiveness and economic implications of a health technology. The reports are written under contract with the Alberta Health Technologies Decision Process and contextualized for use in Alberta.

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EXECUTIVE SUMMARY

Social and System Demographics Analysis

Patterns and burden of aneuploidy and open neural tube defects

Definition, progression, comorbidities, risk factors and prognosis

Aneuploidy occurs when the chromosomes do not separate properly resulting in an abnormal number of chromosomes in the fetus. The most common fetal aneuploidies are trisomy 21, trisomy 18, and trisomy 13.

- Trisomy 21 (also known as Down syndrome) is caused by the presence of all or part of an extra chromosome in the 21st chromosomal par. Associated comorbidities include congenital heart defects, digestive tract abnormalities, congenital cataracts and leukemia. Individuals with trisomy 21 present learning, memory, and language difficulties that lead to mild-to-profound impairment in their intellectual functioning. The life expectancy for people with trisomy 21 is substantially greater than for trisomy 18 and trisomy 13 (median survival time around 35 to 50 years).
- Trisomy 18 (also known as Edward syndrome) is caused by the presence of all or part of an extra 18th chromosome par. Associated comorbidities include intrauterine growth restriction, cardiac malformations, hydrocephalus, abdominal wall defects, clenched fists or radial limb defects. Significant psychomotor developmental problems and mental retardation occur in the severe forms of the condition. The median survival time for children with trisomy 18 very short, ranging from 6 to 14.5 days of life (survival probability at one month of life is 25% and beyond the first year of life is between 2% to 10%).
- Trisomy 13, also known as Patau syndrome, is caused by an extra copy of chromosome 13. The condition is associated with the occurrence of multiple malformations including structural heart defects, genital and kidney abnormalities, muscloskeletal problems and central nervous system problems that lead to severe developmental delays and profound intellectual disabilities. Trisomy 13 is associated with serious and fatal birth defects, with death frequently occurring in the first month of life. The median survival time for children with trisomy 13 is between 2.5 and 8.5 days (survival probability at 1 month of life is 30% and beyond the first year of life is between 5% to 10%).
- Advanced maternal age has been recognized as an important risk factor for the occurrence of aneuploidy in the fetus. No lifestyle or environmental factors have been definitively reported to affect aneuploidy risk. The condition has not been attributed to any particular parental behaviour before or during pregnancy, or to other lifestyle, social or environmental factors. Little has been published about the economic burden of trisomy 21 to society or families and economic analyses of the effects of trisomy 18 and trisomy13 were not identified.

Open neural tube defects (ONTD) are a group of congenital malformations in which the normal closure process of the neural tube fails. They include anencephaly, encephalocele, and spina bifida.

- Anencephaly results from a failure of fusion of the cranial portion of the neural tube, producing an absence of all or a major portion of the brain, neurocranium and scalp. The minimal development of the cerebrum permanently rules out the possibility of ever gaining

consciousness. Anencephaly has a multifactorial etiology and both genetic and environmental risk factors have been implicated (maternal obesity, gestational diabetes, maternal folic acid and vitamins deficiency, family history of anencephaly and previous ONTD pregnancies, maternal stress and history of epileptic seizures). Approximately 25% to 32% of babies with this condition are born alive, but survive only hours to days after birth.

- Encephalocele is characterized by the formation of sac-like protrusions of the brain tissue and meninges through bone defects of the skull. It is frequently associated with single-gene and chromosomal syndromes and reported in association with maternal rubella, diabetes, and hyperthermia. The prognosis of individuals with encephalocele depends on a variety of factors such as the type of brain tissue involved, the location of the sacs, the presence of hydrocephalus, and the accompanying brain malformations. The mortality rate for encephalocele is about 44% and among those individuals that survive over time, only about 9% of them achieve a normal intellectual development.

- Spina bifida is characterized by a failure of fusion of the caudal portion of the neural tube and concomitant division of the posterior elements of the vertebrae. Spina bifida has the lowest rate of associated anomalies among all the ONTD. They include other central nervous system defects, lower limb deformities and Arnold-Chiari malformations. The development of spina bifida is linked to both genetic and environmental risk factors such as folic acid deficiency and ethnicity (i.e. more frequent among Caucasians than in Asians or blacks). Over 90% of infants with spina bifida treated in the early neonatal period survive beyond one year of age. Survival of children treated in the early neonatal period is around 40% at 7 years of age.

There is scientific evidence documenting the economic impact of spina bifida, but no Canadian data was identified in this analysis. Evidence on the economic impact of anencephaly and encephalocele on the society and the family was not identified.

Prevalence of fetal aneuploidy and ONTD in Alberta, Canada and internationally

Analysis of international data from 38 birth defects registries showed that, by 2006, the median birth prevalence rates for aneuploidy and ONTD in international registries were:

- Trisomy 21: 17 cases per 10,000 births (interquartile range [IQR]: 12.3, 20.5);
- Trisomy 18: 2.8 cases per 10,000 births (IQR: 1.7, 5.2);
- Trisomy 13: 1.4 cases per 10,000 births (IQR: 0.5, 2.6);
- Anencephaly: 2.4 cases per 10,000 births (IQR: 1.3, 3.6);
- Encephalocele: 0.8 cases per 10,000 births (IQR: 0.3, 1.5); and
- Spina bifida: 3.9 cases per 10,000 births (IQR: 2.4, 5.9).

Data from the Canadian Congenital Anomalies Surveillance System (CCASS) showed that the birth prevalence of aneuploidy and ONTD in Canada vary substantially among provinces and territories, with regional differences likely due to variation in maternal age distribution, the availability and use of prenatal screening and diagnosis services, and differences in termination rates of pregnancies due to these conditions. The period birth prevalence rates for aneuploidy and ONTD in Canada between 2001 and 2004 were:

- Trisomy 21: 14.3 cases per 10,000 births;

- ONTD: 4.6 cases per 10,000 births (anencephaly and encephalocele: one case per 10,000 births and spina bifida: 3.1 cases per 10,000 births.

Analysis of surveillance data of congenital anomalies in Alberta showed the following annual prevalence rates for the period between 2003 and 2007:

- Trisomy 21: 17. 9 cases per 10,000 in 2003 to 16.6 cases per 10,000 of total births (live and stillbirths) in 2007;
- Trisomy 18: 1.2 cases per 10,000 total births in 2003 to 3.1 cases per 10,000 total births in 2007;
- Trisomy 13: 1.2 cases per 10,000 total births in 2003 and 2.5 cases per 10,000 total births in 2007;
- Anencephaly: 2.2 cases per 10,000 total births in 2003 to 1.4 cases per 10,000 total births in 2007;
- Encephalocele: 0.77 cases per 10,000 total births in 2003 to 0. 6 cases per 10,000 total births in 2007; and
- Spina bifida: 2.7 cases per 10,000 total births in 2003 to 3.3 cases per 10,000 total births in 2007.

First and second trimester screening patterns of care and health system capacity

History, characteristics, and standards of care

Prior to the widespread availability of ultrasound and maternal serum prenatal screening, advanced maternal age (usually set at 35 or 40 years or over at the expected time of delivery) was used as a form of screening aimed at targeting a group of women considered at high risk of having a fetus with aneuploidy and other birth defects. Maternal age is currently considered a poor minimum standard for prenatal screening by its own. Guidelines of the Society of Obstetricians and Gynecologists of Canada (SOGC) recommend the availability of prenatal screening and diagnosis for women all ages. Multiple marker screening uses a combination of maternal age and two or more biochemical tests, with or without an ultrasound examination, to produce a single result for risk of fetal aneuploidy and ONTD. There are currently four main components to screening for fetal aneuploidy and ONTD defects:

- first trimester ultrasound (nuchal translucency [NT]),
- first-trimester biochemistry (pregnancy-associated plasma protein A [PAPP-A] and free beta subunit of human chorionic gonadotropin [β-hCG]),
- second-trimester ultrasound, and
- second trimester biochemistry (maternal serum alpha-fetoprotein [AFP], intact human chorionic gonadotropin [hCG], unconjugated estriol [uE3] and dimeric inhibin A [DIA]).

First trimester screening strategies for fetal aneuploidy and ONTD include:

- NT measurement alone;
- serum combined (double test: PAPP-A and free β-hCG), and
- first trimester combined screening (NT, PAPP-A and free β-hCG).

Second trimester screening options include:

- double test (AFP and free β-hCG);
- triple test (AFP, uE3 and intact hCG);
- quad test (AFP, uE3, free β-hCG and DIA), and
- ultrasonography.

A number of practical approaches for risk assessment combine information and tests results completed in the first trimester with information and test results completed in the second trimester:

- Integrated approaches: results are withheld until both first and second trimester screening tests have been obtained (i.e.; integrated prenatal screening); and
- Sequential approaches (i.e. stepwise screening and contingency screening): intermediate results are disclosed.

Screening values that fall above a risk cut-off point are not a definite indication of the presence of fetal aneuploidy or ONTD but they express the probability of the condition being present in the fetus at term or at mid-trimester, suggesting the need for further tests to confirm or refute the diagnosis. Standards of care of prenatal diagnostic techniques include the use of invasive techniques such as amniocentesis in the second trimester and chorionic villus sampling (CVS) in the first trimester of pregnancy.

The SOGC currently recommends that all pregnant women in Canada, regardless of age should be offered prenatal screening test for the most common clinically significant fetal aneuploidy in addition to a second trimester ultrasound for dating, growth, and congenital conditions. The SOGC guidelines indicate that invasive prenatal diagnosis (i.e., amniocentesis or chorionic villus sampling [CVS]) should be limited to women who screen above a set risk cut-off level on first and second trimester screening tests (FASTS). The SOGC guidelines do not recommend a specific screening strategy, suggesting instead that the implementation of any particular screening program is determined by the resources available in a given geographic area.

Standards of care and available FASTS programs in Canada and Alberta

Prenatal screening is funded provincially and offered population-wide in Manitoba, Ontario, British Colombia, Newfoundland, Saskatchewan, and Quebec and is centrally organized—though not provincially funded—in the Maritimes by the Izaak Walton Killam Health Centre in Nova Scotia. Screening practices differ across the country and provinces rely on the self-regulation of practitioners to govern the use of prenatal screening tests with different standards of care being used.

Alberta does not have a provincial screening program. FASTS services in the province are delivered through a variety of patterns of practice without unified criteria. All pregnant women in Alberta are offered the quad test in the second trimester. There is also the option of requesting AFP to screen for ONTD. Alberta Health Services (AHS) provides FASTS through the Edmonton Early Pregnancy Risk Assessment Program and the Early Prenatal Risk Assessment (ERA) Program in Calgary. Biochemical analysis and ultrasound are performed in designated AHS facilities.

Factors that affect the use, access, and provision of FASTS

Factors that affect the provision of FASTS services include those affecting the performance of the screening tests and those related to the access and use of FASTS services.

- Factors that can potentially affect the performance of FASTS tests: gestational dating methods and other measurement issues, maternal weight, the presence of certain clinical conditions in the mother (insulin-dependent diabetes mellitus), multiple pregnancies and the use of assisted reproduction.
- Factors related to the access and use of FASTS: level of knowledge about procedural and practical aspects of the screening tests, expectations and attitudes toward prenatal screening, psychological factors (i.e., anxiety towards screen results), socio-economic and socio-demographic factors, factors related with believes, culture and social norms, health providers attitudes towards testing and patterns of referral and characteristics of the facilities involved in the provision of FASTS services.

Diffusion of FASTS options in Alberta

There are two risk assessment programs in the province:

- The Edmonton Early Pregnancy Risk Assessment Program, located at the Lois Hole Hospital for Women at the Royal Alexandra Hospital in Edmonton: The program is funded by AHS with the laboratory component delivered through Edmonton Laboratory Services. The target group of the program is pregnant females desiring an early pregnancy risk assessment. First trimester combined screening has limited availability in Edmonton.
- The Early Prenatal Risk Assessment Program (ERA), located at the Southern Alberta Centre for Maternal Fetal Medicine in Calgary. The ERA program is the only program in Alberta that screens all pregnant women regardless of age or risk. The ERA program delivers first trimester combined screening via two models: OSCAR (One Stop Clinic for Assessment of Risk) and modified OSCAR. OSCAR allows for women to have their blood drawn and NT ultrasound in one location during one appointment. Within the modified-OSCAR model, women can have their blood drawn ahead of time for first trimester combined screening.

Utilization trends in Alberta and Canada

Access and utilization of prenatal testing services varies considerably among the provinces and territories. The use of FASTS services in Alberta is not documented in Alberta Health and Wellness surveillance statistics; therefore, current utilization patterns were estimated based on information gleaned from AHS Laboratory Services and the two risk assessment programs in the province:

- Data from the ERA program indicate that first trimester combined screening access is currently limited to 7000 women per fiscal year.
- Overall, an average of 812 first trimester screening tests per month was performed at Calgary Laboratory Services (CLS) during 2010. With current instrumentation and no staff increase, approximately 70,000 specimens per year can be analyzed.
- An average of 88 second trimester screening tests and 1.58 maternal AFP screening tests per month were performed at CLS during 2010. With current instrumentation and staffing there is no issue with capacity.

- Data from AHS Edmonton Zone Laboratory Services on the number of first and second trimester prenatal serum screening tests conducted per year indicate on average, 11,000 second trimester prenatal serum tests per year are conducted. Approximately 2800 first trimester prenatal serum tests (for PAPP-A and β-hCG each) are performed every year. First trimester prenatal screening testing has increased by more than 100% since January 2010. First trimester prenatal serum testing is increasingly monthly and the forecast for 2011 is more than 4000 tests per year.
- Edmonton Zone Laboratory Services is currently running at capacity for first trimester prenatal screening. A significant increase in workload will require more staff and equipment. The second trimester screening testing would allow an increase of 20% in utilization with existing staff. Equipment for second trimester screening testing is adequate.
- The current volume of the first trimester combined screening and the second trimester quad screening were estimated based on data from Calgary and Edmonton zone laboratory services. There were yearly 12,543 first trimester combined tests and 12,062 second trimester quad tests conducted across Alberta.

Service providers capable of providing various FASTS options in Alberta

- Data on the number of physicians that refer their pregnant patients to FASTS services is scarce. There is some evidence that 22% of Northern Alberta physicians routinely offer prenatal screening for fetal aneuploidy to all pregnant women.

System support needs for the provision of the FASTS services in Alberta

- The SOGC guidelines and evaluations conducted abroad on system support characteristics for the provision of prenatal screening services have recommended the development of standards, training packages for health providers, the provision of information and counselling services for pregnant women, the availability of invasive diagnostic procedures and mechanisms of follow-up.
- Prenatal screening services should be implemented with resources that support the informed decision making by patient and healthcare providers, timely access to audited screening and diagnostic laboratory and ultrasound services; counselling and follow up services as well as resources for administration, training, clinical audit, and data management and surveillance.
- The implementation of first trimester combined screening in Alberta has special implications for training, technical skills and resources, and the provision of adjunct diagnostic services.

Technological Effects and Effectiveness

Objective

The objective of the technology section of this report is to perform a systematic review and critical appraisal of the available evidence on the efficacy and safety, as measured by, respectively, the detection rate (DR) and false positive rate (FPR), of various first and second trimester screening methods (Table T.A) to determine the optimal screening test for use in pregnant women who wish to obtain a risk assessment for fetal trisomy 21, 18, 13, or open neural tube defects (ONTD).

Table T.A: Screening tests considered in technology assessment

Test	Description	Conditions for which risk estimate is generated	
		Trisomy 21, 18, 13	ONTD
First trimester	Tests conducted between 8 and 13^{+6} weeks' gestation		
Nuchal translucency (NT)	Ultrasound measurement	Yes	No
Double serum	PAPP-A, hCG serum tests	Yes	No
Combined	NT and PAPP-A, hCG serum tests	Yes	No
Second trimester	Tests conducted between 14 and 22 weeks' gestation		
Dual serum	AFP, hCG serum tests	Yes	Yes
Triple serum	AFP, hCG, uE3 serum tests	Yes	Yes
Quadruple serum	AFP, hCG, uE3, inhibin-A serum tests	Yes	Yes
Ultrasound	Ultrasound detection of open neural tube defects	Not assessed	Yes
Two-step screens	Use first and second trimester screens to provide sequential risk assessment and a final risk based on the combination of first and second trimester screens		
Full integrated	NT, PAPP-A + quadruple screen	Yes	Yes
Integrated – inhibin A	NT, PAPP-A + triple screen	Yes	Yes
Integrated serum	PAPP-A, HCG serum test + quadruple test	Yes	Yes
Sequential	NT, PAPP-A + quadruple or triple screen Women are divided into high and low risk groups based on first trimester screen. High risk group offered diagnostic test and low risk group offered second trimester screen.	Yes	Yes
Contingent	NT, PAPP-A + quadruple or triple screen Women are divided into high, medium and low risk groups based on first trimester screen. High risk group offered diagnostic test and medium risk group offered second trimester screen. Low risk group not offered further testing.	Yes	Yes
Repeated measures 1	PAAP-A and uE3 measured in first and second trimester	Yes	No
Repeated measures 2	NT + PAAP-A and uE3 measured in first trimester and PAAP-A and uE3 in second trimester	Yes	No

Results

A comprehensive electronic literature search for publications between 2000 and December 2010 identified and summarized 72 accuracy studies on NT and serum screening and one systematic review on second trimester ultrasound that met the predefined inclusion criteria. Most studies were conducted prospectively and the study populations were assembled as clinical cohorts. The women

included in the studies varied in age from late adolescence to middle age and most studies reported only results for singleton pregnancies. The studies were conducted mainly in Western industrialized countries at academic and community hospitals.

In general, the accuracy studies suffer from several major methodological limitations with all studies subject to more than one source of potential bias. There is good empirical evidence that three of the potential biases (differential verification—the most common bias among the included studies, not adequately describing the index test, and not adequately describing the study population) are associated with 1.5 to 2-fold overestimation of diagnostic test performance. An informal sensitivity analysis conducted for the combined screen and the quadruple serum screen did not indicate a substantial difference between the DR of all studies and those studies considered at lowest risk of bias.

The following are highlights from the reviewed evidence:

- The majority of evidence exists for the first trimester screens (NT, double serum, and combined) and second trimester serum screens (dual, triple, and quadruple serum).
- Little evidence exists regarding the performance of the two-step screens (tests that use both a first and second trimester screen to provide a sequential risk assessment and a final risk based on the combination of first and second trimester screens. The existing evidence suggests that these tests provide the highest DR and lowest FPR. However, these tests are also the most resource intensive and impose the greatest demands on women.
- The Society of Obstetricians and Gynecologists of Canada (SOGC) 2011 practice guideline recommends that acceptable first trimester screens have a minimum 75% DR at a 3% FPR for trisomy 21. Based on the evidence summarized in this report, the first trimester combined screen (already in use in southern Alberta), and the full integrated and serum integrated (integrated screen without an NT measurement) screens met this threshold.
- The SOGC also recommends that acceptable second trimester screens have a minimum performance threshold of 75% DR at a 5% FPR for trisomy 21. Based on the evidence summarized in this report the quadruple serum (already in use in northern Alberta) is acceptable (Tables T.B–T.E).
- There is strong evidence that second trimester ultrasound provides the most accurate information regarding ONTDs, while second trimester AFP screening provides comparatively much lower accuracy (Table T.F).
- Though the relative accuracy of the first and second trimester screens is well-established, no studies were found that examined the impact of screening results on physician decision-making or maternal or fetal outcomes. Importantly, the review has not examined the utility of the test results to support women's decision making regarding pregnancy. Other jurisdictions in Canada and internationally have considered an assessment of this utility, as well as of the consistency of prenatal screening with societal values, to be crucial before implementing prenatal screening programs.

Conclusions

For the first trimester risk assessment for trisomy 21 (and other aneuploidies), empirical evidence most strongly supports the use of the combined test; nuchal translucency may also be an acceptable screening option; the quadruple serum test is an acceptable second trimester screens. The

appropriate provision of either of these screens requires well-trained sonographers (for NT), high-quality equipment, and a program of quality control. More large empirical studies may strengthen the little existing evidence that suggests that the two-step screens may exceed the combined test in terms of increasing detection and reducing the number of false positives. Second trimester ultrasound is superior to second trimester serum screening for screening for ONTDs. These results are consistent with and support the SOGC practice guidelines on the selection of screening tests for prenatal screening for fetal aneuploidy.

Table T.B: Summary of screening test performance for estimating risk of trisomy 21

Test	Total no. studies (total +T21/total –T21)	Median DR % (range)	Median FPR % (range)	Within study prevalence %	PPV %
First Trimester					
Nuchal translucency	23 (756/170,347)	75 (40–100)	5 (1–23)	0.08–2.41	1.59–25.45
Double	9 (220/66,129)	76 (62–88)	9 (5–19)	0.17–0.56	1.02–6.01
Combined	30 (1706/395,315)	88 (50–100)	5 (1–9)	0.15–3.56	1.96–82.4
Second Trimester					
Dual	8 (423/222,592)	65 (50–76)	6 (3–11)	0.08–0.81	0.47–7.67
Triple	14 (1,268/631,160	80.5 (60–100)	9.5 (4–54)	0.10–1.92	1.04–4.95
Quadruple	7 (350/181,871)	85 (81–90)	7 (5–9)	0.05–0.63	0.92–9.89
Full integrated	4 (89/39,713)	85 (80–91)	7 (3–6)	0.18–0.51	5.3–10.87
Integrated – inhibin A	3 (141/49,824)	84.5 (87–100)	3.5 (2–5)	0.23–0.33	4.35–12.06
Serum integrated	2 (81/39,067)	88	3	0.18–0.21	4.76–5.24
Sequential	2 (148/41,603)	94–95	11–13	0.26–0.74	2.18–5.37
Contingent	No studies	---	---	---	---
Repeated measures	No studies	---	---	---	---

Table T.C: Summary of screening test performance for estimating risk of trisomy 18

Test	Total no. studies (total +T18/total –T18)	Median DR % (range)	Median FPR % (range)	Within study prevalence %	PPV %
First Trimester					
Nuchal translucency	7 (145/59,269)	90 (67–100)	4 (2–14)	0.03–0.51	0.63–4.62
Double	No studies	---	---	---	---
Combined	9 (119/79,181)	90 (33–100)	6 (0–8)	0.09–0.31	0.58–15.15
Second Trimester					
Dual	1 (9/25,521)	89	3	0.04	0.90
Triple	6 (192/543,432)	63.5 (53–86)	0.75 (0–36)	0.08–0.81	0.79–15.0
Quadruple	2 (22/51,718)	44–100	0.3–0.5	0.04–0.05	4.71–15.0
Full Integrated	1 (3/2,253)	100	6	0.13	2.16
Integrated – Inhibin A	No studies	---	---	---	---
Serum Integrated	No studies	---	---	---	---
Sequential	No studies	---	---	---	---
Contingent	No studies	---	---	---	---
Repeated measures	No studies	---	---	---	---

Table T.D: Summary of screening test performance for estimating risk of trisomy 13

Test	Total no. studies (total +T13/total – T13)	Median DR % (range)	Median FPR % (range)	Within study prevalence %	PPV %
First Trimester					
Nuchal translucency	5 (39/52,762)	97 (33–100)	3 (2–15)	0.02–0.13	0.16–1.69
Double	No studies	---	---	---	---
Combined	4 (41/39,910)	78 (57–100)	8 (4–8)	0.09–0.23	0.94–2.03
Second Trimester					
Dual	No studies	---	---	---	---
Triple	1 (2/1,053)	50	36	0.26	0.19
Quadruple	No studies	---	---	---	---
Full integrated	No studies	---	---	---	---
Integrated – inhibin A	No studies				
Serum integrated	No studies	---	---	---	---
Sequential	No studies	---	---	---	---
Contingent	No studies	---	---	---	---
Repeated Measures	No studies				

Table T.E: Summary of screening test performance for estimating risk of ONTDs

Test	Total no. studies (total +ONTD/total – ONTD)	DR %	FPR %	Within study prevalence %	PPV %
Triple					
Spina bifida	1 (2/32,923)	100	1	0.01	1.14
Anencephaly	2 (44/83,196)	90–100	0–3	0.04–0.07	1.32–13.07
Quadruple					
Spina bifida	1 (8/17,273)	50	1	0.05	2.12
Anencephaly	1 (6/17,273)	100	1	0.03	3.14

Table T.F: Summary of performance of second trimester ultrasound screening for detecting ONTDs (from Ritchie et al.[1])

Condition	Total no. studies (no. + condition/no. - condition)	Median DR % (range)	Median FPR % (range)	Within study prevalence %	PPV %
Spina bifida	6 (37/42,780)	92 (35–100)	0 (0–0)	0.05–0.26	100
Anencephaly	6 (43/42,783)	100 (100–100)	0 (0–0)	0.04–0.26	100
Encephalocele	No studies	---	---	---	---

Reference

1. Agaard-Tillery KM, Malone FD, Nyberg DA, Porter T, Cuckle HS, Fuchs K, et al. Role of Second-Trimester Genetic Sonography After Down Syndrome Screening. Obstetrics & Gynecology 2009;114(6):1189-96.

Economics Analysis

Objective

The objective of the economic analysis was to assess the evidence on cost effectiveness of alternative FASTS screening strategies and to evaluate the cost effectiveness and cost impact of 15 alternative screening strategies in Alberta.

Methods

Cost effectiveness was addressed through a systematic review of economic studies and an economic evaluation using a decision analytic model. The decision analytic model compared the health benefits and resource expenditures associated with each alternative screening strategy. The analysis adopted a payer perspective and considered direct medical service costs to the Alberta health system, including costs of physician, outpatient, and laboratory services but excluded abortions. The time horizon for the analysis considered costs from initial screen to final diagnosis and adopted a constrained program optimization approach. That is, the analysis elucidated the screening strategy that provided the highest accuracy at the lowest cost to the health system. The analysis focused on Trisomy 21 and excluded other abnormalities (e.g. T13, T18, or ONTD) due to lack of available data.

The analysis was conducted from a payer's perspective and adopted a time horizon from pregnancy until final diagnosis. Cost components included costs and services associated with genetic counseling, GP visits, invasive diagnosis tests (CVS and AC), prenatal tests, and induction of labour including physician, outpatient, and laboratory services.

Test performance came from a review of empirical studies (taken from T-section) for the majority of algorithms with the exception of contingent and repeated measures screening. Evidence to assess the test performance of contingent and repeated measures screening were derived from mathematical simulation studies which are considered lower in quality compared to empirical studies. Hence, contingent and repeated measures screening were excluded from the primary analysis and considered in a secondary analysis. Epidemiological, health service utilization, and cost data were derived primarily from Alberta administrative databases.

Effectiveness was defined as the number correctly identified pregnancies which accounted for both sensitivity and specificity of the screening strategies. From an economic perspective, the most cost effective strategy is the one that is the most efficient at identifying cases that are suitable for confirmatory testing and non-cases that do not require further testing particularly at lower rates of incidence where specificity can become a stronger driver of cost effectiveness than sensitivity.

Cost impact was addressed through a budget impact analysis including a cost attribution analysis which identified potential resource shifting. The BIA was conducted for the following scenarios:

1. Expanding existing combined screening to the entire province.
2. Expanding existing quad screening to the entire province.
3. Replacing existing combined screening and quad screening with the cost-effective algorithm demonstrated in the cost effectiveness analysis using total pregnancies correctly identified as the primary outcome measure.

Cost and clinical inputs applied in the BIA model were identical to the data used in the decision analytic model. The BIA considered a 1-year time horizon (all pregnancies should resolve within 1 year).

Results

Review of economic studies

There were 25 first and second trimester screening strategies for fetal anomalies that were economically assessed by the 12 reviewed studies. Based on the existing economic evidence, cost effectiveness of specific screening strategies were dependent on a variety of factors and it is unclear which screening algorithm was the most cost effective. Furthermore, several factors limited the generalizability of the published evidence to the Alberta setting including but not limited to differences in the incidence of DS, the demand for screening services, and the associated health systems cost of screening. Consequently, it is unclear which screening strategy would be cost effective in Alberta.

Primary economic analysis

Value for money

Primary analysis (excludes algorithms that were informed by mathematical simulation studies):

1. Among the algorithms dual and serum IPS were the most cost effective with serum IPS being more costly and more effective than dual ($2890 per additional correctly identified pregnancy).
2. When only considering the algorithms currently available in Alberta, compared to second trimester quad screening, first trimester combined screening was associated with greater costs and greater effectiveness with a cost per additional correctly identified pregnancy of $18,900. Note that combined and quad screening are dominated by dual and serum IPS.

Secondary analysis (considers all algorithms):

1. Serum IPS is dominated by repeated measures without NT. This suggests that while the evidence around the test performance of repeated measures is in the early stages, repeated measures without NT has the potential to be the most cost effective algorithm.

Cost impact

1. Physician services account for approximately 70% of all costs associated with screening.
2. When considering combined, quad, repeated measures without NT and serum IPS, the budget impact is as follows (note that budget impact represents additional cost to current cost of services):

Algorithm	At 2010 Alberta Screening Volumes (≈35% coverage)	Total Eligible Pregnancies in Alberta (100% coverage)
Adopting Combined Screening for AB	$2.2m	$25.27m
Adopting Quad Screening for AB	-$2.3m	$12.72m
Adopting Serum IPS Screening for AB	-$1.6m	$14.53m
Adopting Repeated Measures without NT for AB	-$1.7m	$14.48m

Conclusion

From an overall value perspective that looks at detecting both true cases and true non-cases, serum IPS provides the most value for money among the algorithms evaluated but it should be acknowledged that repeated measures without NT has the potential of being the most cost effective. Within the algorithms available in Alberta, combined screening is associated with additional benefit and additional costs compared to quad screening. Determining the cost effectiveness of any of these algorithms depends on whether their additional effectiveness is deemed to be worth their additional cost from the perspective of the health system (i.e. would those resources invested elsewhere provide greater value?). Furthermore, the cost impact of establishing a systematic province wide program with increased coverage of pregnancies will result in net budget increases to physician, outpatient, and laboratory services.

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ABBREVIATIONS

All abbreviations that have been used in this report are listed below unless the abbreviation is well known, has been used only once, or is a nonstandard abbreviation used only in figures, tables, or appendices in which case the abbreviation is defined in the figure legend or below the table.

95% CI	95% confidence interval
AC	Amniocentesis
ACASS	Alberta Congenital Anomalies Surveillance
AFP	alpha-fetoprotein
AHS	Alberta Health Services
AHW	Alberta Health and Wellness
AMA	advanced maternal age
β-hCG	free beta subunit of human chorionic gonadotropin
BC	British Columbia
BCPGSP	British Columbia Prenatal Genetic Screening Program
BIA	budget impact analysis
BMI	body mass index
CA	chromosome abnormalities
CARF	Congenital Anomaly Reporting Form
CBA	cost-benefit analysis
CCASS	Canadian Congenital Anomalies Surveillance System
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CI	confidence interval
CIHI	Canadian Institute for Health Information
CLS	Calgary Laboratory Services
CNS	central nervous system
CUA	cost-utility analysis
CVS	chorionic villus sampling
DIA	dimeric inhibin A
DR	detention rate
DS	Down syndrome
EDD	expected delivery date

EFW	Elliott Fong Wallace
EPR	early pregnancy review
ERA	Early Risk Assessment
EUROCAT	European Surveillance of Congenital Anomalies
FASTS	first and second trimester screening
FATC	Fetal Assessment and Treatment Centre
FISH	Fluorescent *in situ* hybridization
FMF	Fetal Medicine Foundation
FN	false negatives
FP	false positives
FPR	false positive rate
FT	First trimester
FTS	first trimester combined screening
GP	General Practitioner
hCG	human chorionic gonadotropin
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICER	Incremental Cost-Effectiveness Ratio
ICSI	intracytoplasmic sperm injection
IDDM	insulin-dependent diabetes mellitus
Inhibin-A	Dimeric inhibin-A
IPS	integrated prenatal screening
IQ	intelligence quotient
IQR	interquartile range
IUGR	intra-uterine growth restriction
IVF	in vitro fertilization
IWK	Izaak Walton Killam
LB	live births
LR+	positive likelihood ratio
LR-	negative likelihood ratio
MACS	magnetic-activated cell sorting
MoM	multiple of the median
MS	maternal serum
MSS	maternal serum screening

MSSS	Ministère de la Santé et des Services Sociaux
NA	not applicable
ND	not described
NI	not indicated
NPS	National Physician Survey
NR	not reported
NT	nuchal translucency
NTD	neural tube defects
NWT	Northwest Territories
OMMMS	Ontario Maternal Multiple Marker Screening
ONTD	open neural tube defects
OSCAR	One Stop Clinic for Assessment of Risk
PAPP-A	pregnancy-associated plasma protein-A
PCR	polymerase chain reaction
PPV	positive predictive value
PRA	Prenatal Risk Assessment
PSA	probabilistic sensitivity analysis
QALY	Quality Adjusted Life Years
QF-PCR	Quantitative Fluorescence Polymerase Chain Reaction
QHES	Quality of Health Economic Studies
RAD	Rapid Aneuploidy Diagnosis
RCP	Reproductive Care Program
ROC curve	Receiver operating characteristic curve
SB	Stillbirths
SDCL	Saskatchewan Disease Control Laboratory
SIPS	serum integrated prenatal screening
SOGC	Society of Obstetricians and Gynecologists of Canada
SSDA	social systems and demographics analysis
ST	serum tests
STS	Second Trimester Screening
SURUSS	Serum, Urine, and Ultrasound Screening Study
T21	Trisomy 21
T18	Trisomy 18

T13	Trisomy 13
TA	transabdominal ultrasound
ToPBD	termination of pregnancy for birth defects
TOP	Toward Optimized Practice
ToP	termination of pregnancy
TV	transvaginal ultrasound
uE3	unconjugated estriol
UK	United Kingdom
WTP	Willingness to Pay

Glossary/Dictionary[a]

Alpha fetoprotein (AFP): Second trimester maternal serum biochemical marker for ONTD, also effective for other open fetal defects such as gastroschisis, omphalocele and trisomy 21 (in combination with uE3 and hCG). Also screens for placental dysfunction, Smith-Lemil-Opitz syndrome, and trisomy 18.

Amniocentesis: Amniocentesis (also referred to as amniotic fluid test or AFT), is a medical procedure used in prenatal diagnosis of chromosomal abnormalities and fetal infections, in which a small amount of amniotic fluid, which contains fetal tissues, is extracted from the amnion or amniotic sac surrounding a developing foetus, and the fetal DNA is examined for genetic abnormalities.

Anencephaly: A congenital malformation characterized by the total or partial absence of the cranial vault, the covering skin, and the mrain missing or reduced to small mass.[1]

Aneuploidy: an abnormal number of chromosomes. It is due to the absence of a chromosome or the presence of an extra chromosome. The normal human karyotype has 46 chromosomes, 22 pairs of somatic chromosomes and one pair of sex chromosomes.[2]

Balanced translocation: Alteration in the structure of two chromosomes, without any change in the quantity of genetic material. An individual presenting with a balanced translocation is a carrier but is unaffected by the chromosomal aberration.[3]

Chronic villus sampling (CVS): A form of an invasive prenatal diagnostic test performed in pregnant women to identify any chromosomal abnormalities in the fetus by karyotyping.. A needle is used to remove a small amount of chorionic villus tissue from the placenta. The needle may be inserted via the cervix (transcervical) or abdomen (transabdominal).[4]

Clinical cohort: A cohort refers to a group of people that share a common characteristic or set of characteristics or exposure. In the context of this review, a "clinical cohort" refers to a group of women who are identified by the shared characteristics (or "exposure") of having had prenatal screening for fetal aneuphoidy or open neural tube defects.

[a] All references within the Glossary are cited in chronological order in the "S" section of the report

Contingent screening: An alternative to IPS where the majority of women receive their results after first trimester combined screening. All women have first trimester screening and are divided into three groups based on results: high, intermediate and low risk. High risk women have diagnostic test; low risk women are reassured and have no further screening. All others have second trimester screening tests. For these women the results of first and second trimester testing is combined to produce one integrated result.[4]

Detection rate: the detection rate reflects a test's sensitivity, that is, its ability to detect individuals having a condition. It is closely associated with the risk cut-off level used and the false-positive rate, but it is independent of the prevalence of trisomy 21.[2]

Dimeric inhibin A: Second trimester maternal serum biochemical marker. A relatively weak marker alone, it is used to increase the detection rate of trisomy 21 when combined with AFP, uE3, and hCG.

Double test: Second trimester serum screening using AFP and hCG (β-hCG or intact hCG**)** and incorporating maternal age.[4]

Down syndrome: Trisomy 21, or trisomy G, is a chromosomal disorder caused by the presence of all or part of an extra 21st chromosome. It is the most common genetic cause of mental retardation. Down syndrome is also associated with decreased levels of maternal serum AFP and uE3 and higher than average hCG levels. Low PAPP-A, high free β-hCG and NT thickness also are used to screen for the disorder.

Encephalocele: A congenital malformation characterized by herniation of the brain and/or meninges through a defect in the skull. Encephalocele is not counted when present with spina bifida.[1]

False-negative rate: the proportion of affected pregnancies considered to be at low risk upon screening.[2]

False negative: A negative test result in a person who *does* have the condition being tested for.[2]

False-positive rate: the proportion of unaffected pregnancies considered to be at high risk upon screening. This rate is independent of the prevalence of the condition and is equal to the complement of specificity (1 – specificity).[2]

False positive: A positive test result in a person who *does not* have the condition being tested for.[2,4]

Fetal loss: Interruption of pregnancy after the 20th week and before the fetus is viable. In this report, the term .fetal loss is used interchangeably with .abortion. in view of the difficulty in establishing the actual time point of the event in a particular pregnancy.[3]

Free β-hCG First trimester maternal serum biochemical marker. Higher in trisomy 21 pregnancies.

First trimester combined screening: First trimester trisomy 21 screening test based on combining first trimester maternal serum screening (PAPP-A, and β-hCG) and NT with maternal age.[4]

High risk after screening: The estimated risk is equal to or higher than the selected risk cutoff point. The risk cutoff ratio generally used when screening for trisomy 21 is between 1:250 and 1:385.[3]

Human chorionic gonadotropin (hCG): Second trimester maternal serum biochemical marker used to detect trisomy 21 (in combination with uE3 and AFP), ONTD, and other open fetal defects

such as gastroschisis and omphalocele. Also screens for placental dysfunction, Smith-Lemil-Opitz syndrome, and trisomy 18.

Inhibin-A: Dimeric inhibin-A is a dimeric glycoprotein hormone producted during pregnancy by the corpus luteum, the deciduas, and the placenta.

Integrated prenatal screening: Any method which integrates measurements performed during the first and second trimester of pregnancy into a single test result.[4]

Integrated test: the integration of NT and PAPP-A measurements in the first trimester with the quad test markers in the second trimester. It is the also known as the fully integrated test.[4]

Invasive testing: used in this context to describe prenatal diagnostic tests, e.g. amniocentesis or chorionic villous sampling, which involve removal of tissue or fluid from the placenta or uterus.[4]

Incidence: The number of new events (cases with a condition or disease) occurring during a certain period, in a specified population.[4]

Likelihood ratio: A measure of the increase or decrease of the odds of the presence of a disease based on the results of a test. Positive likelihood ratio (LR+) as calculated by sensitivity/1-specificity. Negative likelihood ratio (LR-) is calculated by 1-sentivity/specificity.

Live birth*:* a complete expulsion or extraction from the mother, irrespective of the duration of the pregnancy, of a foetus in which, after expulsion or extraction, there is breathing, beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscle.[5]

Meiosis: Cell reproduction that results in the formation of the gametes (the spermatozoon and ovum). Unlike autosomal cells which contain 46 chromosomes (22 different pairs of autosomal chromosomes and one pair of sex chromosomes), gametes obtained through meiosis are haploid . i.e. they only contain 23 different chromosomes.[3]

Mosaicism: The combination of more than one cell line, one of which presents a free trisomy or a translocation. This generally involves non-disjunction after formation of the zygote (i.e., the fertilized egg resulting from the combination of the two gametes, the spermatozoon and ovum).[3]

Multiples of the median (MoM): in a pregnant woman, the concentration of a given serum marker divided by the median value of the concentration of that marker in all pregnant women of the same gestational age, after eliminating the pregnancies characterized by a condition that can affect serum marker levels. Depending on the test, an abnormal value will be expressed as a fraction (e.g., 0.5) or as a multiple (e.g., 2.0) of the median value.[2]

Non-disjunction: An error in cell division that occurs during meiosis and which, in trisomy 21, results in the formation of gametes with two chromosome 21.s. Trisomy 21 occurs upon fertilization by a normal gamete possessing one chromosome 21. Non-disjunction is not restricted to chromosome 21 and can give rise to other trisomies or a monosomy.[3]

Nuchal translucency (NT): The subcutaneous layer of fluid behind the fetal neck and lower cranium which can be visualized by ultrasound.[4]

Open neural tube defects (ONTD): An opening in the spinal cord or brain that occurs very early in human development. Examples of ONTDs are anencephaly, encephaloceles, hydranencephaly, iniencephaly, schizencephaly, and spina bifida.

Phenotype: the outward manifestation of a given individual's constitution resulting from the interaction between his or her genetic baggage and his or her environment.[2]

Pregnancy-associated plasma protein A (PAPP-A): First trimester maternal serum biochemical marker. Lower in trisomy 21 pregnancies.

Population-based screening programme: A population-based screening programme is one in which screening is systematically offered by invitation to a defined, identifiable population.[4]

Positive predictive value: A curve based on graphic plot of the sensitivity and specificity of a test.

Prevalence: The number of events in a given population at a designated time (point prevalence) or during a specified period (period prevalence).[4]

Quad test: Second trimester serum screening using AFP, hCG (β-hCG or intact hCG), uE3 and DIA and incorporating maternal age.[4]

Receiver operating curve: A curve based on graphic plot of the sensitivity and specific of a test.

Repeated measures screening: A mathematical model showing the potential value of screening for trisomy 21 using highly correlated repeated measures of serum markers, some of which individually have may have poor discriminatory power. Integrated screening with repeat measurements has the potential to significantly reduce the false positive rate.

Risk: in this report, risk is the relationship between the number of affected and unaffected pregnancies. It is expressed as a ratio (e.g., a risk of 1:20 means one affected pregnancy for 20 unaffected pregnancies) or a proportion (e.g., a risk of 1/21 means one affected pregnancy out of a total of 21 pregnancies).[2]

Risk cut-off level: a value which, during screening, serves to distinguish between high and low risk.[2]

Screening: the examination of asymptomatic people in order to classify them as likely or unlikely to have the condition that is the object of screening.[2]

Sensitivity: Probability that the test result will be positive when the disease is present.

Sequential screening: Screening where results of screening in 1st trimester are combined with second trimester screening in either an independent, contingent, stepwise or integrated manner.[2]

Serum integrated prenatal screening: IPS screening without NT.

Specificity: Probability that the test result will be negative when the disease is present.

Spina bifida: A family or congenital malformation defects in the closure of the spinal column characterized by herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine.[1]

Stepwise screening: All women have first trimester screening and are divided into two groups based on results: high and low risk. Those with a high risk result are offered diagnostic testing. All others have second trimester screening tests. For these women the results of first and second trimester testing are combined to produce one integrated result.[2]

Stillbirth: a complete expulsion or extraction from the mother, after at least 20 weeks pregnancy, *or* after attaining a weight of 500 grams or more of a fetus in which, after the expulsion or extraction, there is no breathing, beating of the heart, pulsation of the umbilical cord or unmistakable movement of voluntary muscle.[5]

Success rate: the technical ability to obtain the desired measurement, e.g., the proportion of fetuses in whom NTmeasurement can be obtained.[2]

Termination of pregnancy (ToP)*:* for our purposes, any pregnancy loss before 20 weeks gestation (< 20 weeks), most of which are therapeutic terminations for congenital anomalies but could include spontaneous abortions or intrauterine fetal deaths with fetal anomalies.

Triple test: Second trimester serum screening using AFP, hCG (β-hCG or intact hCG)**,** and uE3 and incorporating maternal age.[4]

Trisomy: the presence of three, rather than two, homologous chromosomes.[2]

Trisomy 13: A congenital chromosomal malformation syndrome associated with extra chromosome 13 material. Includes: translocation and mosaic trisomy 13.[1]

Trisomy 18: A congenital chromosomal malformation syndrome associated with extra chromosome 18 material. Includes: translocation and mosaic trisomy 18.[1]

Trisomy 21: Also called Down synsrome, trisomy 21 is a chromosomal disorder caused by the presentat of all or part of an extra chromosome in the 21st chromosomal pair.

Ultrasound: Most major fetal anatomic abnormalities should be detected with this screen. In particular, the majority of ONTD should be detected by ultrasound.

Unbalanced translocation: Alteration in the structure of two chromosomes, involving a change in the quantity of genetic material present.[3]

Unconjugated estriol (uE3): Second trimester maternal serum biochemical marker used to detect trisomy 21 (in combination with AFP and hCG), trisomy 18, ONTD, and other open fetal defects such as gastroschisis and omphalocele.

SECTION ONE: SOCIAL AND SYSTEM DEMOGRAPHICS ANALYSIS

Maria Ospina, BSc, MSc

Objective and Policy Questions

The objective of the Social Systems and Demographics Analysis (SSDA) for this STE project is to describe, characterize and provide an epidemiological profile of fetal aneuploidy and open neural tube defects (ONTD) and to describe the patterns of care, utilization trends, and factors affecting the provision of first and second trimester screening (FASTS) services for fetal aneuploidy and ONTD.

The SSDA section of the STE report addresses the following questions:

Patterns and Burden of the Condition:

- What are fetal aneuploidy and ONTD (definition, progression, associated co-morbidities)?
- What are the risk factors related to fetal aneuploidy and ONTD?
- What are the physical, psycho-social and economic effects of these conditions?
- What is the prevalence and incidence of fetal aneuploidy and ONTD in Alberta, Canada and internationally?

Patterns of Care

- What are the patterns of provision of FASTS options for fetal aneuploidy and ONTD (history, characteristics, standard of care in Alberta and Canada, trends in utilization)?
- What factors may affect access to and use of the various FASTS options?
- What are the selection criteria used for the provision of FASTS services among Albertan and Canadian pregnant woman?

System Capacity

- What is the number and distribution of service providers capable of providing various FASTS options in Alberta?
- What are the characteristics of system supports necessary for appropriate provision of the FASTS options in Alberta?
- What is the status of the diffusion of FASTS options in Alberta?
- What patient and population characteristics can affect the capacity of the system to provide care?

The data sources and method for data synthesis and analysis are described in Appendix A.

Patterns and Burden of the Condition

Fetal aneuploidy

Cells in the human body (except the egg and sperm cells) have 46 chromosomes, made up of 23 pairs. One copy of each pair is inherited from the mother and the other copy is inherited from the father; the two versions are called homologues. The first 22 pairs of chromosomes are autosomes (that is, they contain information available to both sexes) and have been numbered from one to 22 according to their size (from the largest to the smallest). The 23rd pair of chromosomes constitutes the sex chromosomes (XX for normal females and XY for normal males).

During normal cell division, when germ cells are divided to create gametes (egg and sperm cells), the chromosome pairs separate so that there is only one of each pair in these cells (23 chromosomes instead of 46). **Aneuploidy**, a type of chromosome anomaly, occurs when the chromosomes do not separate properly between the two cells during either meiosis or mitosis (non-disjunction) resulting in an abnormal number of chromosomes.[1] Aneuploidies can involve either missing a chromosome from a pair (monosomy) or having more than two chromosomes of a pair. **Trisomy** occurs when there are three copies of a particular chromosome in the cells rather than the usual two copies. Three trisomy variants have been described: full trisomy occurs when an extra copy of a particular chromosome affects *all* the cells in the body. Mosaicism occurs when *some* cell lines have the normal number of chromosomes, while others are either trisomic or monosomic.[1] Translocation is defined as a rearrangement of an entire chromosome or detachment of a piece of a chromosome from its normal location during cell division and its reattachment to another chromosome.[1] Translocations are termed *balanced* if the cell contains two complete, properly functioning copies of all chromosomal material. *Unbalanced* translocations imply a rearrangement of chromosomal material that results in either complete or partial trisomy or monosomy.[1] Translocations that involve the fusion of the whole long arms of two chromosomes, are known as Robertsonian translocations.[1]

The most common form of aneuploidy in humans is trisomy 16; however, this condition is the most frequent chromosomal cause of spontaneous miscarriage during the first trimester of pregnancy because fetuses with the full version of the condition in which all cells of the body are affected seldom survive to term. The most common fetal aneuploidies that an infant can survive and the only three autosomal trisomies for which development can proceed to live birth are trisomy 21, trisomy 18, and trisomy 13. These conditions can present either as complete forms (in which case, they are also known as Down syndrome, Edward syndrome, and Patau syndrome), in mosaic or translocation forms, in which there is a partial expression of the pattern of anomalies, with several degrees of variation between nearly normal and the full syndrome.[1]

Trisomy 21

Definition, clinical characteristics and co-morbidities associated to Trisomy 21

Trisomy 21 was first described by the English physician John Langdon Down in 1866.[2] Trisomy 21 is a fetal aneuploidy caused by the presence of all or part of an extra chromosome in the 21st chromosomal pair.[3] Three variants of the condition have been described: a) non-disjunction full trisomy 21, in which an additional copy of chromosome 21 is present in all the body cells, b) mosaic trisomy 21, in which an additional copy of chromosome 21 affects some of the body cells, and c) translocation trisomy 21, in which the long arm of chromosome 21 is attached to another chromosome.[4] Approximately 95% of trisomy 21 cases result from the full form of the condition. The remaining 5% of cases results from translocation or mosaic variants of trisomy 21.[5,6]

Individuals with trisomy 21 exhibit all or some of the following physical characteristics: low muscle tone, brachycephaly (broad, short head), flat appearance of the face, low-set ears with a flat or absent helix, excess skin folds on eyelids with slanting almond-shaped eyes, narrow and short palate, protruding tongue, a short neck, white spots on the iris of the eye, and a single, deep transverse crease on the palm of the hand.[4,7] Associated comorbidities include congenital heart defects, digestive tract abnormalities, congenital cataracts, and leukemia.[7-9] There is a wide variation in the mental abilities, behavior, and developmental characteristics of individuals with trisomy 21. Some degree of intellectual disability is expected, ranging from mild to severe.

Risk factors for Trisomy 21

Advanced maternal age has been considered for many years as an important risk factor for the occurrence of trisomy 21, particularly for the non-disjunction type.[10-14] The risk for women 35 years of age is approximately one out of 350 births, which increase to around one out of 25 births for women 45 years and older.[10,11] The causative mechanisms involved in the age-dependent occurrence of trisomy 21 are poorly understood and, more recently, it has been considered that measures of ovarian aging should better predict the risk of trisomy 21 and other aneuploidy than simple chronological age.[10,11,13] Likewise, the recurrence risk for trisomy 21 has been reported in about 1%, regardless of maternal age.[13,15] The influence of paternal age on the incidence of trisomy 21 is unclear[16] as studies have failed to assert an age-dependent risk for men fathering children with trisomy 21 or other fetal aneuploidies.[4,8,11,17]

Maternal age does not seem to be the main predictor of the risk of translocation or mosaic trisomy 21.[4,11] Rather, the translocation type of trisomy 21 can run in families increasing the likelihood of recurrence in subsequent pregnancies compared to non-disjunction trisomy 21.[12,14] Certain factors such as alcohol use,[18] maternal irradiation,[19,20] use of fertility drugs, oral contraceptives and spermicides,[21] multiparity,[22] and low social economic status[23] have been implicated as risk factors for the development of trisomy 21; however, none of these associations have been confirmed.[8,14] Therefore, trisomy 21 has not been attributed to any particular parental behaviour before or during pregnancy, or to other factors such as education, income, culture or race.[7]

Progression and effects of Trisomy 21

Trisomy 21 is one of the few autosomal trisomies that survive to term. However, trisomy 21 has a high incidence of spontaneous fetal loss during pregnancy. The proportion of miscarriages between 11 weeks of gestation and term has been calculated around 43%.[8] Between 16 weeks of gestation and term, the percent of miscarriages is to be 23%.[8] The life expectancy for people with trisomy 21 is substantially greater than for trisomy 18 and trisomy 13. The median survival time for an individual with non-disjunction trisomy 21 is around 35 to 50 years.[24] However, the lifespan of individuals with trisomy 21 is likely to be shortened due to a cluster of comorbidities associated with the condition that can affect their health status virtually at every stage of life and that can become more severe over time.

During the first days and months of life, some disorders are immediately evident. Congenital heart problems, such as septal defects, aortic regurgitation, and mitral valve prolapsed, are common, with incidences calculated around 40% of the total cases of trisomy 21.[9,24]

In the early years of life, children with trisomy 21 are 10 to 15 times more likely than other children to develop leukemia; both acute lymphoblastic leukemia as well as myeloid leukemia.[4,25] Infants with trisomy 21 are also more susceptible to transient myelodysplasia (the defective development of the spinal cord). Compared to the general population, individuals with trisomy 21 have a 12-fold higher

mortality rate from infectious diseases, if these infections are left untreated and unmonitored.[9] They are also more likely to develop chronic respiratory infections, middle ear infections, and recurrent tonsillitis.[4] In addition, they have a 62-fold higher incidence of pneumonia compared to the general population.[9] Individuals with trisomy 21 are more likely to develop auditory and visual problems.[9] Individuals with trisomy 21 have a significantly higher level of hearing impairments over time, with incidences of mild-to-moderate hearing loss of more than 15 to 20 decibels in at least one ear that range from 66% to 89% of 77%.[4] In addition to hearing problems, visual disorders such as refractive errors and cataracts are also common early in life.[26] Seizure disorders occur in a bimodal distribution in trisomy 21, with approximately 40% of people with the disorder having seizure onset before 1 year of age and another 40% having seizure onset in the third decade of life or later.[26] Seizures affect between 5% and 13% of individuals with trisomy 21, a 10-fold greater incidence than in the general population.[27,28] There is an unusually high incidence of infantile spasms or seizures in children less than 1 year of age, some of which are precipitated by neonatal complications, infections or cardiovascular disease.[9]

Individuals with trisomy 21 present learning, memory, and language difficulties that lead to mild-to-profound impairment in their intellectual functioning.[29] In general, individuals with trisomy 21 have intelligence quotient (IQ) levels that vary from 40 to 72.[30] The cognitive profiles of individuals with trisomy 21 are diverse in terms of both the severity of cognitive disability and the type of cognitive function affected.[31] Relative cognitive weaknesses are consistently associated with expressive language, syntactic and morphosyntactic processing, and verbal working memory.[32] Individuals with trisomy 21 are susceptible to disruptive behaviour, aggressiveness, attention problems, and conduct-oppositional disorders. As the child ages, it appears that externalizing symptoms decrease, whereas internalizing symptoms of depression and withdrawal increase during adolescence and adulthood.[30,33]

Premature aging is a characteristic of adults with trisomy 21.[34] It is claimed that virtually 100% of persons with trisomy 21 over 40 years of age develop a progressive deterioration in memory and other cognitive functions that correspond to a diagnosis of Alzheimer disease, as evidenced by post-mortem findings.[9,29,31,35]

Little has been published about the economic burden of trisomy 21 to society or families. The economic costs associated with trisomy 21 were evaluated in the United States in 1992 using data from the California Birth Defects Monitoring Program.[36] The economic burden of a new trisomy 21 case was calculated in US$451,000 in 1992 and the total economic burden of all new cases in the US was US$1848 million for that year.[36] The economic burden of trisomy 21 was evaluated in China in 2003 using a survey methodology.[37] Study results showed that average lifetime economic burden of a new trisomy 21 case from a family perspective and a societal perspective amounted to US$47,000 and US$55,000 per year, respectively. Indirect (productivity) costs were responsible for most of the total economic expenditure.[37]

Trisomy 18

Definition, clinical characteristics and co-morbidities associated to Trisomy 18

Trisomy 18 was first described in 1960.[38] Trisomy 18 is a fetal aneuploidy caused by the presence of all or part of an extra 18th chromosome par in some or all cells of the body. Trisomy 18 is the second most common autosomal trisomy in liveborn infants after trisomy 21.[39] There are three possible types of trisomy 18: non-disjunction full trisomy, mosaicism, or unbalanced translocation. Full trisomy 18 is the most common form of trisomy 18, which is responsible for 90% to 95% of the cases.[26,40] Approximately 5% to 10% of the cases are the result of mosaicism or unbalanced translocation.[26]

Individuals with trisomy 18 have certain craniofacial characteristics such as prominent occiput, microcephaly, microphtalmia, mandibular hypoplasia and malocclusion, microstomia, low-set ears, and redundant skin at the back of the neck.[41] The condition is associated with the occurrence of cardiac (ventricular or atrial septal defects, patent ductus arteriosus), pulmonary (pulmonary hypoplasia), gastro-intestinal (hernias, intestine malrotation, diaphragmatic eventration), genitourinary (genitalia malformations, micro multicystic kidneys), and skeletal malformations (severe growth retardations, short sternum, distinctively clenched fingers, small fingernails and toenails, underdeveloped or altered thumbs, rocker-bottom feet).[41-43] Significant psychomotor and developmental problems occur in the severe forms of the condition. The range and severity of the clinical features depends on the number and distribution of cells containing the extra copy of chromosome 18.[41]

Prenatally, a number of comorbidities have been identified on ultrasound examination, including intrauterine growth restriction (IUGR), polyhydramnios or oligohydramnios, cardiac malformations, choroid plexus cysts, hydrocephalus, myelomeningocele, abdominal wall defects, single umbilical artery, and clenched fists or radial limb defects.[1,43]

Risk factors for Trisomy 18

The risk of carrying a fetus with trisomy 18 occurs at all maternal ages, but the incidence increases with advanced maternal age, particularly after 35 years of age.[15,41] A higher risk of trisomy 18 associated with increased paternal age has not been yet described.[44] Race of the parents has not been found to influence the risk of developing trisomy 18 in the fetus.[44,45]

The sex of the fetus has been associated to the risk for developing trisomy 18. Compared to males, female fetuses are two to three times more likely to have the condition.[1] However, data suggest that there is a statistically higher proportion of female live births for trisomy 18 and that there is an excess of male mortality in the perinatal period.[1,46]

The recurrence risk for trisomy 18 has been reported to be approximately 1%;[41,44] the risk of trisomy 18 increases for women who have had previous trisomy pregnancies, regardless of whether these pregnancies were viable or not.[15]

No lifestyle or environmental factors such as alcohol, tobacco, drug use,[41] living near solid waste incinerators or landfills,[47] exposure to cholorination byproducts and nitrate in drinking water,[48] or pesticides[49] have been definitively implicated in the risk of trisomy 18. On the other hand, the use of multivitamins or other supplements prior or during pregnancy are not associated with a decreased risk of trisomy 18.[50]

Although most cases of trisomy 18 are non-inherited and sporadic (as is the case with trisomy 18 of non-disjunction etiology), approximately 10% are the result of an unbalanced translocation.[41] A child with the unbalanced translocation form may have a parent with a balanced translocation of chromosome 18 yet inherit this rearrangement in an unbalanced manner, resulting in mosaic trisomy 18.[41]

Progression and effects of Trisomy 18

Trisomy 18 results in a high rate of miscarriages during pregnancy. Data from congenital anomaly registries have shown that 72% to 86% of pregnancies diagnosed with trisomy 18 end in miscarriage.[51,52] The proportion of miscarriages between 18 weeks of gestation and delivery term is around 65% to 70%[51,52] and as high as 59% between 24 weeks of gestation and term. Male fetuses with trisomy 18 appear to be more likely to be miscarried than female fetuses.[51] Complications

during delivery have been described and they include an increase in the number of Caesarean section deliveries, primarily due to breech presentation, fetal distress, and IUGR.[1]

The median survival time for children with full trisomy 18 has been calculated from 6 to 14.5 days of life.[53-56] Analysis of data collected from congenital anomaly registries have shown that survival probability until 1 month of life is 25%[55,57] and the probability of survival beyond the first year of life has been estimated between 2% to 10%.[39,53,55] One-month to 1-year survival of trisomy 18 seems to be affected by sex and race, with girls and infants of races other than white surviving longer.[39,53] The presence of structural heart defects does not shorten the life expectancy during the first year of life.[53] Limited information on factors associated with long-term survival have suggested that race (black) and gender (being female) play a significant role in median survival time after the first year of age.[53] Reported causes of death among trisomy 18 include cardiac and renal failure, central apnea caused by central nervous system (CNS) defects,[55] sepsis, and pneumonia.[41,57] The clinical expression of trisomy 18 is less severe and survival is usually longer among individuals who have the translocation or mosaic forms of the condition.

A small number (1%) of infants with trisomy 18 survive beyond the first decade of life[41] and a few live into their adolescence and early adulthood.[57] Although they present severe growth, psychomotor and developmental problems, and a limited social response, individuals with trisomy 18 may be in time able to interact, relate to their families, and acquire some psychomotor skills.[41,57,58] The magnitude of the economic impact of trisomy 18 on the society and family is unknown.

Trisomy 13

Definition, clinical characteristics and co-morbidities associated to Trisomy 13

Trisomy 13, also known as Patau syndrome, is a chromosomal condition in which all or some parts of an extra copy of chromosome 13rd appear in some or all cells of the body. Trisomy 13 is the third most frequent trisomy among live births after trisomy 21 and trisomy 18[59] and the most severe of the viable autosomal trisomies. Both the range and severity of the clinical features of trisomy 13 depend on the number and distribution of cells containing the extra copy of chromosome 13. Non-disjunction full trisomy 13 constitutes 80% of all the trisomy 13 cases, with about 20% occurring as a result of mosaicism or chromosomal translocation.[1] Clinical features of trisomy 13 vary widely; however, certain phenotypical characteristics are present such as holoprosencephaly (incomplete or absent division of the forebrain into distinct lateral cerebral hemispheres), scalp defects, low-set ears, polydactyly, rocker-bottom feet, cutis aplasia, unusually small eyes, and facial clefting (lip and palate).[1,46] Trisomy 13 is associated with the occurrence of multiple malformations. They include structural heart defects (e.g., atrial or ventricular septal defects, patent ductus arteriosus, dextrocardia), genital (cryptorchidism and an abnormal scrotum in males and bicornuate uterus in females), kidney abnormalities (polycystic kidneys, hydronephrosis, and hydroureter), muscloskeletal problems (postaxial polydactyly of either the hands or feet or both, hyperconvex narrow fingernails, and abnormal dermatoglyphics) and CNS problems that lead to severe developmental delays and profound intellectual disabilities.[54,60] Individuals with trisomy 13 fail to grow and gain weight at the expected rate and often develop episodes in which there is temporary cessation of spontaneous breathing.[60]

Risk factors for Trisomy 13

Maternal age is the most important risk factor related to fetal trisomy 13.[41,61] There is no higher risk of trisomy 13 associated with increased paternal age.[44,45] Race has not been reported to influence trisomy 13 risk.[44] Fetal sex influences the risk for trisomy 13. Males are more likely than females to

have the aneuploidy.[1] Trisomy 13 is also associated with lower birth weight, prematurity, and IUGR.[53] The risk of recurrence for trisomy 13 has been reported to be approximately 1%.[44] If a woman has had a child with trisomy 13 there may be a small additional increase in risk for having another child with the condition.[15] No lifestyle or environmental factors have been definitively associated to an increase in the risk of trisomy 13.

Progression and effects of Trisomy 13

Trisomy 13 is associated with a high rate of miscarriages in pregnancy. Analyses of data collected from congenital anomaly registers have shown that about 49% of pregnancies diagnosed with trisomy 13 end in a miscarriage that occurs between 12 weeks of gestation and pregnancy term.[51,52] The proportion of miscarriage due to trisomy 13 occurring between 18 weeks of gestation and term has been estimated from congenital anomaly registries to be as high as 42%[51,52] and miscarriages due to trisomy 13 occurring between 24 weeks of gestation and term have been calculated as high as 35%.[51]

Trisomy 13 is associated with serious and fatal birth defects, with death frequently occurring in the first month of life. Severe forms of trisomy 13 among surviving infants are associated with abnormalities in multiple systems that are not compatible with prolonged life and that lead to poor and usually fatal outcomes. The median survival time for children with full trisomy 13 has been calculated between 2.5 days and 8.5 days.[55,62-64] Survival probability until the first month of life is 30%[63,64] and the probability of survival beyond the first year of life has been estimated between 5% to 10%.[59,62-64] One-month to 1-year survival does not seem to be affected by sex, race, or the presence of structural heart defects that may shorten life expectancy.[51,53] Information on factors associated with long-term survival are limited, but several studies have suggested that race and gender seem to affect survival in trisomy 13, with girls and blacks showing higher median ages at death.[53] Long survival beyond the first year of life also seems to be associated with the presence of non-lethal congenital anomalies[62] and the absence of holoprosencephaly and septal defects in the clinical presentation.[59,62] Individuals that survive long enough and pass the first or the second decade of life are likely to be mosaic trisomy 13 cases. They present other multiple impairments that include the development of multiple fractures, chronic respiratory problems, early puberty, and psychomotor retardation.[62] The severity of the clinical presentation of mosaic trisomy 13 depends on the number and type of body cells that contain the extra copy of chromosome 13. The magnitude of the economic impact of trisomy 13 on the society and the family is unknown.

Open neural tube defects

The formation of the human brain and spinal cord begins with the development of the neural tube through the embryonic process of neurulation. In this process, the neural plate originates as a thickening of the dorsal surface ectoderm that folds up and fuses in the midline to create the neural tube.[65] The neural tube is a narrow channel that is temporally opened at both ends and that communicates with the amniotic cavity. By week six of gestation, both ends close to form the brain and spinal cord. Neural tube defects are a group of malformations that occur very early in pregnancy (around the 28th day after conception) in which the normal closure process of the neural tube fails.[66] The failure of the embryonic process of neural tube closure yields to exposure of brain and/or spinal cord neural tissue to extra-embryonic environment that leads to neurodegeneration *in utero*, with loss of neurological function at and below the level of the lesion.[67] Neural tube defects can be classified based on the anatomical type or the location of the lesion, or based on the open/closed status of the defect, depending on whether the skin over the lesion is intact or not.[68] The phenotype of the ONTD varies depending on the region of neural tube that remains open (rostral or caudal).

The most common classification schema for ONTD includes: anencephaly, encephalocele, and spina bifida.[66]

Overall, common associated anomalies secondary to ONTD include hydrocephalus, Arnold-Chiari malformation (a condition characterized by herniation of the cerebellar vermis through the foramen magnum that constitutes the major cause of hydrocephalus among these infants), lower limb deformations, spinal curvature, or vertebral anomalies.[67] Specific anomalies that occur with greater frequency include facial cleft, cardiac defects, anotia or microtia, limb reduction defects, anophthalmia or microphthalmia, abdominal wall defects, and renal anomalies. Less common anomalies include holoprosencephaly, amniotic bands, and polydactyly. Trisomy 18, trisomy 13, and triploidy are the most common fetal aneuploidies associated with ONTD (particularly with anencephaly and spina bifida).[66]

Anencephaly

Definition, clinical characteristics and co-morbidities associated to Anencephaly

Anencephaly results from a failure of fusion of the cranial portion of the neural tube, resulting in the absence of all or a major portion of the brain, neurocranium, and scalp.[65,66] Clinical characteristics of anencephaly include the absence of cerebral hemispheres with preservation of the brainstem and some portions of the midbrain. The frontal bone is defective above the supraorbital region and the parietal bones, as well as the squamous portion of the occipital bone are absent.[69] Protruding eyes, cleft palate, a very short neck, low-set ears, and missing bones around the front and sides of the head are common craniofacial defects.[66,70] The condition is characterized by a minimal development of the cerebrum, the area of the brain that is responsible for thinking, vision, hearing, touch, and movement.[71] Therefore, an infant born with anencephaly usually is blind, deaf, unconscious, and unable to feel pain. Although some individuals with anencephaly may be born with a rudimentary brain stem and display some basic reflexes such as breathing and some responses to sound or touch, the lack of a functioning cerebrum permanently rules out the possibility of ever gaining consciousness.[66,69] Two types of anencephaly are generally described - holoanencephaly and meroanencephaly. In holoanencephaly, the lesion extends through the level of the foramen magnum, while the defect in meroanencephaly is confined to the midbrain.[68,70] Associated malformations include spina bifida (present in about 17% of anencephaly cases), cleft lip or palate, lower limbs, or vertebrae malformations in about 2% of the cases.[72] Trisomy 18, trisomy 13, and triploidy are the most common chromosomal conditions associated with anencephaly.[66]

Risk factors for Anencephaly

Anencephaly has a multifactorial etiology and both genetic and environmental risk factors have been implicated: maternal obesity, diabetes during pregnancy, folic acid and vitamin deficiencies in the mother, family history of anencephaly and previous ONTD pregnancies, maternal stress, and history of epileptic seizures.[13,66,73,74] Increased birth order has not been associated with an increased risk for anencephaly.[66]

A number of teratogenic agents such as radiation, trypan blue, salicylates, sulfonamides, amniopterin, and carbon dioxide excess have been found to increase the risk of anencephaly in experimental animals; however, evidence from human studies is not conclusive regarding the role that these substances have in the genesis of the condition.[66,68,73]

Progression and effects of Anencephaly

Anencephaly is one of the most severe forms of ONTD and typically not compatible with life. It almost always results in stillbirth or death shortly after birth.[71,72] Approximately 25% to 32% of

babies with this condition may be born alive, but will survive only hours to days.[66] The magnitude of the economic impact of anencephaly on the society and family is unknown.

Encephalocele

Definition, clinical characteristics and co-morbidities associated to Encephalocele

Encephalocele is an ONTD characterized by the formation of sac-like protrusions of the intracranial contents (brain tissue and meninges) through bone defects of the skull.[66] Encephaloceles are commonly subdivided into occipital, parietal, and frontal. The malformation is usually midline, more likely to affect the occipital area and, less commonly, the parietal area, frontal skull, or upper part of the face.[66] Encephaloceles are often accompanied by craniofacial abnormalities or other CNS abnormalities. They may include hydrocephalus (excessive accumulation of cerebrospinal fluid in the brain), spastic quadriplegia (paralysis of the arms and legs), microcephaly, uncoordinated movement of the voluntary muscles, vision problems, developmental delays, mental and growth retardation, and seizures.[68] Some individuals with encephalocele may have normal intelligence.[68] Encephalocele has the highest rate of associated anomalies among the ONTD[66] and is a frequent component of a number of congenital syndromes such as amniotic band syndrome, Meckel syndrome, Von Voss-Cherstvoy syndrome, Dandy-Walker syndrome, fetal Warfarin syndrome, and cryptophthalmos syndrome. Spina bifida is found in 7% to 15% of the encephalocele cases.[66]

Risk factors for Encephalocele

Encephalocele is frequently associated with single-gene and chromosomal syndromes.[66,75] It has also been reported in association with maternal rubella,[76] diabetes, and hyperthermia and can be produced experimentally in animals by the administration of several teratogens, such as amniopterin, X-ray radiation, trypan blue, and hypervitaminosis A.[66,77]

Progression and effects of Encephalocele

The prognosis for individuals with encephaloceles depends on a variety of factors such as the type of brain tissue involved, the location of the sacs, the presence of hydrocephalus, and the accompanying brain malformations. Mortality rates for encephalocele in live births are reported to be between 44% and 71%.[66] Among individuals that survive over time, only about 9% of them achieve normal intellectual development.[66,77] Among babies born with encephalocele, approximately 76% die during the first day of life. The survival probability to 1 year of age is around 70% and to 20 years of age has been reported around 67%.[78] The magnitude of the economic impact of encephalocele on the society and the family is unknown.

Spina bifida

Definition, clinical characteristics and co-morbidities associated to Spina Bifida

Spina bifida is a ONTD characterized by a failure of fusion of the caudal portion of the neural tube and concomitant schisis of the posterior elements of the vertebrae.[68] Spina bifida can occur at the cervical, thoracic, lumbar, or sacral level and is subdivided into ventral and dorsal defects.[71] Ventral defects are extremely rare and are characterized by the splitting of the vertebral body and the occurrence of neuroenteric cysts. The lesion is generally located at the lower cervical or upper thoracic vertebra. Dorsal defects are subdivided into spina bifida *aperta* and spina bifida *occulta*. Spina bifida *aperta* (open spina bifida) is the most frequent lesion. Accounting for approximately 85% of the cases,[68] it occurs when the neural canal is exposed or the defect is covered by a thin meningeal membrane. Spina bifida *occulta* (15% of spina bifida cases) is characterized by a small defect surrounded by an area of hypertrichiosis, pigmented and dimpled skin, or the presence of

subcutaneous lipoma. The defect is completely covered by skin and although in many cases it is asymptomatic and diagnosed only incidentally by radiographic spina examination, the clinical importance of this lesion is its frequent association with infection of the neural contents.

Meningomyeloocele is a type of spina bifida lesion commonly located in the lumbosacral region and characterized by a central neural placode (splayed-open, malformed spinal cord) that is covered by a sac-like membrane containing cerebrospinal fluid.[68] A similar lesion and a more rare form of spina bifida known as myeloschisis or myelocele lacks a membranous sac and the open neural tissue lies at the bottom of the spinal canal. A meningomyelocele or myeloschisis seldom affects only one-half of the split cord; a condition that is known as hemimeningomeylocele or hemimyeloschisis.[68]

Spina bifida symptoms vary depending on the position of the opening along the spine and on how much of the spinal cord or the meninges protrudes through the vertebrae. The condition tends to have more severe effects when the opening is higher up the spine.[68] Likewise, if only the sac protrudes, the condition is less severe than if the cord itself and the associated nerves protrude.

Spina bifida has the lowest rate of associated anomalies among all the ONTD.[66] They include other CNS defects and lower limb deformities. In almost all cases of spina bifida *aperta*, atypical abnormalities in the posterior fossa such as Arnold-Chiari malformations are found and almost invariably associated with obstructed hydrocephalus. Deformities of the aqueduct of Sylvius are also concurrent with spina bifida and secondary to ventricular enlargement and brain stem compression. Spina bifida can be accompanied by chromosomal conditions, among which trisomy 18, trisomy 13, and triploidy are the most common.[66]

Risk factors for Spina Bifida

The incidence of spina bifida seems to vary according to race. The condition has been reported more frequently among Caucasians than in Asians or Blacks.[73] These differences are likely to persist even after migration, suggesting a genetic rather than an environmental defect.[73] It has been reported that increased birth order is associated with a higher risk of spina bifida, especially after the woman already had three children.[27] Because grand multiparity (greater than four offsprings) is associated with low socio-economic status and low education, poorer prenatal care, smoking and alcohol consumption, and that grand multiparas have a high body mass index (BMI) and a high rate of insulin-dependent gestational diabetes, any putative association between increased parity and elevated risk for spina bifida should account for these factors.[66] It has been hypothesized that stress may be one of the putative causes for smoking more, drinking more, or eating poorly and that these behaviours are factors that interact with the stress levels to influence the risk of ONTD in the infant.[10,66]

An increased risk associated with advanced maternal age have been detected, with the effect being stronger for spina bifida than for anencephaly.[66,79] The relationship between maternal age and the risk for spina bifida and other ONTD is likely to be U-shaped; that is, highest among the youngest (less than 19 years of age) and oldest women (older than 40 years of age).[66,72] A pattern of a moderately high risk in younger fathers has been also reported.[66,79]

Folic acid deficiency in the fetus environment has been identified as the most conclusive non-genetic factor contributing to the development of spina bifida and other ONTD.[73] However, a series of animal studies have demonstrated that folic acid deficiencies cause ONTD only in the presence of a genetic predisposition.[73,79-81]

Maternal obesity has emerged as a consistent risk factor for spina bifida and other ONTD,[67,79,82] with women with the highest BMI having a 3.5-fold higher risk of carrying a fetus with a ONTD than

women with lower BMI.[72,79,82] Likewise, maternal hyperthermia in early pregnancy (under the form of high maternal fever or extreme sauna use) has been identified as an important risk factor for ONTD.[72,79,83]

Other non-genetic factors with a demonstrated link to spina bifida and other ONTD include diabetes mellitus,[73,79] use of antiepileptic drugs (valproic acid) and zinc, and vitamin-12 deficiencies.[67,73,79,81]

Other exposures that are of current interest but that require further investigation to establish the relationship they have with the development of ONTD include exposure to mercury, organic solvents, and pesticides both in the mother and the father.[66,73,80]

Any population group can be affected; however, studies examining the presence of socio-economic inequities in congenital defects have documented that there is an increased risk for ONTD among low socio-economic status families, as measured by parental occupation, education level, and household income.[66,74,79]

Progression and effects of Spina Bifida

Spina bifida is a condition that is compatible with postnatal survival but that frequently results in serious disability. The stillbirth rate has been calculated around 25%.[28] Over 90% of infants with spina bifida treated in the early neonatal period survive beyond the first year of life.[28,72] Prognostic factors include the level and the extent of the lesion, with higher mortality among those with high versus low lesions.[2] Survival of infants treated in the early neonatal period is around 40% at 7 years of age.[28] Effects associated with spina bifida vary in severity from mild motor impairments to severe effects such as paralysis, sensory loss, bladder and bowel dysfunction, scoliosis, and hydrocephaly.[71] If the spinal abnormality is slight, minor effects that do not require surgery are present; however, in most cases, the opening and protrusion of the spinal cord require surgery. Some degree of disability can remain; neurological impairment below the lesion can lead to lack of sensation, inability to walk, and incontinence,[84] all of which may cause difficulties in everyday functional activities. Twenty-five percent of individuals with spina bifida are totally paralyzed, 25% are almost totally paralyzed, 25% require intense rehabilitation, and 25% have no significant lower limb dysfunction.[84] Neurodevelopmental effects across a number of domains have been described and result in a combination of core deficits affecting motor function, perception, language, reading skills, and mathematics.[84]

The economic costs associated to spina bifida were evaluated in the United States in 1992 using data from the California Birth Defects Monitoring Program.[36] The economic burden of a new spina bifida case was US$294,000 in 1992 and the total economic burden of all new cases in the USA was US$489 million for that year.[36]

Population Dynamics

Epidemiological investigations using retrospective methods and analysis of data from central registries of perinatal health were used to describe the burden of fetal aneuploidy and ONTD, and to identify temporal or geographic variations in their occurrence. Outcomes of interest stratified by mothers' age were also reported, if available.

Population dynamics of fetal aneuploidy

International epidemiological data

International data on the epidemiology of fetal aneuploidy was obtained from the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR). Established in 1974 and affiliated with the World Health Organization, the ICBDSR brings together 38 birth defect surveillance and research programs established in a variety of countries around the world. In some instances, countries have more than one birth defect surveillance database contributing to the international database (e.g., Canadian registries in the ICBDSR include the Alberta and British Columbia provincial registries), or birth defect cases are registered on a regional basis (e.g. South America). Therefore, the international epidemiological data presented in this SSDA should be interpreted with caution as the prevalence rates are not necessarily reported per country but for the catchment area covered by the registry. Appendix B provides international data on the birth prevalence of trisomy 21, trisomy 18, and trisomy 13 obtained from ICBDSR registry members.

Analysis of ICBDSR birth prevalence data (including live births, stillbirths, and termination of pregnancy for fetal anomaly following prenatal diagnosis) for the year of 2006 (Appendix B, Table S.B.1) showed that the median birth prevalence for trisomy 13 in a sample of 38 international birth defects registries was 1.4 cases per 10,000 births (interquartile range [IQR: 0.5, 2.6]). The median birth prevalence for trisomy 18 calculated from international registries was 2.8 cases per 10,000 births (IQR: 1.7, 5.2). The median birth prevalence for trisomy 21 among international registries was 17 cases per 10,000 births (IQR: 12.3, 20.5).

Analyses of 5-year grouped birth prevalence data reported in 38 international birth defects registries (Appendix B, Table S.B.2) showed that overall, birth prevalence of trisomy 13 recorded in international registries has decreased over time (median reduction of 0.3 cases per 10,000 births; IQR: -0.6, 0.0). Overall reductions in birth prevalence rates for trisomy 18 have been also observed in international registries (median reduction of trisomy 18: 0.5 cases per 10,000 births; IQR: -1.5 - 0.06). Finally, birth prevalence rates of trisomy 21 in the registries have also decreased (median reduction of 0.4 cases per 10,000 births; IQR: -3.4, 0.3).

The European Surveillance of Congenital Anomalies (EUROCAT) is a European network of population based congenital anomaly registers covering 1.2 million births per year, at 40 European sites.[85,86] A cumulative analysis of EUROCAT birth prevalence data (including live births, fetal deaths/stillbirths from 20 wk gestation and termination of pregnancy for fetal anomaly following prenatal diagnosis) from full-member registries for the time period of 2004 to 2008 (Appendix B, Table S.B.3) showed that the period birth prevalence rate of trisomy 13 was 1.49 cases per 10,000 births in the European Union. The period birth prevalence rate of trisomy 18 and trisomy 21 were 3.85 and 18.06 cases per 10,000 births, respectively. Analyses of longitudinal birth prevalence data from EUROCAT full-member registries from 2002 to 2004 (Appendix B, Table S.B.4) showed that overall; prevalence rates for trisomy 21, trisomy 18, and trisomy 13 have remained steady over time, with minor fluctuations in the population estimates.

Canada

Currently, Canada has three congenital anomalies surveillance systems: the Canadian Congenital Anomalies Surveillance System (CCASS) and two provincial systems in Alberta and British Columbia each. Apart from British Columbia and Alberta, congenital anomaly surveillance systems in Canada are incomplete in their data collection, consisting primarily of perinatal systems (Ontario

and Nova Scotia), maternal serum screen systems (Ontario and Manitoba) or medical genetics registries (Newfoundland). Nova Scotia also has a fetal anomaly register.

Canadian data at a national level was obtained from reports CCASS reports on the epidemiology of fetal aneuploidy.[87,88] Established by Health Canada in 1966, CCASS is a national surveillance database which was a founding member of the ICBDMS. In the early 1990s, CCASS discontinued its ICBDSR status and reinstated it as an associate member in 1996. Based on data primarily collected from the Canadian Institute for Health Information (CIHI) acute in-patient Discharge Abstract Database, the CCASS is an ongoing population-based congenital anomaly surveillance database that allows estimating the Canadian birth prevalence of specific congenital anomalies. It monitors about 330,000 births annually and captures virtually all births in the provinces and territories. Data on live births up to 1 year of age and registered stillbirths (a birth weight of greater or equal to 500 grams, or greater than or equal to 20 weeks in pregnancy) were collected until 2000. Since 2001 only period data on 30-days follow-up is included in the database.

Epidemiological indicators of the prevalence of trisomy 13 and 18 at a national level were not identified in the CCASS and only data on trisomy 21 is presented. Data on the prevalence of trisomy 13 and 18 is available for British Columbia.

Longitudinal birth prevalence data from the CCASS from 1995 to 2004 (Table S.1) showed that the birth prevalence of trisomy 21 increased slightly from 13.4 per 10,000 total births in 1995 to 15.5 per 10,000 total births in 2003, before dropping to 13.5 per 10,000 total births in 2004.[88] The overall prevalence rate for the 1995-2004 period was 13.8 cases per 10,000 total births.

Table S.1: Birth prevalence of trisomy 21 in Canada (1995-2004)

Year	Total births	Number of cases	Rate per 10,000 total births
1995	368,100	493	13.4
1996	366,811	450	12.3
1997	351,139	478	13.6
1998	343,823	490	14.3
1999	388,407	498	14.7
2000	330,398	515	15.6
2001	336,835	462	13.7
2002	331,527	484	14.6
2003	338,417	524	15.5
2004	339,662	460	13.5
Total	**3,495,119**	**4854**	**13.8**

Source: Public health Agency of Canada, Canadian Congenital Anomalies Surveillance System (CCASS)[88]

Analysis of CCASS birth prevalence of trisomy 21 in Canada for the years 2001-2004 (Table S.2) showed that prevalence of trisomy 21 varied substantially among Canadian provinces and territories. Rates of trisomy 21 ranged from 10.4 cases per 10,000 births in Quèbec to 21.7 per 10,000 births in Prince Edward Island. The regional differences may be due to variation in maternal age distribution, the availability and use of prenatal screening and diagnosis, and differences in termination rates of pregnancy.[88] The 2001-2004 period birth prevalence rate of trisomy 21 in Canada was 14.3 cases per 10,000 births (95% confidence interval [CI]: 13.7 to 15.0)

Table S.2: Birth prevalence of trisomy 21 in Canada by province/territory (2001-2004)

Province/territory	Number of T21 cases	Total births	T21 rate (95% CI) per 10,000 total births
Newfoundland and Labrador	20	18,148	11.0 (6.7 to 17.0)
Prince Edward Island	12	5528	21.7 (11.2 to 37.9)
Nova Scotia	58	34,949	16.6 (12.6 to 21.5)
New Brunswick	36	28,035	12.8 (9.0 to 17.8)
Quèbec	300	287,409	10.4 (9.3 to 11.7)
Ontario	801	536,754	14.9 (13.9 to 16.0)
Manitoba	78	54,869	14.2 (11.2 to 17.7)
Saskatchewan	66	47,282	14.0 (10.8 to 17.8)
Alberta	224	161,951	13.8 (12.1 to 15.8)
British Columbia	317	157,801	20.1 (17.9 to 22.4)
Yukon	§	1826	§ (0.0 to 30.5)
Northwest Territories	§	2611	§ (0.0 to 27.7)
Nunavut	§	1362	§ (0.0 to 40.9)
Unknown	14	7916	17.7 (9.7 to 29.7)
Total Canada	**1926-1938**	**1,346,441**	**14.3 (13.7 to 15.0)**

Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System (CCASS);[88] § Number/rate suppressed due to small cell size < 5; 95% CI = 95 percent confidence interval; T21 = trisomy 21

Surveillance data of congenital anomalies in British Columbia[89] for the year 2006 showed that the birth prevalence rate for trisomy 21 was 19.04 cases per 10,000 births (Table S.3). Higher prevalence rates were identified in babies/fetuses of women aged between 35 and 39 years (32.3 cases per 10,000 births), 40 and 44 years (95.1 cases per 10,000 births), and over 45 years of age (90.9 cases per 10,000 births). The prevalence of trisomy 18 and trisomy 13 in British Columbia was 4.52 and 1.43 cases per 10,000 total births, respectively.

Table S.3: Birth prevalence of trisomy 13, trisomy 18 and trisomy 21 in British Columbia (year 2006)

Birth defect	Number of cases			Rates per 10,000 total births
	LB	SB	ToPBD	Total rate
Trisomy 13	3	3	NR	1.43
Trisomy 18	9	10	NR	4.52
Trisomy 21	53	27	NR	19.04
≤ 20 yr	1	1	NR	13.59
20-24 yr	3	1	NR	6.51
25-29 yr	11	1	NR	10.34
30-34 yr	9	7	NR	11.96
35-39 yr	14	11	NR	32.38
40-44 yr	9	6	NR	95.12
45+	1	0	NR	90.91
Unknown age	5	0	NR	---

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] live births (LB): 41,673; total stillbirths (SB): 335; total births: 42,008; number of terminations of pregnancy for birth defects (ToPBD): not reported (NR)

Analyses of 5-year grouped birth prevalence data in the British Columbia registry of congenital anomalies (Table S.4) showed that, overall, birth prevalence rates of trisomy 13 and trisomy 21 have remained stable over time. Birth prevalence rates of trisomy 18 have slightly increased from 3.55 cases per 10,000 during 1997 and 2001 to 4.06 cases per 10,000 during the years of 2002 to 2006.

Table S.4: Birth prevalence of trisomy 13, trisomy 18 and trisomy 21 in British Columbia (1997-2006)

	1997-2001	2002-2006
Trisomy 13	1.47	1.42
Trisomy 18	3.55	4.06
Trisomy 21 (all ages)	17.55	17.25
≤ 20 yr	9.16	6.82
20-24 yr	8.63	7.15
25-29 yr	10.95	8.84
30-34 yr	15.15	12.37
35-39 yr	28.67	31.18
40-44 yr	57.64	79.82
45+	301.89	179.49
Total births	211,365	204,627

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] birth prevalence rates: (live births + stillbirths + termination of pregnancy) per 10,000

Alberta

The Alberta Congenital Anomalies Surveillance System (ACASS) is a population-based surveillance system aimed at obtaining baseline statistics for live and stillborn infants with congenital anomalies in Alberta.[90] The program began in 1966 as a General Registry for Handicapped Children. This registry was later disbanded in 1980 and continued as a surveillance program. Since 1997, terminations of pregnancy with congenital anomalies were added into the system. Reporting is voluntary. The system is located at the Department of Medical Genetics, Alberta Children's Hospital, University of Calgary, and reports to Alberta Vital Statistics and Alberta Health and Wellness. Sources of case ascertainment include vital statistics documents (physicians notice of live birth or stillbirth, medical certificate of death, medical certificate of stillbirth), and the Congenital Anomaly Reporting Form (CARF), which is forwarded from hospitals and special outpatient clinics to Vital Statistics for record validation and linkage to the birth or death registration. All hospitals in Alberta submit a CARF on any inpatient under 1 year of age. Because the vast majority of births in Alberta occur in hospital settings (approximately 97%), the ACASS database covers virtually all live and stillbirths in the province.[90] Anomalies are coded, by means of the British Paediatric Association's adaptation of the International Classification of Diseases.[91] Additional ascertainment sources are medical genetics and crytogenetics laboratories, outpatient clinics including the two regional genetics clinics and public health units.

Surveillance data from ACASS and Alberta Health and Wellness data of congenital anomalies in Alberta[89] for the year 2006 showed that the birth prevalence rate for trisomy 21 was 19.35 cases per 10,000 births (Table S.5). Higher prevalence rates were identified in babies/fetuses of women aged between 35 and 39 years (52.5 cases per 10,000 births), 40 and 44 years (146.9 cases per 10,000 births) and over 45 years of age (769.2 cases per 10,000 births). The prevalence rates of trisomy 18 and trisomy 13 in Alberta were 4.89 and 2.67 cases per 10,000 total births, respectively.

Table S.5: Birth prevalence of trisomy 13, trisomy 18 and trisomy 21 in Alberta (year 2006)

Birth defect	Number of cases			Rates per 10,000 total births
	LB	SB	ToPBD	Total rate
Trisomy 13	4	4	4	2.67
Trisomy 18	3	10	9	4.89
Trisomy21 (all ages)	47	13	27	19.35
≤ 20 yr	0	0	0	0.00
20-24 yr	6	0	1	8.10
25-29 yr	10	2	2	10.00
30-34 yr	8	4	5	13.15
35-39 yr	15	5	10	52.57
40-44 yr	6	1	8	146.91
45+	2	1	1	769.23

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] live births (LB): 44,659; stillbirths (SB): 297; total births: 44,956; number of terminations of pregnancy for birth defects (ToPBD): 72

Analyses of 5-year grouped birth prevalence data in the ACASS (Table S.6) showed that, overall, birth prevalence rates of trisomy 21, trisomy 18, and trisomy 13 have slightly increased over time in the province.

Table S.6: Birth prevalence of trisomy 13, trisomy 18 and trisomy 21 in Alberta (1997-2006)

	1997-2001	2002-2006
Trisomy 13	1.71	2.19
Trisomy 18	4.49	4.82
Trisomy 21 (all ages)	17.60	21.32
≤ 20 yr	7.92	10.04
20-24 yr	4.98	6.93
25-29 yr	10.32	10.45
30-34 yr	16.08	15.86
35-39 yr	42.05	60.32
40-44 yr	162.40	157.40
45+	265.49	380.95
Total births	186,930	205,458

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] birth prevalence rates: (live births + stillbirths + termination of pregnancy) per 10,000

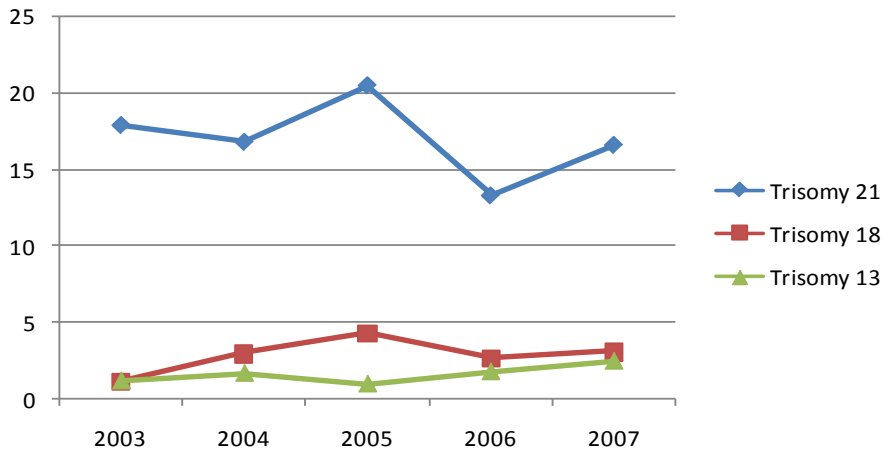
Annual birth prevalence data for trisomy 21 between 2003 and 2007 ranged from 17.9 cases per 10,000 in 2003 to 16.6 cases per 10,000 of total births (live and stillbirths) in 2007 (Table S.7 and Figure S.1). Trisomy 18 rates for the same time period ranged from 1.2 cases per 10,000 total births in 2003 to 3.1 cases per 10,000 total births in 2007. Trisomy 13 rates varied between 1.2 cases per 10,000 total births in 2003 and 2.5 cases per 10,000 total births in 2007.

Table S.7: Birth prevalence rates for trisomy 21, trisomy 18 and trisomy 13 in Alberta 2003-2007

Year	Trisomy 21		Trisomy 18		Trisomy 13	
	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)
2003	72	17.9 (14.1, 22.6)	5	1.2 (0.4, 2.9)	5	1.2 (0.4, 2.9)
2004	68	16.8 (13.0, 21.2)	12	3.0 (1.5, 5.1)	7	1.7 (0.7, 3.5)
2005	86	20.5 (16.4, 25.3)	18	4.3 (2.6, 6.8)	4	1.0 (0.3, 2.4)
2006	60	13.3 (10.2, 17.2)	12	2.7 (1.4, 4.6)	8	1.8 (0.8, 3.5)
2007	81	16.6 (13.2, 20.7)	15	3.1 (1.7, 5.1)	12	2.5 (1.3, 4.3)

Source: ACASS, 2009;[92] Rates are expressed as number of cases (live births and stillbirths ≥ 20 weeks or ≥ 500 g) per 10,000 total births. 95% CI = 95% confidence interval

Figure S.1: Fetal aneuploidy rates in Alberta 2003-2007



Data source: ACASS, 2009;[92] birth prevalence rates per 10,000 (total births: live births, stillbirths)

Aggregate birth prevalence rates for trisomy 21, trisomy 18, and trisomy 13 in Alberta are reported in Table S.8. Trisomy 21, trisomy 18, and trisomy 13 rates have increased over time.

Table S.8: Aggregated birth prevalence rates for trisomy 21, trisomy 18 and trisomy 13 in Alberta 1980-2007

Year	Trisomy 21		Trisomy 18		Trisomy 13	
	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)
1980-1989	402	9.3 (8.4, 10.3)	72	1.7 (1.3, 2.1)	32	0.7 (0.5, 1.0)
1990-1999	452	11.4 (10.4, 12.5)	101	2.5 (2.1, 3.1)	44	1.1 (0.8, 1.5)
2000-2004	301	15.6 (13.8, 17.4	57	2.9 (2.2, 3.8)	22	1.1 (0.7, 1.7)
2005-2007	227	16.7 (14.6, 19.1)	45	3.3 (2.4, 4.4)	24	1.8 (1.1, 2.6)

Source: ACASS, 2009;[92] Rates are expressed as number of cases (live births and stillbirths ≥ 20 weeks or ≥ 500 g) per 10,000 total births. 95% CI = 95% confidence interval

The increase in trisomy 21 prevalence rates is correlated with increasing maternal age (35 years of age and over).[92] Table S.9 shows how trisomy 21 prevalence rates have increased over time as maternal age advances. This result is consistent across the entire observation period from 2003 to 2007. Terminations of pregnancies do not seem to affect the rates of trisomy 21 markedly until rates for maternal age over the age of 30 years are examined.

Table S.9: Trisomy 21 birth prevalence rates by maternal age in Alberta 2003-2007 (total births: live, still)

Maternal age (years)	Year				
	2003	2004	2005	2006	2007
< 20	18.7 (18.7)	4.7 (4.7)	13.8 (18.4)	0.00 (0.00)	8.0 (8.0)
20-24	8.7 (8.7)	10.1 (10.1)	5.0 (6.2)	6.9 (8.1)	5.5 (7.6)
25-29	9.7 (9.7)	7.1 (7.8)	13.7 (15.2)	8.5 (9.9)	8.4 (10.3)
30-34	13.0 (17.4)	11.9 (15.3)	16.5 (20.6)	9.2 (13.0)	15.1 (19.4)
35-39	44.2 (56.3)	58.0 (68.0)	49.1 (66.1)	34.8 (52.2)	36.3 (61.5)
≥ 40	118.1 (206.7)	69.9 (109.8)	141.8 (207.9)	91.3 (173.5)	132.0 (214.5)
All ages	17.9 (22.9)	16.8 (20.2)	20.5 (26.5)	13.3 (19.4)	16.6 (23.8)

Data source: ACASS;[92] Birth prevalence rates = expressed as number of cases per 10,000 total births. Birth prevalence rates: (live births + stillbirths ≥ 20 weeks or ≥ 500 g). Rates including ToPs in brackets

Population dynamics of neural tube defects

International epidemiological data

Analysis of ICBDSR birth prevalence data (including live births, stillbirths, and termination of pregnancy for fetal anomaly following prenatal diagnosis) for the year of 2006 (Appendix B, Table S.B.5) showed that the median birth prevalence for anencephaly in a sample of 38 international birth defects registries was 2.4 cases per 10,000 births (IQR: 1.3, 3.6). The median birth prevalence for encephalocele reported in international registries was 0.8 cases per 10,000 births (IQR: 0.3, 1.5). Finally, the median birth prevalence for spina bifida among all international registries was 3.9 cases per 10,000 births (IQR: 2.4, 5.9).

Analyses of 5-year grouped birth prevalence data reported in 32 registries (Appendix B, Table S.B.6) showed that overall birth prevalence of anencephaly reported in international registries has remained relatively stable over time (median increase of 0.31 cases per 10,000 births; IQR: -0.1, 0.8). Birth prevalence rates for encephalocele and spina bifida have remained also stable (median increase of encephalocele cases: 0.1 per 10,000 births; IQR: -0.05 0.03; median increase of spina bifida cases: 0.5 per 10,000 births; IQR: 0.09, 1.08).

Cumulative analyses of EUROCAT birth prevalence data (including live births, fetal deaths/stillbirths from 20-week gestation, and termination of pregnancy for fetal anomaly following prenatal diagnosis) for the time period of 2004 to 2008 (Appendix B, Table S.B.7) showed that the period birth prevalence rate of anencephaly was 2.7 cases per 10,000 births in the European Union. The period birth prevalence rate of encephalocele and spina bifida were 1.05 and 4.5 cases per 10,000 births, respectively.

Analyses of longitudinal birth prevalence data from EUROCAT full-member registries from 2004 to 2008 (Appendix B, Table S.B.8) showed that overall prevalence rates for anencephaly, encephalocele and spina bifida have remained steady over time, with minor fluctuations in the population estimates.

Canada

Longitudinal birth prevalence data from the CCASS from 1995 to 2004 (Table S.10) showed that the birth prevalence of ONTDs in Canada decreased by more than half from 9.2 to 4.0 cases per 10,000 total births. Reductions in birth prevalence for anencephaly and encephalocele (from 1.8 to 1.1 per 10,000 total births) and spina bifida (from 6.5 to 2.6 per 10,000 total births) were observed.[88] The overall prevalence rate for the 1995 to 2004 period was 13.8 cases per 10,000 total births.

Table S.10: Birth prevalence of open neural tube defects in Canada (1995-2004)

Year	Total births	All ONTD		Anencephaly and encephalocele		Spina bifida	
		Number of cases	Rate per 10,000 total births	Number of cases	Rate per 10,000 total births	Number of cases	Rate per 10,000 total births
1995	368,100	340	9.2	65	1.8	238	6.5
1996	366,811	278	7.6	42	1.1	200	5.5
1997	351,139	267	7.6	54	1.5	188	5.4
1998	343,823	196	5.7	31	0.9	144	4.2
1999	388,407	203	6.0	31	0.9	143	4.2
2000	330,398	176	5.3	38	1.2	115	3.5
2001	336,835	171	5.1	39	1.2	109	3.2
2002	331,527	152	4.6	29	0.9	105	3.2
2003	338,417	160	4.7	33	1.0	108	3.2
2004	339,662	136	4.0	36	1.1	90	2.6
Total	**3,495,119**	**2079**	**5.9**	**398**	**1.1**	**1440**	**4.1**

Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System (CCASS);[88] ONTD = open neural tube defects

Analysis of CCASS 2001-2004 birth prevalence data across Canada (Table S.11) showed that birth prevalence of anencephaly and encephalocele and spina bifida varied substantially across provinces and territories. Regional differences may be due to variation in maternal age distribution, the availability and use of prenatal screening and diagnosis, and differences in termination rates of pregnancies among provinces and territories.[88] The 2001-2004 period birth prevalence rate of ONTD in Canada was 4.6 cases per 10,000 births (95% CI: 4.2 to 5.0). The period prevalence of both anencephaly and encephalocele was one case per 10,000 births (95% CI: 0.9 to 1.2) and for spina bifida was 3.1 cases per 10,000 births (95% CI: 2.8 to 3.4).

Table S.11: Birth prevalence of open neural tube defects, anencephaly, encephalocele and spina bifida in Canada by province/territory (2001-2004)

Province/territory	Total births	ONTD		Anencephaly and encephalocele		Spina bifida	
		Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)
Newfoundland and Labrador	18,148	7	3.9 1.5 to 7.9)	§	§ (0.6 to 5.6)	§	§ (0.6 to 5.6)
Prince Edward Island	5528	§	§ (0.0 to 10.1)	0	0.0 (0.0 to 6.6)	§	§ (0.0 to 10.1)
Nova Scotia	34,949	20	5.7 (3.5 to 8.8)	9	2.6 (1.2 to 4.9)	10	2.9 (12.6 to 21.5)

New Brunswick	28,035	10	3.6 (1.7 to 6.6)	§	§ (0.0 to 2.0)	9	3.2 (1.5 to 6.1)
Quèbec	287,409	101	3.5 (2.9 to 4.3)	11	0.4 (0.2 to 0.7)	79	2.7 (2.2 to 3.4)
Ontario	536,754	230	4.3 (3.7 to 4.9)	45	0.8 (0.6 to 1.1)	153	2.9 (2.4 to 3.3)
Manitoba	54,869	35	6.4 (4.4 to 8.9)	13	2.4 (1.3 to 4.1)	19	3.5 (2.1 to 5.4)
Saskatchewan	47,282	24	5.1 (3.3 to 7.6)	§	§ (0.0 to 2.2)	18	3.8 (2.3 to 6.0)
Alberta	161,951	59	3.6 (2.8 to 4.7)	16	1.0 (0.6 to 1.6)	31	1.9 (1.3 to 2.7)
British Columbia	157,801	122	7.7 (6.4 to 9.2)	35	2.2 (1.5 to 3.1)	79	5.0 (4.0 to 6.2)
Yukon	1826	§	§ (0.0 to 30.5)	0	0.0 (0.0 to 20.1)	§	§ (0.0 to 30.5)
Northwest Territories	2611	§	§ (0.0 to 21.3)	0	0.0 (0.0 to 14.0)	§	§ (0.0 to 21.3)
Nunavut	1362	0	§ (0.0 to 26.9)	0	0.0 (0.0 to 26.9)	0	0.0 (0.0 to 26.9)
Unknown	7916	8	10.1 (4.4 to 19.9)	0	0.0 (0.0 to 4.6)	7	8.8 (3.5 to 18.2)
Total Canada	1,346,441	1926-1938	4.6 (4.2 to 5.0)	129-141	1.0 (0.9 to 1.2)	405-421	3.1 (2.8 to 3.4)

Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System (CCASS);[88] Rate expressed per 10,000 total births; § Number/rate suppressed due to small cell size < 5; 95% CI = 95 percent confidence interval; ONTD = open neural tube defects

Surveillance data of congenital anomalies in British Columbia[89] for the year of 2006 (Table S.12) showed that there were no cases of encephalocele for that time period. Birth prevalence rates for aneuploidy and spina bifida were 0.95 and 2.38 cases per 10,000 births, respectively.

Table S.12: Birth prevalence of anencephaly, encephalocele and spina bifida in British Columbia (year 2006)

Birth defect	Number of cases			Rates per 10,000 total births
	LB	Total rate	ToPBD	Total rate
Anencephaly	0	4	NR	0.95
Encephalocele	0	0	NR	0.00
Spina bifida	6	4	NR	2.38

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] total live births (LB): 41,673; total stillbirths (SB): 335; total births: 42,008; number of terminations of pregnancy for birth defects (ToPBD): NR

Analyses of 5-year grouped birth prevalence data in the British Columbia registry of congenital anomalies (Table S.13) showed that, overall, birth prevalence rates of anencephaly, encephalocele, and spina bifida have decreased over time.

Table S.13: Birth prevalence of anencephaly, encephalocele and spina bifida in British Columbia (1997-2006)

	1997-2001	2002-2006
Total births	211,365	204,627
Anencephaly	1.70	1.47
Spina bifida	4.64	3.13
Encephalocele	0.52	0.44

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] birth prevalence rates:(live births + stillbirths + termination of pregnancy) per 10,000

Alberta

Surveillance data of congenital anomalies in Alberta[89] for the year 2006 showed that the birth prevalence rate for anencephaly was two cases per 10,000 births (Table S.14). The prevalence of encephalocele and spina bifida in Alberta were 0.44 and 5.78 cases per 10,000 total births, respectively.

Table S.14: Birth prevalence of anencephaly, encephalocele and spina bifida in Alberta (year 2006)

	Number of cases			Rates per 10,000 total births
Birth defect	**LB**	**SB**	**ToPBD**	**Total rate**
Anencephaly	1	6	2	2.00
Encephalocele	2	0	0	0.44
Spina bifida	16	9	1	5.78

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] live births (LB): 44,659; stillbirths (SB): 297; total births: 44,956; number of terminations of pregnancy for birth defects (ToPbd): 72

Analyses of 5-year grouped birth prevalence data in the ACASS (Table S.15) showed that, overall, birth prevalence rates of anencephaly have decreased over time, while the rate of encephalocele has slightly increased. Spina bifida rates have remained steady during the observation period.

Table S.15: Birth prevalence of anencephaly, encephalocele and spina bifida in Alberta (1997-2006)

	1997-2001	2002-2006
Total births	186,930	205,458
Anencephaly	3.10	2.29
Encephalocele	1.23	1.31
Spina bifida	3.64	3.65

Source: International Clearing House for Birth Defects Surveillance and Research annual report 2008;[89] birth prevalence rates: (live births + stillbirths + termination of pregnancy) per 10,000

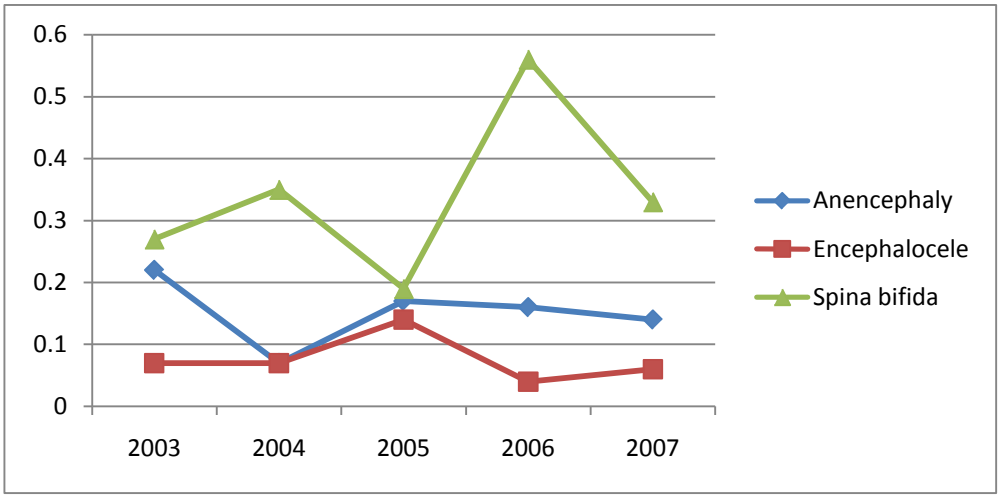
Annual birth prevalence data for anencephaly between 2003 and 2007 ranged from 2.2 cases per 10,000 total births in 2003 to 1.4 cases per 10,000 total births in 2007 (Table S.16 and Figure S.2). Encephalocele rates for the same time period ranged from 0.7 cases per 10,000 total births in 2003 to 0.6 cases per 10,000 total births in 2007. Spina bifida rates varied from 2.7 cases per 10,000 total births in 2003 to 3.3 cases per 10,000 total births in 2007.

Table S.16: Birth prevalence rates for anencephaly, encephalocele and spina bifida in Alberta 2003-2007

Year	Anencephaly		Encephalocele		Spina bifida	
	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)
2003	9	2.2 (1.0, 4.2)	3	0.7 (0.2, 2.1)	11	2.7 (1.4, 4.9)
2004	3	0.7 (0.1, 2.1)	3	0.7 (0.1, 2.1)	14	3.5 (1.9, 5.8)
2005	7	1.7 (0.7, 3.4)	6	1.4 (0.5, 3.1)	8	1.9 (0.8, 3.7)
2006	7	1.6 (0.6, 3.2)	2	0.4 (0.1, 1.5)	25	5.6 (3.6, 8.2)
2007	7	1.4 (0.6, 2.9)	3	0.6 (0.1, 1.7)	16	3.3 (1.9, 5.3)

Source: ACASS, 2009;[92] Rates are expressed as number of cases (live births and stillbirths ≥ 20 weeks or ≥ 500 g) per 10,000 total births. 95% CI = 95% confidence interval

Figure S.2: Open neural tube defect rates in Alberta 2003-2007



Data source: ACASS, 2009;[92] birth prevalence rates per 10,000 (total births: live births, stillbirths)

Aggregate birth prevalence rates for anencephaly, encephalocele, and spina bifida in Alberta are reported in Table S.17. Data showed that ONTD rates have declined over time. Reductions in ONTD rates have been more pronounced since 1998, when folic acid fortification of flour and cereal/grain products was introduced,[92] and then after Health Canada launched a national awareness campaign in 2002 about the importance of folic acid supplementation during pregnancy.[93]

Table S.17: Aggregated birth prevalence rates for anencephaly, encephalocele and spina bifida in Alberta 2003-2007

Year	Anencephaly		Encephalocele		Spina bifida	
	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)	Number of cases	Rate (95% CI)
1980-1989	148	3.3 (2.8, 3.9)	42	1.0 (0.7, 1.3)	218	5.1 (4.4, 5.8)
1990-1999	75	1.9 (1.5, 2.4)	36	0.9 (0.6, 1.3)	198	4.9 (4.3, 5.7)
2000-2004	26	1.3 (0.9, 2.0)	24	1.2 (0.8, 1.8)	48	2.5 (1.8, 3.3)
2005-2007	21	1.5 (1.0, 2.4)	11	0.8 (0.4, 1.4)	49	3.6 (2.7, 4.8)

Source: ACASS;[92] Rates are expressed as number of cases (live births and stillbirths ≥ 20 weeks or ≥ 500 g) per 10,000 total births. 95% CI = 95% confidence interval

First and second trimester screening patterns of care

Screening is a strategy that involves the testing of a large group of individuals to identify those at high risk of having a disease or condition enough to justify the consideration of further investigation leading to a diagnosis.[3,94-96] Screening is generally directed only toward conditions or diseases that are clinically significant and prevalent in the population[3] for which a diagnostic test exists to confirm the screen results.[95] In the determination of the importance of the disease or condition, the morbidity, mortality, and quality of life of those with the condition as well as the interests of the community responsible of providing care should be considered.[97] A small number of screening tests are, indeed, diagnostic. In most circumstances however, the screening test is only a marker for the condition or disease. Table S.18 summarizes some of the differences between screening and diagnostic tests.

Table S.18: Differences between screening and diagnostic tests

Screening test	Diagnostic test
To identify a health problem in the population	Used to identify a health problem in an individual presenting specific problems.
A positive result does not confirm the diagnosis. It indicates an elevated risk of the disorder being present, and suggests the need for diagnostic tests	A positive result confirms the diagnosis and is an indication to treat the patient.
Carried out on all individuals in a group	Carried out on one individual

Adapted from Jenicek 1995[98]

A screening procedure must be able to identify a significant proportion of people within a population that have an elevated risk for the disorder with minimal misidentification of unaffected persons (false positives). As the screening performance improves, the *detection rate* (DR) increases while the *false positive rate* (FPR) decreases. A highly accurate diagnostic test should determine whether a positive result in the screening test truly reflects the presence of the disorder. Ideally, an intervention must be available to all persons who eventually are diagnosed as having the condition. It is also expected that the screening procedure, the diagnostic test and the intervention are affordable and acceptable to the population.[96]

The primary purpose of prenatal screening is to identify pregnant women at high risk of carrying a fetus with aneuploidy or ONTD. Diagnostic methods can be used subsequently to confirm or refute the presence of these conditions. Prenatal screening for fetal aneuploidy and ONTD comprises the use of multiple markers that include maternal age, biochemical markers in maternal blood, or ultrasonography of the fetus during the first and/or second trimester of pregnancy to produce a single result for the risk of carrying a fetus with these conditions.[95,99,100] A risk cut-off is established based upon a desired value for the DR and/or the FPR. Screening values that fall above a risk cut-off point are not a definite indication of the presence of aneuploidy or ONTD but they express the probability of the condition being present in the fetus at mid-trimester or term,[96] suggesting the need for further tests to confirm or refute the diagnosis.[99,100] Biochemical marker screening results can be expressed in terms of the multiples of the median (MoM), which is the observed value of a specific marker divided by the median value for that marker in a specified population (usually pregnancies of the same gestational age). The MoM is used to calculate a likelihood ratio, which is then multiplied by the prevalence of the condition for age to obtain an estimate of risk, expressed as 1/N, for each woman. The MoM is the value observed for serum markers in unaffected pregnancies of the same gestational age in a reference population of pregnant women. The expected value of the MoM is 1.0. A value of 2.0 in the MoM is interpreted as having the concentration levels as twice as high as expected.[99]

Characteristics and history of first and second trimester screening tests

The following section provides an overview of the markers (i.e., maternal age, biochemical markers in maternal blood, and ultrasonography) that are incorporated into the prenatal screening strategies for fetal aneuploidy and ONTD during the first and second trimester of pregnancy. The history and characteristics of the various FASTS options and their applications are outlined. Finally, we will present how FASTS options have been integrated into a variety of clinical algorithms recommended by clinical practice guidelines in Canada and Alberta.

Maternal age

Prior to the widespread availability of prenatal screening using ultrasound and maternal serum markers, it was standard practice to offer amniocentesis to all advanced maternal age women. The effect of maternal age on pregnancy outcomes was first documented in 1933.[100] Although not a technique in itself, maternal age is a form of screening aimed at targeting a group of women considered at high risk of having a fetus with aneuploidy and other birth defects.[101] Most screening programs do not take maternal age into consideration when screening for ONTD.[95] In Canada, prenatal screening for fetal aneuploidy started in the mid 1960s, using maternal age as the screening criteria. The age cut-off point for considering a pregnant women to be at high risk was set at 35 years or over at the expected time of delivery. This cut-off value was determined to be the point at which the risk of fetal loss associated with invasive diagnostic procedures was virtually equal to that of giving birth to an infant with a chromosomal anomaly.[100] The cut-off value changed over time to 40 years at time of delivery.[102] Regardless of the selected cut-off, maternal age is currently considered a poor minimum standard for prenatal screening by its own and it is recommend that the practice of offering invasive prenatal testing for age alone as an indication should be abandoned.[96,103] The more recent American College of Obstetrics and Gynaecology and the American College of Medical Genetics guidelines recommend the availability of prenatal screening and diagnosis for women of all ages.[104]

Morphological markers

First trimester

Nuchal translucency: Nuchal translucency (NT) refers to the measurement of the thickness of the subcutaneous layer of fluid behind the neck and lower cranium of the developing fetus in the late first trimester.[105] NT screening can be carried out during an extended ultrasound scan between 10 and 14 weeks of pregnancy.[106] The accuracy of NT measurement is gestational-age dependent and appears to be related to the time allowed for the examination, the standardization of procedures, and the expertise of the providers involved. NT measurement requires a standardized technique that guarantees its repeatability. Typically, the measurement should be taken when the fetus is in a sagittal position with the back of the neck in a neutral position, that is, when the angle between the sagittal spine and the occiput is equal to zero. In 1995, Pandya and associates[107] proposed a protocol for the measurement of NT that formed the basis of the Fetal Medicine Foundation (FMF) approach to training, certification and ongoing audit of sonographers and obstetricians in the first trimester scan.

Studies have shown a direct correlation between a significantly thicker nuchal fold identified in fetal ultrasound and the risk of trisomy 21, trisomy 18, and trisomy 13, certain other chromosomal or developmental abnormalities, numerous genetic syndromes, and adverse pregnancy outcomes.[4,97,105,108,109] The NT does not screen for ONTD.

Second trimester

Ultrasound: Second trimester ultrasound has both screening and diagnostic capabilities. Second trimester ultrasonography may identify fetal anatomic defects, such as congenital heart defect or markers that increase the a priori risk of fetal aneuploidy; such as a thickened nuchal fold, absent nasal bone, renal pyelectasis, or echogenic bowel.[87,110] When used alone, however, second trimester sonographic markers are not indicated as a primary screening tool for fetal aneuploidy as they do not effectively discriminate unaffected fetuses from those with trisomy 21.[96] Alternatively, second trimester ultrasound is recommended for screening of ONTD at 18 to 22 weeks of gestation.[96,103]

Maternal serum markers

Over the past 15 years, various markers in maternal blood have been studied as screening tests for fetal anomalies. Screening based on the measurement of serum marker levels evaluates the individual risk for each pregnant woman, independently of the risk estimate based on maternal age only. These screening procedures analyze the levels of certain proteins and/or hormones found in serum of pregnant women as indicators or predictors of the risk of carrying a fetus with fetal aneuploidy or ONTD. Closed neural tube defects cannot be detected with maternal serum-based techniques. Maternal serum markers are reported in MoM rather than mass units, in order to control for the effect of factors that contribute to measurement variations across patients and centres.

First trimester

Serum markers for first trimester screening include the pregnancy-associated plasma protein A (PAPP-A) and the free beta subunit of human chorionic gonadotropin (β-hCG). The time for sampling withdrawal can vary between the 8th and the 13th week of pregnancy.

Pregnancy-associated plasma protein A (PAPP-A): Normally found in the blood of all pregnant women, PAPP-A is a glycoprotein synthesized in the placental trophoblasts and released into the maternal circulation. The function of PAPP-A remains unclear.[111] Detectable as early as 8-week gestation, maternal PAPP-A increases rapidly with gestation in unaffected pregnancies.[101] Accurate gestational age assessment is critical in the interpretation of PAPP-A values.[111] PAPP-A levels are noticeably reduced in trisomy 21, trisomy 18, and trisomy 13 pregnancies at 9 to 14 weeks.[101,105] PAPP-A levels are usually not indicated for ONTD detection.[112] Because there is little difference in PAPP-A concentration between affected and unaffected pregnancies by the second trimester, the marker is not suitable for use in later screening.

Free beta subunit of human chorionic gonadotropin (β-hCG): The β-hCG is a glycoprotein produced by trophoblast soon after implantation. Normally found in the blood of all pregnant women, β-hCG levels rise rapidly until about 10 weeks' gestation and then normally decline to approximately 25% of maximal levels by 20 weeks' gestation.[105] β-hCG is the sole biochemical marker presently used in both first and second trimester screening. Maternal levels of β-hCG are elevated with trisomy 21[105] and the difference between these and those of normal pregnancy levels increases with advancing gestation. Levels of β-hCG are dramatically reduced in trisomy 18 and 13 pregnancies.[101,112] The β-hCG does not screen for ONTD.

Second trimester

Maternal serum alpha-fetoprotein (AFP): AFP is a glycoprotein sequentially secreted by the fetal yolk sac, the gastrointestinal tract, and the liver. It is excreted into the fetal urine and amniotic fluid from where it is transferred across the placenta into the maternal blood.[104] AFP reaches the maternal circulation by a combination of transplacental and transamniotic diffusion and this forms the

pathophysiological basis of the maternal serum screening test for ONTD. Maternal serum AFP levels peak between 28 and 32 gestation weeks and then slowly decline.[66] Higher concentrations of maternal serum AFP constitute the primary marker to detect ONTD.[3] Lower concentrations of AFP are found in trisomy 21, 18, and 13 pregnancies.[66,105]

Intact human chorionic gonadotropin (hCG): Human chorionic gonadotropin (hCG) is a dimeric glycoprotein produced by the trophoblast.[113] Maternal serum hCG levels peak at 8 to 10 gestation weeks; then decline by 10 to 12 weeks and reach the lowest level by 20 weeks. Levels then remain relatively stable throughout the reminder of gestation. Levels of intact hCG are altered in the late second trimester (18 to 25 weeks) in pregnancies complicated by fetal aneuploidy. The levels of hCG are increased by approximately two-fold in trisomy 21 pregnancies and reduced in association with trisomy 18.[38] Levels of hCG have not been firmly determined for trisomy 13; however there is some evidence of low levels of the marker in pregnancies affected by trisomy 13.[114] Measurement of hCG levels is not useful in predicting the occurrence of ONTD.[112]

Unconjugated estriol (uE3): Estriol (uE3) is a steroid hormone formed by the fetoplacental unit in increasingly greater quantities as gestation progresses.[113] Early in the second trimester, the fetus synthesizes large amounts of uE3 through a complex series of enzymatic reactions involving the fetal adrenal glands, liver, and placenta.[112] Unconjugated estriol passes through the placenta into the maternal circulation; its measurement, therefore, offers a convenient and quick evaluation of current fetal status. The concentration of uE3 in plasma increases gradually during the first 20 weeks gestation and more rapidly during the third trimester. Maternal serum uE3 levels are reduced in pregnancies with trisomy 21, as they are also in cases with trisomy 18[3] and likely in trisomy 13 affected pregnancies.[104] A decreased level early in the second trimester is an independent predictor of ONTD.[112]

Dimeric inhibin A: Dimeric inhibin A (DIA) is a dimeric glycoprotein hormone produced during pregnancy by the corpus luteum, the deciduas, and the placenta.[113] Levels of DIA follow a bimodal distribution during pregnancy: the concentrations increase during the first trimester reaching a peak at 10 weeks gestation and then decline and remain stable from 15 to 25 weeks, until raising again to peak near term.[113] A unique and valuable characteristic of DIA is that serum levels do not fluctuate over the period when screening is performed, making interpretation of DIA concentrations less susceptible to dating errors.[113] Maternal levels of DIA are elevated with trisomy 21[105] Levels for detection of trisomy 18 and 13 are not clearly established.[115,116] Measurement of DIA levels is not useful in predicting the occurrence of ONTD.[112,117] Table S.19 summarizes the pattern of markers typically seen for fetal aneuploidy and ONTD.[61,103]

Table S.19: Typical prenatal screening marker patterns for fetal aneuploidy and open neural tube defects

	Test	Trimester		Fetal aneuploidy			ONTD		
		1st	2nd	T13	T18	T21	Spina bifida	Anencephaly	Encephalocele
Mother characteristics	AMA	✓	✓	↑	↑	↑	NI	NI	NI
Morphological	NT	✓		↑	↑	↑	↑	NI	NI
	US	✓	✓	NI	NI	NI	↑	↑	↑
Maternal serum markers	PAPP-A	✓		↓	↓	↓	NI	NI	NI
	β-hCG	✓	✓	↓	↓	↑	NI	NI	NI
	AFP		✓	↓	↓	↓	↑	↑↑	↑
	hCG		✓	↓	↓	↑	NI	NI	NI
	uE3		✓	↓	↓	↓	↓	↓	↓
	DIA		✓	NI	NI	↑	NI	NI	NI

↑ = high concentrations; ↓ = low concentrations; ↑↑ = very high concentrations; AFP = alpha-fetoprotein; AMA = advanced maternal age; DIA = dimeric inhibin A; hCG = intact human chorionic gonadotropin; NI = not indicated; NT = nuchal translucency; ONTD = open neural tube defect(s); PAPP-A = pregnancy-associated plasma protein A; uE3 = unconjugated estriol; US = ultrasound

History of first and second trimester screening tests

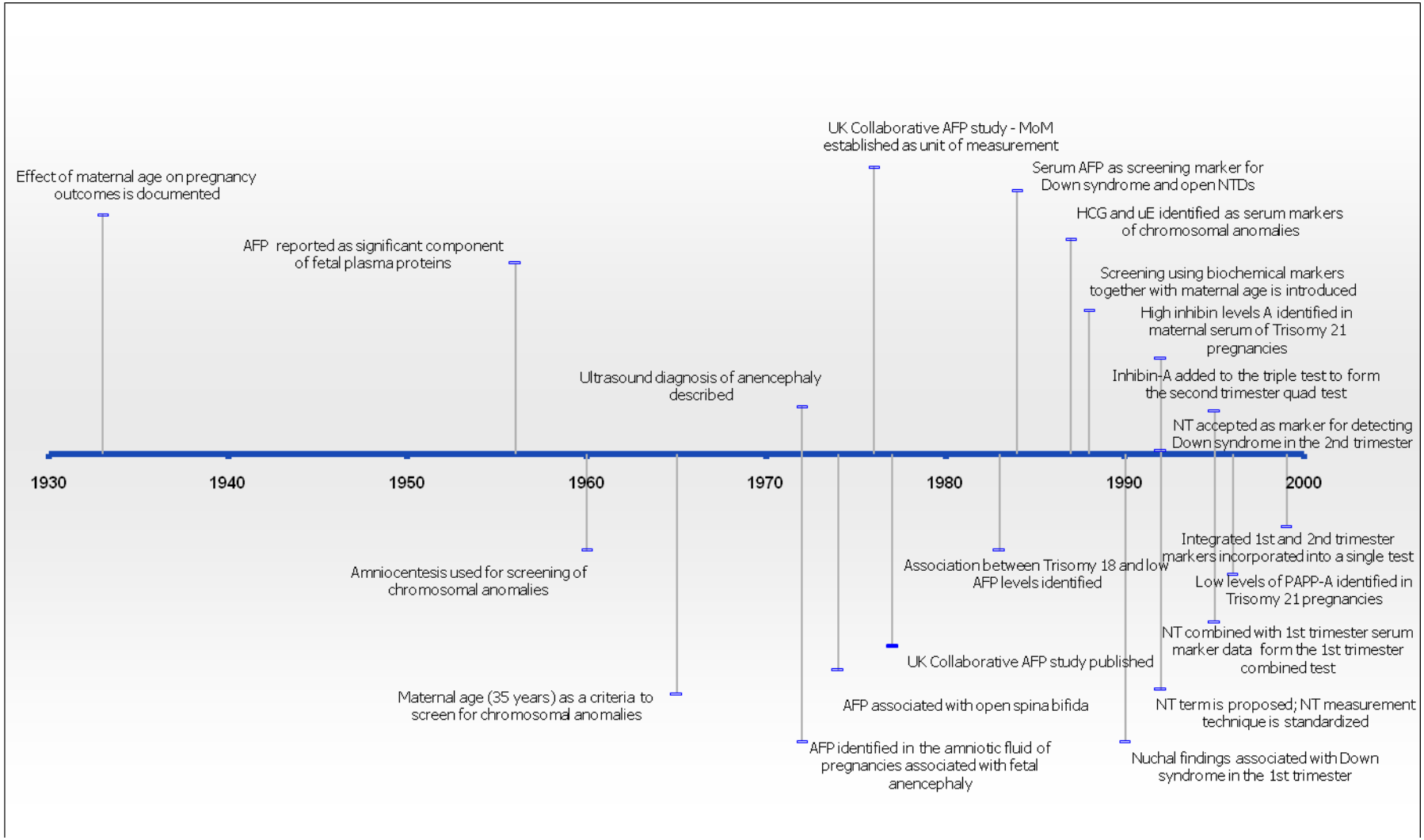
Over the last 40 years, both sonographic and maternal blood prenatal screening markers have been put forth in an attempt to detect fetuses at risk of having aneuploidy or ONTD. The history and evolution overtime of these markers is summarized in Table S.20 and Figure S.3.

Table S.20: Development of first and second trimester screening tests

Time period	Key advances in first and second trimester screening
1933	The effect of maternal age on pregnancy outcomes was first documented.[100]
1956	AFP first reported as significant component of fetal plasma proteins.
1960	Screening for fetal aneuploidy began with amniocentesis.[102]
1965	Maternal age (35 years of age and over at the expected date of delivery) was used as a criteria to screen for fetal aneuploidy.
1972	Brock and Sutcliffe[118] discover that high concentrations of AFP were present in the amniotic fluid of pregnancies associated with fetal anencephaly.
1972	Stuart Campbell and colleagues described the ultrasound diagnosis of anencephaly.[119]
1974	Wald and colleagues[120] discovered that raised serum AFP was also associated with open spina bifida.
1976	The United Kingdom Collaborative AFP study[121] was launched, using the MoM as unit of measurement for many serum and some ultrasound markers.
1977	Publication of the United Kingdom Collaborative AFP study[121] demonstrates conclusively that amniotic fluid AFP is elevated during the early second trimester in both anencephaly and open spina bifida. It sets the foundation of the science of prenatal screening—bringing together the varied disciplines of epidemiology, statistics, laboratory medicine and obstetrics.[122]
1983	Merkatz and colleagues[123] showed that pregnancies with fetal aneuploidy, particularly trisomy 18, tended to have low maternal serum AFP levels.
1984	The association between trisomy 21 and serum AFP was quantified, and serum AFP became a screening marker for trisomy 21 as well as for ONTDs.[122,124]
1987 – 1988	Human chorionic gonadotropin[125] and unconjugated estriol (uE3)[126,127] are identified as serum markers of fetal aneuploidy.

1988	Serum screening using various biochemical markers together with *maternal age* is introduced. The triple test, which combined the three serum markers (AFP, hCG, uE3) with maternal age arose as a screening option in the second trimester of pregnancy.[128]
1989-1990	Ultrasound nuchal findings were found to be associated with trisomy 21 in the first trimester.[129,130]
1991	Brambati and colleagues[131] demonstrated that decreased levels of PAPP-A were present in the pregnancy of fetus affected by trisomy 21.
1992	van Lith and colleagues[132] demonstrated that elevated concentrations of immunoreactive inhibin A were present in maternal serum of trisomy 21 pregnancies.
1992	The term nuchal translucency was proposed and the measurement technique is developed and standardized.[109]
1995	Nuchal translucency became accepted as a powerful marker for detecting trisomy 21 in the second trimester.[133]
1995 – 1997	Work on nuchal translucency is combined with first trimester serum marker data from the First Trimester Serum Screening study[134] to form the first trimester combined test.[135]
1996	Dimeric inhibin A was added to the triple test to form the second trimester quad test.[136]
1999	Integrated first and second trimester markers are incorporated into a single test.[137]

Figure S.3: Development of first and second trimester screening tests



Screening strategies

There are currently four main components of contemporary screening for fetal aneuploidy and ONTD: 1) first trimester ultrasound, 2) first-trimester biochemistry, 3) second-trimester ultrasound, and 4) second trimester biochemistry. They can be used in isolation or combined with one another for greater accuracy.[103] Multiple marker screening uses a combination of maternal age and two or more biochemical tests, with or without ultrasound examination, to produce a single result for risk of fetal aneuploidy and ONTD.[3,41,57,96] The following section outlines the various FASTS strategies that incorporate morphological and biochemical markers for fetal aneuploidy and ONTD.

First trimester screening

The following screening options are available for first trimester screening:

1. NT measurement alone
2. Blood serum combined (double test): plasma PAPP-A and serum free β-hCG)
3. First trimester combined screening (FTS): NT, PAPP-A and free β-hCG

First-trimester blood serum combined screening (double test) is based on the measurement of two markers, PAPP-A and free β-hCG. Blood samples are typically withdrawn between the 11th and 13th week of gestation.[138] Blood serum screening during the first trimester does not permit the detection of ONTD. If blood screening rather than ultrasound is used to detect such malformations, a second screening is required to measure AFP during the second trimester.

The FTS uses maternal age, NT measurement, and biochemical markers (free β-hCG and PAPP-A) to estimate the risk for fetal trisomy 21 and trisomy 18. This is the most popular screening strategy during the first trimester.[103,105]

The major advantage of first-trimester screening is the earlier gestational age of detection so that diagnostic testing (chorionic villous sampling or amniocentesis) can be available for women considered at highest risk of carrying a fetus with aneuploidy. In this way, first trimester screening can help triage women for subsequent testing.[103]

Second trimester screening

The following screening options are available for second trimester screening:

1. Double test (AFP and free β-hCG)
2. Triple test (AFP, uE3 and intact hCG)
3. Quad test (AFP, uE3, free β-hCG and DIA)
4. Ultrasonography

The double test measures two serum biochemical markers: AFP and free β-hCG. The combined use of three biochemical markers (AFP, uE3, and hCG) in maternal blood is the basis of the triple test. The triple test has two variants, depending on whether total intact hCG or its two subunits, α and β are measured. The triple test is used to screen for pregnancies at risk for trisomy 21, trisomy 18, and for ONTD.[138] The most widely used second trimester screening test is the quad test, so named because it uses four biochemical markers: AFP, hCG, uE3, and DIA.[96,110] The quad marker approach is currently considered standard of care in second trimester serum screening for trisomy 21.[3,96,139]

Risk assessment in both the first and second trimesters

A number of practical approaches for risk assessment of fetal aneuploidy and ONTD can be used to combine information and tests results completed in the first trimester with information and test results completed in the second trimester. There are integrated approaches, in which results are withheld until both first and second trimester screening tests have been obtained (i.e.; integrated prenatal screening) and sequential approaches (i.e. stepwise screening, and contingency screening) in which intermediate results are disclosed.[140,141]

Integrated prenatal screening (IPS): IPS combines second trimester screening with first trimester results which are withheld until completion of second trimester testing. The goal of IPS is to generate a single specific risk indicator for fetal aneuploidy.[111,141] Integrated screening, by definition, requires that women are not offered diagnostic testing until all components of the screening have been completed.[138] The goal of integrated screening is to provide screening with an increased DR and a lower FPR, reducing the number of women undergoing invasive diagnostic testing and thereby preventing procedure-related pregnancy losses and anxiety.[142]

The IPS can be full- integrated or serum-integrated. A full-integrated screening strategy consists of measuring NT and PAPP-A in the first trimester and performing the quad test in the second trimester.[96,97] No individualized risk assessment in the first trimester is provided for NT and PAPP-A results but, rather, they are combined with those of the quad test to give a single estimate of a patient risk for fetal aneuploidy in the second trimester.

There are many instances in which NT measurements are not universally available. In these cases, a blood-only version of the IPS (i.e., serum integrated prenatal screening [SIPS]) is offered.[96] In this case, maternal PAPP-A is measured in the first trimester, followed by triple or quad screening in the second trimester.[96,141] Alternatively, PAPP-A and free β-hCG tests can be offered in the first trimester followed by AFP and uE3 in the second.[3,96,141] SIPS constitutes a practical option for geographic areas where there is limited or no access to NT screening.

In either case, the results are combined with maternal age and a single risk estimate is given at the conclusion of the second trimester testing.[137] A major disadvantage of IPS is that results are communicated only after completion of the second-trimester serum screening. Thus, screen-positive women do not have the option of chorionic villus sampling (CVS) for early definitive diagnosis and ultrasound information obtained in the first trimester is suppressed.[103] The integrated test has been controversial, since the integration of first- and second-trimester markers into a single risk assessment could pose a problem with respect to the withholding of first-trimester results.[140,141]

Stepwise sequential screening: It involves both first and second trimester screening but allows for the immediate release of first-trimester results for use in clinical management.[97] It involves carrying out a firs- trimester screening test (i.e., NT, hCG, and PAPP-A) to assess an interim risk. If that interim risk is sufficiently high (e.g., ≥ 1 in 25 or ≥ 1 in 50), such women would be informed of their screen-positive result and offered early diagnostic intervention; otherwise, women are offered second-trimester testing and receive a full-integrated risk assessment based on first and second trimester markers.[103,140,143] Stepwise sequential screening has gained rapid acceptance and it is expected to be widely adopted into clinical practice in the near future[103,143] as it provides women with the option of having available the results in the first trimester.[105]

Contingent sequential screening: Contingent sequential screening is similar to stepwise sequential screening but only those with borderline risk in the first trimester go on to have second trimester tests. Based on the results from the first-trimester risk assessment, women are grouped into one of

three risk categories: high-risk, intermediate-risk, and low-risk. The cut-off points and their specific risks vary, depending upon how the groups are defined. Women at high risk (e.g., risk > 1/50) are offered early diagnostic testing whereas women at low risk (e.g., risk < 1/1000) require no further testing. Those of intermediate risk (e.g., risk between 1/50 and 1/1000) are offered second trimester testing after which an integrated risk is issued.[141]

The rationale for finalizing a screen-negative group in the first trimester is that a substantial proportion of women (as many as 60% to 70%) will be provided a screening result before the end of the first trimester. This has the potential to reduce costs and relieve a large group of screened women of the anxiety of waiting 3 to 6 weeks for a final result. Likewise, physician satisfaction may increase with this screening approach as obstetricians would not have to hold back information or wait until the second trimester to disclose the test results.[140] The contingent screening approach has the advantage of providing early reassurance and obviating the need for second trimester testing for the majority of women that obtain a low-risk assessment in the first trimester.[144]

Standards of reference

Standards of reference for FASTS are aimed to determine whether a pregnant woman with a fetus considered to be at risk of having a chromosomal disorder, genetic disorders, or major malformations by prenatal screening process does, in fact, carry a fetus with the condition in question.

Standards of care of prenatal diagnostic techniques include the use of invasive techniques such as amniocentesis and CVS.[142] Indications for using invasive techniques for prenatal diagnosis are based on data demonstrating that the risk for a fetal anomaly is at least as great as or greater than that for fetal loss from the procedure. These invasive techniques allow amniotic fluid or tissue containing fetal cells to be obtained for chromosomal, biochemical or genetic testing.[100] Subsequent analysis of the structure and number of chromosomes in the fetal cells through karyotyping, fluorescence in situ hybridization, or polymerase chain reaction enables diagnoses of many disorders including fetal aneuploidy.[4] Alternatively, non-invasive ultrasonography permits the indirect visualization of the fetus and the diagnosis of structural or anatomical abnormalities. Non-invasive ultrasonography is also used in conjunction with invasive diagnostic techniques to guide the sample collection. There are differences in applications availability, expertise necessary, laboratory resources required, reliability, and risks among the standard diagnostic techniques.[145]

Amniocentesis

Amniocentesis involves a transabdominal puncture of the amniotic sac under ultrasound visualization to obtain a sample of amniotic fluid for analysis. The fluid contains fetal cells that shed from fetal skin, mucous membranes, amnion, and umbilical cord. This fetal material is collected and cultured to detect chromosomal, biochemical and DNA abnormalities in the fetus before birth.[99] Over 40 different chromosomal abnormalities, inborn errors of metabolism, and ONTD can be diagnosed with amniocentesis.[142]

Amniocentesis can be performed in any of the three trimesters of pregnancy and the timing of the procedure is crucial. The practice of first-trimester (between the 11th and 14th week of pregnancy) amniocentesis began in 1980 as a possible alternative to CVS for the purpose of early detecting genetic anomalies.[138] From a technical standpoint, the procedure is identical to that performed during the second trimester; however, the small amount of amniotic fluid available before the 13th week requires the removal of a greater proportion of fluid. This further increases the risk of miscarriage, clubfoot, post procedural amniotic fluid leakage and cell culture problems for

karyotyping. Early amniocentesis is generally considered to be contraindicated because of the increased risks associated with the early procedure for both mother and child.[100,146]

Amniocentesis performed between the 15th and 19th week of pregnancy has become a standard second-trimester prenatal diagnostic procedure.[138] It is performed to detect chromosomal abnormalities, evaluate the fetal condition when the woman is sensitized to the Rh-positive blood, diagnose intrauterine infections, and investigate amniotic fluid AFP when the maternal serum AFP level is elevated.[99] This timing seems to be optimal in that there is sufficient amniotic fluid to allow for the withdrawal of 20 to 30 mL safely and the amount of viable cells is greatest compared with later in gestation.[142] In the third trimester amniocentesis is most commonly indicated to determine fetal lung maturity after the 35th week of gestation and to evaluate the fetal condition with Rh isoimmunization.

Amniocentesis is an invasive procedure with the potential for complications, the most serious of which is the iatrogenic loss of an unaffected fetus.[100] While the maternal risks associated with the procedure are small, it can cause iatrogenic fetal loss in 0.5 of cases.[100,142] Sample errors may also be present and due to sample quality, either because maternal rather than fetal cells are cultured or because the cells are contaminated during the puncture.

Typically, amniocentesis is indicated when abnormality is suspected in the second trimester or if it has not been practical to carry out CVS in the first trimester.[145]

Chorionic villus sampling (CVS)

The procedure of CVS involves the sampling of tissue from the villous area of the chorion in order to obtain viable cells, which are cultured for the purpose of a cytogenic analysis.[145] Chorionic villi are finger-like projections that derive from the trophoblast and form in the placenta. They cover the embryo and anchor it to the uterine lining before the placenta is developed. Because they are of embryonic origin, CVS provides information about the developing fetus for prenatal evaluation of chromosomal disorders, enzyme deficiencies, and numerous genetic disorders.[147] ONTD and abdominal wall defects cannot be identified by CVS.[148] Because the cells that form the villi are actively dividing, it may not be necessary to culture them in the laboratory and, therefore, karyotyping of cytotrophoblastic cells can be done with initial results available within a few days.[142] Depending on how the testing is performed, a diagnosis may be provided 2 to three weeks earlier than with amniocentesis.[147,148]

CVS is usually performed between 10 weeks' gestation onwards. It is preceded by an ultrasound to confirm gestational age and viability by the presence of fetal cardiac activity. It may not be possible to perform CVS if more than one fetus is present, unless it is certain that a sample can be collected from each fetal placenta. CVS can be performed either transcervically by the insertion of a catheter or transabdominally, both under continuous ultrasound guidance.[148] To avoid contamination by maternal tissues and thus misdiagnosis if maternal cells are karyotyped, all maternal tissue must be removed under a dissecting microscope. Therefore, more specialist expertise is required for CVS compared with amniocentesis.[146]

The main advantage of CVS lies in the fact that it can be performed reliably and relatively safely early in pregnancy and, thus, CVS provides women with diagnostic information within the first trimester. A substantial limitation however, is that CVS does not detect ONTD. Thus subsequent screening and/or testing (via ultrasound and amniocentesis) is necessary to provide diagnostic information regarding these conditions.[99,147] The major risk associated with CVS is miscarriage, which has been found to be approximately 1% to 2% above the background risk for fetal loss and

may be operator-dependent.[142] It is also associated with a high rate of false positive and false negative results, in addition to an increase in fetal limb malformation.[100,147] The risks to the mother are the same as those posed by amniocentesis, namely, amniotic fluid leakage, hemorrhage, infection and intra-abdominal lesions.[138]

Despite recent data calling into question the age assumptions underlying current testing guidelines, including those inherent in the risk-based threshold for offering invasive testing, CVS and amniocentesis are still typically offered only to women whose likelihood of carrying a fetus with a chromosomal disorder is at least as high as that of the average 35-year-old women. The most recent update of the Society of Obstetricians and Gynaecologists of Canada (SOGC) guidelines published in July 2011 recommends that age should not be an indication of invasive testing.[96]

Standards of care and available FASTS programs in Canada and Alberta

Traditionally, screening for fetal aneuploidy in Canada was offered only to pregnant women 35 years or over at the expected date of delivery. In 1996, a statement by the Canadian Task Force on the Periodic Health Examination recommended that maternal serum screening should be offered to pregnant women under 35 years and that it may be offered as an alternative to amniocentesis or CVS in women 35 years and older.[149] The SOGC[96] currently recommends that all pregnant women in Canada, regardless of age, disease history, or risk status, should be offered prenatal screening for the most common clinically significant fetal aneuploidy in addition to a second trimester ultrasound for dating, growth, and congenital conditions. The SOGC guidelines indicate that invasive prenatal diagnosis should be offered to women who, after counselling, choose to go directly to amniocentesis or CVS because they are considered to be at increased risk of fetal aneuploidy on the basis of a non-invasive screen result above the risk cut-off, because of ultrasound findings, because the pregnancy was conceived by ICSI or because of previous history of previous child or fetus with a chromosomal abnormality.[96] The SOGC guidelines do not recommend a specific screening strategy, suggesting instead that the implementation of any particular screening program is determined by the resources available in a given geographic area.[96]

Table S.21 summarizes the recommendations of the SOGC guidelines regarding current available screening options. Table S.22 details the timing of results for options that meet the minimum standards of SOGC guidelines.

Table S.21: Current available screening options that meet SOGC guidelines minimum standard

Screening option	Markers	Trimester
FTS	NT, free β-hCG, PAPP-A, MA	First trimester
Quad screening	AFP, uE3, free β-hCG, DIA, MA	Second trimester
IPS	NT, PAPP-A, AFP, uE3, free β-hCG/total hCG, DIA, MA	First and second trimester
IPS without DIA	NT, PAPP-A, AFP, uE3, total hCG, MA	First and second trimester
SIPS	PAPP-A, AFP, uE3, free β-hCG/total hCG, DIA	First and second trimester

Source: SOGC, 2011[96]
β-hCG = beta unit of human chorionic gonadotropin; DIA = dimeric inhibin A; FTS = first trimester combined screening; hCG = intact human chorionic gonadotropin; IPS = integrated prenatal screening; MA = maternal age; NT = nuchal translucency; PAPP-A = Pregnancy-associated plasma protein A; SIPS = serum integrated prenatal screening; uE3 = unconjugated estriol

Table S.22: Timing of results for screening strategies that meet SOGC guidelines minimum standard

Screening strategy	Timing of results
1st trimester screening	First trimester
2nd trimester quad screen	Second trimester
Two-step screening	
Contingent	Results available in 1st trimester for most patients; small proportion requiring 2nd trimester screening
Integrated	Single result in 2nd trimester
Serum integrated	Single result in 2nd trimester
Sequential	Results in 1st and 2nd trimester for the same patient

Source: SOGC, 2011[96]

Prenatal screening has become a routine practice within the prenatal care services offered to Canadian pregnant women. Typically, physicians in Canada monitor the vast majority of pregnancies with at least one ultrasound; however, maternal serum screening is fast becoming a component of standard medical prenatal management.[99] Prenatal screening programs exist in most Canadian provinces; however, screening practices differ, many provinces rely on the self-regulation of practitioners to govern the use of prenatal screening tests,[96,99] and different standards of care are used.[87] In the following section, a summary of the FASTS programs available in Canada is provided along with a description of the selection criteria for the provision of FASTS services.

Newfoundland and Labrador

The Provincial Medical Genetics Program of Newfoundland and Labrador introduced the maternal serum screening program at the beginning of 2002 with the goal of providing a risk estimate of fetal aneuploidy and ONTD for every pregnancy in the province.[150] Screening tests for trisomy 21, trisomy 18, and ONTD are offered to women during their second trimester of pregnancy. Three biochemical markers (AFP, hCG, and uE3) are used in combination with maternal age to provide an estimate of a fetus's risk for having one of the associated abnormalities.[151]

Nova Scotia, New Brunswick, and Prince Edward Island

The Reproductive Care Program (RCP) of Nova Scotia, a program funded by the Nova Scotia Department of Health and Wellness, has developed guidelines for prenatal screening in the province. As of July 2007, the guidelines recommend the following tests be provided to all pregnant women: first trimester maternal serum screening at nine to 13^{+6} weeks gestation, second trimester maternal serum screening at 15-20^{+6} weeks gestation, and detailed ultrasound at 18 to 21 weeks gestation.[152,153] For women thought to be at an increased risk of carrying a fetus with aneuploidy (including age greater than 35 years), the RCP recommends adding NT at 11-13^{+6} weeks.[153]

Prenatal screening services are offered at the Izaak Walton Killam (IWK) Health Centre in Halifax (Nova Scotia). The centre also provides health care to pregnant women from other Maritime provinces, namely New Brunswick and Prince Edward Island. Although neither province appears to have a structured prenatal screening program, pregnant women may be referred to Halifax by their attending physicians. Patients requiring additional screening or diagnostic tests beyond the maternal serum screening are referred to the Fetal Assessment and Treatment Centre (FATC) at the IWK Health Centre.[152] Table S.23 summarizes the screening options available in Nova Scotia.

Table S.23: Screening options available in Nova Scotia

Possible timeframes	Screening strategy	Description
9-13^{+6} wk	MSS	First trimester MSS is offered to all women regardless of age. 2nd trimester must be performed in conjunction with 1st trimester testing for an integrated screen
11-13^{+6} wk	EPR	Women with specific risk factors and all women over age 35 years at their EDD should be offered an EPR in the FATC at the IWC. The EPR includes NT. EPR is best if used in conjunction with MSS.
15-20^{+6} wk	MSS	First trimester MSS is offered to all women regardless of age.
	SIPS	The test incorporates maternal age, first trimester MSS and second trimester MSS into a combined/integrated risk assessment.
	IPS	Same as above but also includes the EPR in the integration
18 -21 wk	Ultrasound	Offered to all pregnant women

Source: Nova Scotia Reproductive Care Program, 2007[152,153]

EDD = expected delivery date; EPR = Early Pregnancy Review; FATC = Fetal Assessment and Treatment Centre; IPS = integrated prenatal screening; IWC = Izaac Walton Killam; MSS = maternal serum screening; NT = nuchal translucency; SIPS = serum integrated prenatal screening; wk = week(s)

Québec

In 2008, the Ministère de la Santé et des Services Sociaux (MSSS) in Québec considered putting in place a prenatal screening program for trisomy 21. The main objective of the program is to provide prenatal screening services for trisomy 21 through the public health and social services system to all pregnant women in Québec, regardless of their age.[154] The trisomy 21 prenatal screening program has been introduced gradually in the form of pilot projects in all regions of Québec and it is currently available in the Capitale-Nationale, Chaudière-Appalaches, Bas-Saint-Laurent, Montérégie, and Côte-Nord regions.[155]

The screening technique used in the prenatal screening program for trisomy 21 in Quèbec is the SIPS with ultrasound offered during the second trimester of pregnancy (Table S.24).[154] Tests with varying degrees of reliability are offered in certain public institutions and regions of the province, without any provincial assessment or quality control mechanisms in place. Private companies also offer these tests to women and couples who are willing and able to pay for them. Availability of tests in the private sector also varies according to the place of residence. In situations where tests are not offered through the public system, access depends entirely on the parents' initiative.[154]

NT measurement is not systematically incorporated as part of the Prenatal Screening Program for Trisomy 21 in the province. However, certain health providers with competence certified by the FMF can submit NT results that are integrated to the trisomy 21 risk calculations under the Québécoise screening program. The NT test, however, is not covered by the Régie de l'Assurance Maladie du Québec and the cost should be covered by the patient.

Table S.24: Screening options available in Québec

Screening strategy	Markers	Possible timeframes	Criteria
SIPS			All pregnant women who present for their first visit at ≤ 13^{+6} wk
SIPS blood test #1	PAPP-A	10-13^{+6} wk	
SIPS blood test #2	AFP, uE3, hCG, DIA	14-16^{+6} wk	
2nd trimester ultrasound	Detailed assessment of fetal anatomy	18 wk and onward	All pregnant women in their 18 wk of pregnancy and onward

Source: Santé et Services Sociaux du Québec, 2011[155]

DIA = dimeric inhibin A; hCG = intact human chorionic gonadotropin; PAPP-A = Pregnancy-associated plasma protein A; SIPS = serum integrated prenatal screening; uE3 = unconjugated estriol; wk = week(s)

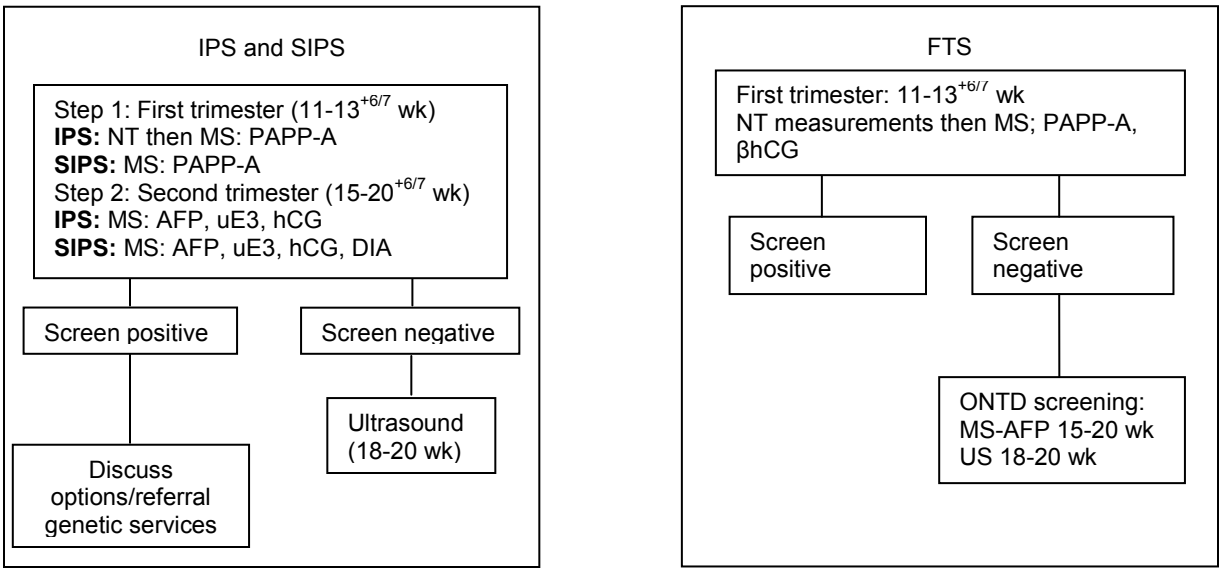
Ontario

The Ontario Maternal Multiple Marker Screening (OMMMS) Program was funded by the Ontario Ministry of Health and Long-Term Care in July 1993. The program offers prenatal screening for trisomy 21, trisomy 18, and ONTD to all pregnant women in Ontario. Triple-marker second trimester maternal serum screening was used in the first 10 years of screening. In 2003, DIA was introduced as part of the quad test to improve DR and reduce FPR.[156] The maternal serum screening program became the OMMMS Program, which supports the provision of a variety of prenatal tests depending upon whether women decide to have prenatal screening tests early or later in pregnancy.[157] Women over 35 years of age at their due date can decide not to have a prenatal screening test but go directly to diagnostic testing such as CVS and amniocentesis. In some areas in the province, this practice has changed and applies to women 40 years of age and over at their due date.[157] Serum tests are performed in seven designated laboratories across the province. A steering committee is responsible for the quality of these laboratories, and has established uniform standards with respect to medians, analysis and interpretation of results, and presentation of reports.[100]

Option 1: Patient presents before 14 weeks gestation:

Care givers in Ontario should offer all pregnant women who present for prenatal care before 14 weeks gestation any of the following options: IPS, SIPS, or FTS.[158] Figure S.4 shows the algorithms that are applied in the OMMMS Program for screening.

Figure S.4: Screening algorithms offered to pregnant women before 14 weeks gestation in Ontario



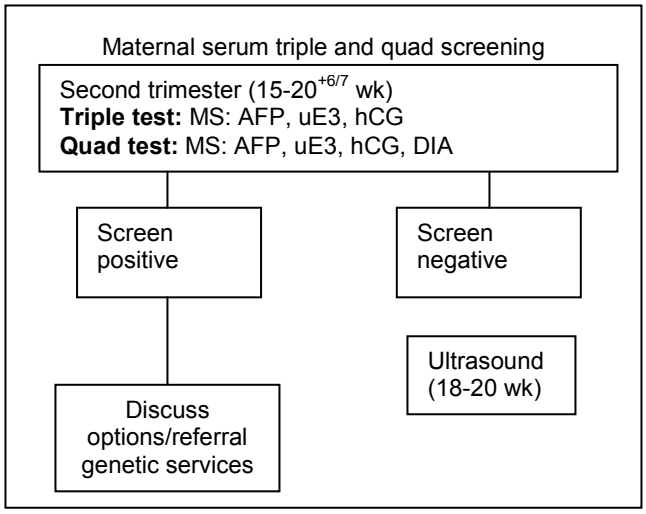
Source: The Genetics Education Project[158]

AFP = alpha-fetoprotein; DIA = dimeric inhibin A; FTS = first trimester combined screening; hCG = intact human chorionic gonadotropin; IPS = integrated prenatal screening; MS: maternal serum; NT = nuchal translucency; ONTD = open neural tube defects; PAPP-A = pregnancy-associated plasma protein A; SIPS = serum integrated prenatal screening; uE3 = unconjugated estriol; wk = week(s)

Option 2: Patient presents 15-20 weeks gestation:

All pregnant women who present for prenatal care in Ontario between 15-20 weeks of gestation are offered the triple or the quad screening tests (Figure S.5).

Figure S.5: Screening algorithms offered to pregnant women at 15-20 weeks gestation in Ontario



Source: The Genetics Education Project[158]

AFP = alpha-fetoprotein; DIA = dimeric inhibin A; hCG = intact human chorionic gonadotropin; MS: maternal serum; uE3 = unconjugated estriol; wk = week(s)

Manitoba

In 1985, Manitoba became the first Canadian province to offer a public prenatal serum screening program (the Manitoba Maternal Serum Screening Program) for all pregnant women between 15 weeks to 20 weeks of gestation. The intent of the program was to offer all pregnant women maternal serum screening with counselling about the test, possible outcomes, options for further testing, and evaluation of risks. As of February 2010, the program uses the quad test.[159] A pregnant woman's risk of carrying a fetus with trisomy 21, trisomy 18, or ONTD is calculated from the values of these markers, combined with maternal age for the chromosome disorders. Maternal blood samples are usually obtained between 16 to 18 weeks of gestation; however, samples received between 15 weeks and 20^{+6} weeks can be interpreted. A limited maternal screening AFP interpretation can be made up to 23^{+6} weeks. Results of maternal serum screening can be combined with NT to give an integrated risk. Follow-up of abnormal results is the responsibility of the Human Genetics Department at the University of Manitoba.[159]

Saskatchewan

Since 2000 Saskatchewan has screened pregnant women for trisomy 21, trisomy 18, and ONTD.[160] Initially, the triple test (AFP, hCG, and uE3) was offered during the second trimester between 15 and 20 weeks of gestation. In October 2008, the Saskatchewan Disease Control Laboratory (SDCL)[161] switched to the quad test by adding DIA to the screening program. Second trimester serum screening is currently offered to pregnant women between 15 and 20 weeks gestation. From these values and maternal age, the risk of trisomy 21, 18, and ONTD are calculated. On July 2010, the Aneuploidy Screening Program for Saskatchewan was established. First trimester serum screening was added to Saskatchewan's prenatal screening program: PAPP-A and ß-hCG are measured in the plasma and serum of pregnant women between 11 and $13^{+6/7}$ weeks.[161] From these values and maternal age, the risk of trisomy 21 and 18 is calculated. For women who are tested during the first trimester, it is still necessary to be tested for ONTD. This is done by collecting a blood sample during the second trimester and sending it to the SDCL for measurement of AFP only.[161] These samples must be sent with a requisition for maternal serum screening, which has AFP only written on it. When such a sample arrives at the lab, AFP is measured and the risk of ONTD is calculated.[161] NT is offered between 11 and 14 weeks gestation and mid-trimester ultrasound is performed between 18 and 20 weeks.

The Saskatchewan Ministry of Health recommends[160] that women who present for prenatal care must be offered prenatal screening regardless of maternal age. Women should be counselled that screening for fetal trisomy 21 and 18 and ONTDs is available and are provided with a patient information pamphlet. Discussion about the methods of testing available and the performance of the test(s) as well as the implications of having screening must follow. For women choosing to have screening done, the prenatal screening requisition is completed. Information about maternal age, menstrual history, weight, diabetes status, and previous ultrasound scan reports is collected to interpret the test results and therefore, it is included on the requisition. The serum sample may be drawn at any laboratory at the appropriate gestational age and sent to the SDCL. The ultrasound scan must be booked with an accredited diagnostic imaging facility.[160]

The following options are available depending on the gestational age:

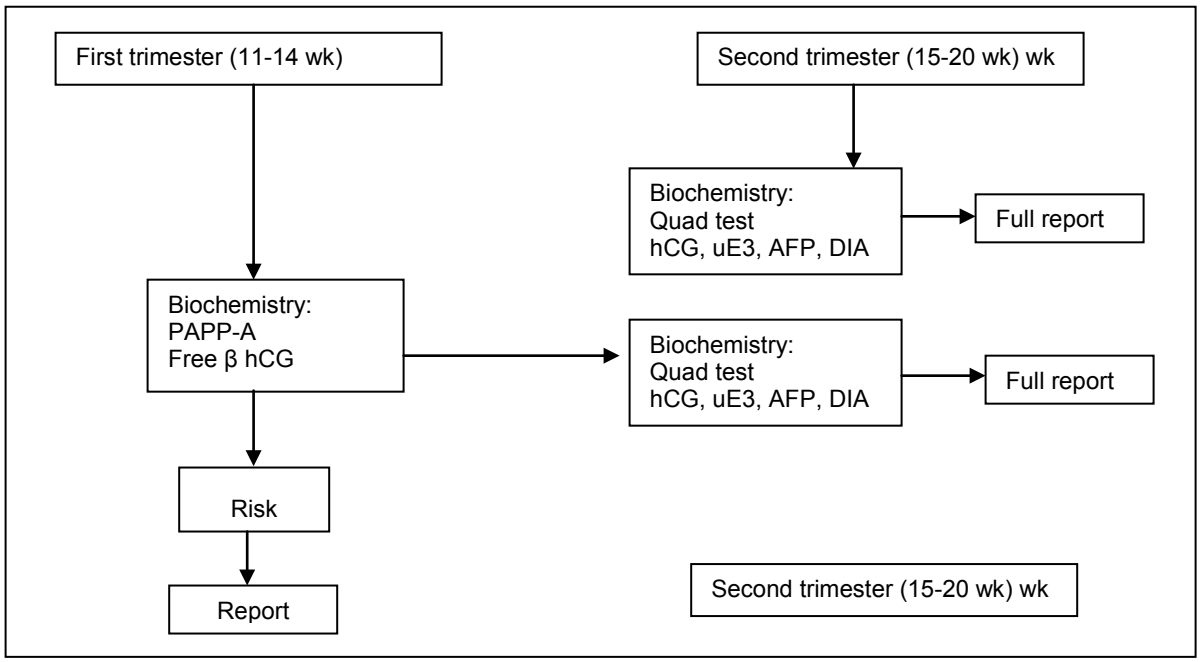
Option 1: Patient presents before 14 weeks gestation

If the results indicate a high risk of aneuploidy, the care giver is notified and NT ultrasound is recommended. When both these elements of testing are complete, a first trimester integrated

aneuploidy report is issued. AFP screening in the second trimester is still recommended to evaluate the risk of ONTD.

If the results indicate a low risk of aneuploidy, no report is issued until second trimester serum screening is completed and then a second trimester serum integrated report is issued to inform the risk of aneuploidy and ONTD. (Figure S.6) This combination is the preferred test in the Aneuploidy Screening Program in Saskatchewan.

Figure S.6: Aneuploidy screening in Saskatchewan: the First Trimester Integrated Option



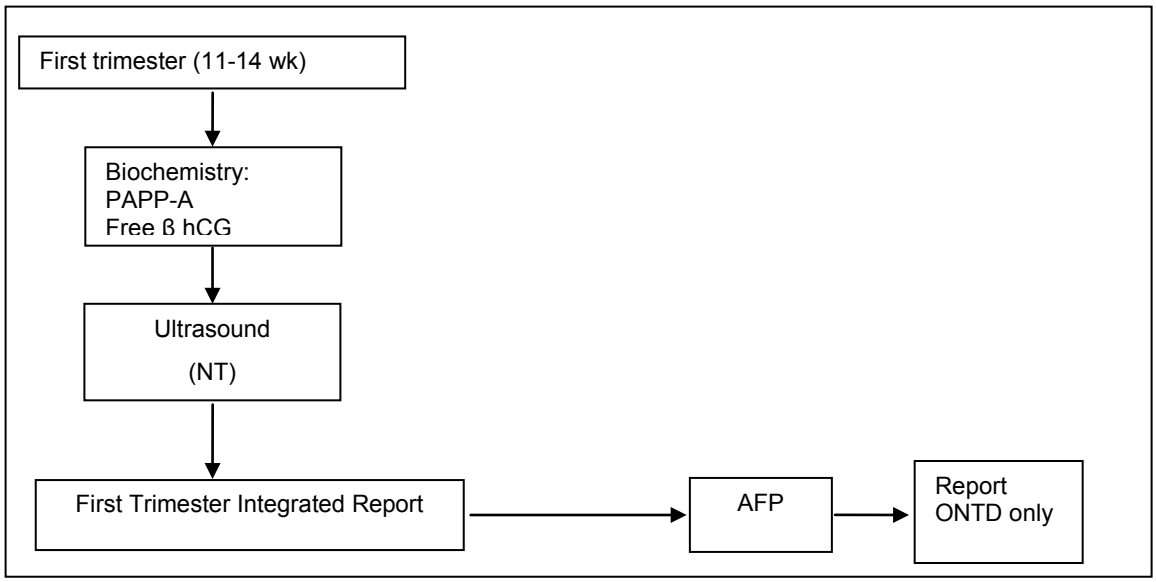
Source: Aneuploidy Screening Program for Saskatchewan[160]

The appropriately counselled patient may choose to have both first trimester biochemistry and first trimester ultrasound and thus complete her risk assessment (except for the second trimester AFP) in the first trimester. This is reported as a first trimester integrated aneuploidy report.

Option 2: Patient presents 15-20 weeks gestation

Second trimester serum screening is offered between 15 and 20 weeks gestation. The risk of aneuploidy and ONTD is reported in a second trimester serum screening report (Figure S.7)

Figure S.7: Aneuploidy screening in Saskatchewan: the biochemistry option



Source: Aneuploidy Screening Program for Saskatchewan[160]

Increased risk in the Aneuploidy Screening Program for Saskatchewan is reported as risk above or below a determined cut-off. Actions following a risk below cut-off include that the care provider inform the patient that no further testing is required. If the result yields a "risk above cut-off", the care provider informs the patient. Initial counselling will take place by the primary care provider and/or obstetrician and/or geneticist/genetic counselor. It is the responsibility of the care provider to provide the counselling and/or initiate any appropriate referrals. Follow-up will vary depending upon increased risk for aneuploidy or ONTD.[160]

Nunavut

Maternal prenatal screening in Nunavut is optional and available to all pregnant women. The quad test is the standard for prenatal care in Nunavut for cases of trisomy 21, trisomy 18 and ONTD. First trimester ultrasound (NT) is not routinely done in Nunavut.[162]

Northwest Territories

Maternal serum screening in the Northwest Territories (NWT) is offered to all pregnant women, regardless of maternal age. The NWT Maternal-Perinatal Committee recommends that all pregnant women in the NWT be offered the quad test as a standard of prenatal care to screen for cases of trisomy 21, trisomy 18, and ONTD.[163] The quad test would be offered optimally between 15 and 16 weeks. Further testing may include amniocentesis, detailed fetal ultrasound, NT with referral to amniocentesis as indicated.[163]

British Columbia

In early 2008, the Ministry of Health Services launched The BC Prenatal Genetic Screening Program (BCPGSP). The mandate of the BCPGSP is to oversee prenatal screening for trisomy 21, trisomy 18, and ONTD across British Columbia. It consists of a centralized, coordinated system to guide prenatal genetic screening across the province. British Columbia has adopted a serum-based approach to prenatal genetic screening. Table S.25 summarizes the screening options currently offered under the BCPGSP.

Table S.25: Screening options available in British Columbia

Screening strategy	Markers	Possible timeframes	Best timeframes	Criteria
SIPS				All pregnant women who present for their first visit at ≤ 13^{+6} wk
SIPS blood test #1	PAPP-A	10-13^{+6} wk	10^{+2}-11^{+6} wk	
SIPS blood test #2	AFP, uE3, hCG, DIA	15-20^{+6} wk	15^{+2}-17 wk	
IPS	Same as SIPS (blood tests #1 and #2)	See SIPS for blood tests	See SIPS for blood tests	Pregnant women who present for their first visit at ≤ 13^{+6} wk with any of the following: 35 yr age at EDD; twin pregnancies; history of trisomy 21, 18 or 13, HIV-positive women, use of IVF/ICSI fertilization
	NT ultrasound	11-13^{+6} wk	12-13^{+3} wk	
Quad test	Same as SIPS blood test #2	15-20^{+6} wk	15^{+2}-17 wk	All pregnant women who present for their first visit between 14 and 20^{+6} wk
AFP	AFP	15-20^{+6} wk	15^{+2}-17 wk	Women with singleton gestation pregnancies who had a first trimester screening and/or CVS; women who declined a SIPS, IPS, or quad screen but wish screening for ONTDs
2nd trimester ultrasound	Detailed assessment of fetal anatomy	18 wk and onward	18-20 wk	All pregnant women in their 18 wk of pregnancy and onward

Source: British Columbia Prenatal Genetic Screening Program, 2011[164]

AFP = alpha-fetoprotein; EDD = expected delivery date; hCG = intact human chorionic gonadotropin; ICSI = intracytoplasmic sperm injection; IPS = integrated prenatal screening; IVF = *in vitro* fertilization; NT = nuchal translucency; SIPS = serum integrated prenatal screening; wk = week(s)

The prenatal screening tests offered depend upon the woman's gestational age at her first prenatal visit and maternal age at the time of delivery. As of March 2011, SIPS for trisomy 21, trisomy 18, and ONTD is available to all pregnant women regardless of age.[164,165] It is the woman's choice to proceed with or decline screening. For reasons of resource limitations (as of March 2011, there were 17 NT operational sites across the province[166]), NT ultrasound assessment is available only to certain women as part of the BCPGSP.[164] The following pregnant women are eligible for NT ultrasound as a component of IPS (SIPS in combination with NT): women 35 years of age or older at their expected date of delivery; women with twin pregnancies; women who have a history of a previous child or fetus with trisomy 21, trisomy 18, or trisomy 13; women who are positive for human immunodeficiency virus; or women pregnant following *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI).[164] Women who have a higher order multiple pregnancy (at any age) qualify for an NT ultrasound alone.[164]

In circumstances where a woman qualifies for an NT ultrasound measurement but cannot get it because there is no NT centre nearby that provides this service, or the nearby centre is fully booked, or she is unable to travel to another site, SIPS is recommended as an alternative.[164] Eligible women able to travel may be accommodated at any NT site.[164] In order to ensure the quality of NT ultrasound, every sonographer must annually perform a minimum number of ultrasounds. As such, pregnant women 30 years and older from the Northern Health Authority and East Kootenay/Kootenay/Boundary regions are also eligible for an NT ultrasound as part of IPS.[164,165] In some parts of the province, NT ultrasound measurement is available on a private pay basis. If a

woman wishes to pay privately for the NT and have the SIPS done through the public system, the NT measurement can be used in the risk calculation as long as a provider accredited by the FMF measures the NT. In such cases, the provider ordering the prenatal screen should send a copy of the NT ultrasound report to the Prenatal Biochemistry Laboratory Child and Women Services.[164]

The current focus of the BCPGSP is to build NT capacity across the province and improve access to screening for all pregnant women and, therefore, FTS (PAPP-A, β-hCG serum biochemistry, and NT ultrasound measurement) is not offered within the provincial screening program.[165] Pregnant women have the choice of paying privately for FTS through private clinics in Vancouver, Burnaby, Kelowna, and Victoria.[164]

Yukon

The Yukon territory does not have an established maternal screening program. Prenatal serum screening tests are offered to Yukon residents through the BCPGSP.[167]

Alberta

Alberta does not have an established provincial screening program. Prenatal screening in the province is currently offered in various forms. The availability of screening tests varies depending on the region, the institution, and the provider ordering the tests. All pregnant women in Alberta are offered maternal serum screening in the second trimester (the quad test; AFP, uE3, hCG, DIA).[168] Blood samples are drawn between 15 to 20^{+6} weeks of pregnancy. There is also the option of requesting AFP to screen for ONTD. Once the requisition form for maternal serum screening is filled out by a doctor or midwife, a blood sample may be drawn at any laboratory in Alberta.[169]

FTS is performed at the Southern Alberta Centre for Maternal Fetal Medicine. On the other hand, FTS has limited availability in Edmonton and it is generally reserved for women who are over 35 years of age.[168]

Guidelines from the Toward Optimized Practice (TOP) program in Alberta recommend that NT screening should only be offered as part of a comprehensive prenatal screening and counseling program by experienced health providers with appropriate quality assurance processes in place.[108] The TOP guideline encourages combining NT with maternal serum biochemistry as part of a program of either concurrent or sequential screening.[108]

A more detailed description of the FASTS options and services available in Alberta is provided in the section *Healthcare system capacity for the provision of first and second trimester screening services in Alberta*.

Table S.26 provides a summary of the public provision of FASTS services across Canadian provinces and territories.

Table S.26: Public provision of FASTS services across Canada

Province/Territory	Provincial program	First trimester testing	Second trimester testing	SIPS available	IPS available
Newfoundland and Labrador	Yes. Provincial Medical Genetics Program	No	Triple test	No	No
Nova Scotia, New Brunswick and Prince Edward Island	Yes. Nova Scotia Reproductive Care Program	First trimester MSS; FTS (limited to women with specific risk factors)	Quad test	Yes	Limited to women with specific risk factors
Québec	Yes. Prenatal Screening Program for Trisomy 21	First trimester MSS; FTS (limited to women with specific risk factors)	Quad test	Yes	Not covered. Limited to women with specific risk factors
Ontario	Yes. Ontario Maternal Multiple Marker Screening Program	FTS	Quad test	Yes	Yes
Manitoba	Manitoba Maternal Serum Screening Program	No	Quad test	No	No
Saskatchewan	Aneuploidy Screening Program	First trimester MSS; FTS (limited to women with specific risk factors)	Quad test	Yes	Limited to women with specific risk factors
Nunavut	No	No	Quad test	No	No
Northwest Territories	No	No	Quad test	No	No
British Columbia and Yukon	BC Prenatal Genetic Screening Program	First trimester MSS; FTS (limited to women with specific risk factors)	Quad test	Yes	Limited to women with specific risk factors
Alberta	No	First trimester MSS; FTS (limited to women with specific risk factors)	Quad test	No	Limited to women with specific risk factors

BC = British Columbia; FTS = first trimester combined screening; IPS = integrated prenatal screening; MSS = maternal serum screening; SIPS = serum integrated prenatal screening

Factors that affect the use, access, and provision of FASTS

Factors that affect the provision of FASTS services include those affecting the performance of the screening tests and those related to the access and use of FASTS services.

Factors potentially affecting screening performance

A variety of factors can potentially affect the performance of FASTS tests. They include gestational dating methods and other measurement issues, maternal weight, the presence of certain clinical conditions, multiple pregnancies, and the use of assisted reproduction.

Gestational dating methods: Interpretation of FASTS tests requires knowledge of the gestational age. Gestational age is best estimated by ultrasound when available, followed by the date of onset of the last menstrual period and finally by physical examination.[170,171] According to clinical practice guidelines by the SOGC and by the Board of the Canadian College of Medical Geneticists,

ultrasound improves the precision of gestational age estimation and, hence, reduces the standard deviation of each screening marker.[96,102]

Measurement issues: Guidelines for measuring serum markers are well-established.[172] To achieve standardization and maintain quality, the use of serum markers in a clinical setting requires a program of quality control and maintenance of skills through an ongoing external audit of serum measurements.

The accuracy of NT measurements is affected by a variety of factors such as fetal position, measurement technique, risk-calculation software used, and sonographer's training and experience.[173] Guidelines for measuring NT have been developed by the FMF in the United Kingdom to maximize reproducibility and accuracy. The FMF has set up a process for certification to ensure that those performing NT have been adequately trained to do so and that high standards of performance are maintained by continuous education and audit.[174] According to the FMF guidelines, NT should be implemented only in centres with appropriately trained sonographers using high-quality equipment and that the results should be subject to regular audit by an external agency. Quality control and training through an ongoing audit of NT measurements are necessary to achieve standardization and use NT in a clinical settings.[96]

Maternal weight: A negative association between the levels of maternal serum markers and maternal weight has been described in the scientific literature.[102] Adjustment for maternal weight is usually done when interpreting measurements of serum markers.[175] It has been suggested that published weight correction formulae may not be optimal because of differences in mean weight between the population served and the populations used to derive the formulae.[96] Therefore, the SOGC guidelines have recommended that each laboratory should calculate its own weight adjustment formulae.[96] Weight adjustments do not appear to be necessary for NT risk adjustment because it increases only by a clinically insignificant amount with increasing maternal weight.[175]

Insulin-dependent diabetes mellitus (IDDM): Studies in the early 1990s showed that the levels of certain biochemical markers (i.e., AFP and uE3) used to screen for trisomy 21 in the second trimester of pregnancy tend to be lower among women with IDDM. On this basis, many screening programs adjust the marker levels to account for this difference.[176] It appears that NT measurement, total and free β-hCG, PAPP-A, and DIA in women with and without insulin dependent diabetes, are not significantly different.[96]

Multiple pregnancies: Twins account for approximately 1% of all pregnancies[177] and is expected to increase worldwide as a result of the widespread use of assisted reproductive techniques and the ageing of mothers, who after 35 years of age are three times more likely to conceive twins than women under the age of 20.[177] Twin and higher order multiple pregnancies present unique and problematic challenges in prenatal screening as the performance of screening tests designed for singleton pregnancies is altered. Although chorionicity (i.e., the type of placentation) determines several aspects of antenatal management and perinatal outcome, it is the zygocity (i.e. the type of conception and genetic make-up of the pregnancy) which determines the risk of fetal aneuploidy and whether or not the fetuses may be concordant or discordant for the anomaly.[177,178] In monozygotic twins, a single fertilized ovum splits into two distinct individuals after a variable number of divisions. In monozygotic twins, the risk of aneuploidy for one fetus can be expected to be the same as the risk for the other and both fetuses are usually affected.[179] Dizygotic twins result when two separate ova are fertilized. These individuals are genetically distinct and most often discordant for aneuploidy as the risk for each fetus is independent.[180] Therefore, for dichorionic twin pregnancies, the pregnancy specific risk based on FASTS results needs to be calculated by summing the individual

risk estimates for each fetus.[140,177] If zygosity is unknown, the risk of at least one aneuploid fetus can be approximated as five-thirds that of the singleton risk.[177] At this time, there are no clear standards for screening for aneuploidy in multiple pregnancies.[180] Biochemical screening in twins has a lower detection rate for fetal aneuploidy and higher rates of false-positive results. The levels of maternal serum markers are, on average, twice as high in unaffected twin pregnancies as in unaffected singleton pregnancies.[177,180] The interpretation of maternal serum markers to risk assessment is clearly more problematic because it is hard to determine the contribution of each individual fetus to the biochemical values.[180] Each serum marker relates to the pregnancy and is not specific to the fetus, deriving solely a pregnancy and not a fetus-specific risk.[177]

Alternatively, NT measurements for singletons can be used for multiple gestations involving up to at least three fetuses[179] and constitute the predominant factor by which women who present with increased risk should be counseled regarding invasive testing.[177]

Assisted reproduction: In the last two decades, the use of various assisted reproduction technologies have increased dramatically. It seems that there is a significant impact of assisted reproduction technologies on second but not first trimester maternal serum markers and the screen positive rates.[181] Both IVF and ICSI may cause these levels to differ from spontaneous pregnancies. Data from most published studies show second trimester serum levels of hCG and β-hCG are higher and uE3 is lower in pregnancies conceived through IVF.[96] Therefore, an appropriate adjustment in the second trimester screening protocol is recommended; however, more studies are needed to define the differences in maternal serum levels observed in the IVF and ICSI groups compared to naturally occurring pregnancies.[181] Centre-specific corrections may be needed to adjust screening parameters for assisted reproductive technology.

Factors related to the access and use of FASTS

Several factors influence why women are or are not likely to have fetal aneuploidy and ONTD screening in the first or second trimester of pregnancy. They can be categorized as factors related with knowledge, expectations, and attitudes toward prenatal screening, psychological factors, socio-economic, and socio-demographic factors, factors related with believes, culture and social norms, health providers attitudes towards testing and patterns of referral and characteristics of the facilities involved in the provision of FASTS services.

Knowledge: In general, women are knowledgeable about procedural and practical aspects of the screening tests.[94,182] Results from a qualitative systematic review of 34 studies assessing knowledge and information concerning prenatal examinations[182] showed that between 70% and 96% of pregnant women are able to describe how the tests are performed, who the tests are offered to, and at what stage of pregnancy the tests are conducted. The preferred source of information in both tested and untested women is face to face counselling with a doctor, followed by pamphlets and videos. Other sources of information include books, the Internet, magazines, friends, and relatives. When making the final decisions regarding to screen or not, 36% of the tested women and 21% of the untested women prefer talking to other women previously tested. The final decision, however, is strongly influenced by the woman's own feelings (90% of the cases). The value assigned to information aimed at increasing the knowledge of the screening tests is less dominant for women who decide not to be tested, with 17% not interested in any information compared to 5% in the test group.[182]

The qualitative review by Dahl et al.[182] also found that, although most pregnant women (91% to 97%) are able to identify the more uncomplicated reasons for prenatal screening (delivery date or number of fetuses), they are much less informed about the use of FASTS tests to trace fetal

aneuploidy. Women have a limited understanding of the meaning of risk calculations based on the screening results and of any potential drawbacks or further consequences of the test results.[94,182] For example, it has been reported that a large group of pregnant women (29% to 68%) are not familiar with the concepts of false negative and false positive results.[182,183] A systematic review of 78 studies on psychosocial aspects of screening programs offered to pregnant women[94] showed that large knowledge gaps remain regarding certain aspects that could complement the decision of whether to undergo the tests and help with decision making once the results are obtained. There are very few studies of the impact of knowledge by partners of women undergoing screening.[94]

Although limited aspects of knowledge have been studied to date, there is evidence of inequalities in knowledge about prenatal testing that are likely influenced by level of education, socio-economic status and ethnicity.[94]

Attitudes and perceptions: The purpose of prenatal technologies is to detect fetal aneuploidy or conditions that may give rise to a disability at birth. Thus, attitudes and perceptions about disability play an important role in the dynamic of why and how prenatal screening are developed and provided.[99] Attitudes towards prenatal screening do not seem to be predicted by knowledge.[182,184] A qualitative systematic review of data from 34 studies[182] found that most pregnant women (about 90%) hold positive attitudes toward prenatal screening. Particularly, uptake rates relate to the type of test offered, with ultrasound having higher uptake rates (50% to 90%) than serum screening (35% to 75%). Reasons given by pregnant women not wishing to participate in screening tests include unfavourable perceptions of the screening tests such as the use of probabilities to report the results, the lack of certainty and reliability in the test results, and the risk of miscarriage related to invasive diagnostic procedures.[182] Results from a systematic review that assessed women's views on the value of prenatal screening for chromosomal disorders showed that most women (60% to 75%) viewed FASTS positively but some have concerns regarding their usefulness and impact on the pregnancy experience and society.[94] Positive perceptions included a sense of empowerment by women to make informed choices and the perception of undergoing screening as a maternal responsibility to ensure the health of the baby. A smaller proportion of women (about 10%) perceived prenatal testing as a procedure that medicalizes pregnancy, creates a false sense of control, generates worry, and increases stigmatization of disability in society.[94]

A systematic review of 40 publications on decisional needs of women and their partners regarding prenatal testing for fetal aneuploidy[185] identified a variety of factors perceived by women and their partners as sources of difficulty or ease in decision-making about prenatal testing. These factors include knowledge, expectations, values, decisional conflicts, norms, social pressure and support, decision participation roles, and personal and external resources. The most frequently reported sources of difficulty in decision-making about prenatal testing for fetal aneuploidy among women came from social pressures, emotions generated by the testing procedures and their potential results, and lack of information about the tests or the consequences of being tested. Sources of difficulty reported by the women's partners were related to social pressures, emotions, and a non-directive approach adopted by health providers. The most important sources of ease in decision making included personal values, religious views or beliefs favouring the acceptance of a child with a disability and respect of natural pregnancy and life, understanding the risks and benefits of prenatal testing, and confidence in the medical system.[185] Sources of ease for the women's partners also include the access to information from external sources and personal values. The perceived effectiveness of screening procedures also contributed to facilitate the decision process.[185]

Psychological factors. Systematic reviews of studies on psychosocial aspects of screening programs of pregnant women[94,183] have shown that, although some anxiety might be an appropriate

response that help with coping and decision-making processes, anxiety is clearly increased in women receiving positive screening results, particularly in young women. Anxiety levels are reported to be higher with ultrasound procedures rather than with maternal serum screening procedures.[183]

Evidence is lacking regarding a reassuring effect of receiving a screen negative result. Although anxiety in women that screened positive in the first trimester decreases on receipt of subsequent negative results during the second trimester, some residual anxiety may remain.[41,94]

As FASTS tests generate false-positive and false-negative results, women that are informed of screening results may learn their false-positive or false-negative status only after subsequent diagnostic tests are performed or after the baby is born. It has been well documented that false-negative cases suffer significant distress albeit from a population perspective these numbers are likely to be small.[94] Alternatively, false-positives are likely to affect larger numbers of pregnant women. In all of these situations, anxiety plays an important role in the health status of pregnant women and their decision-making process regarding prenatal screening. Because anxiety might alter the woman's ability to respond to the advice of healthcare providers, and might even have physiological effects on the pregnancy and development of the baby, it constitutes an important topic on its own to evaluate the impact of FASTS services.[94] Anxiety in partners of women undergoing screening has not been studied extensively.[94]

The concept of risk for fetal aneuploidy is constituted entirely by screening systems operating at the limits of technological innovation.[183] FASTS generate risk categories that indicate whether pregnant women have lower or higher probabilities of having a baby with fetal aneuploidy or ONTD. Some women reject screening in order to avoid the psychosocial and medical risks associated with being on a higher risk status, or because they rule out pregnancy termination.[183] However, in some instances, women may acquire a higher risk status unintentionally through screening tests results to which they have not consented as blood tests or ultrasound during pregnancy are used for multiple purposes that are not necessary related to screening for fetal aneuploidy or ONTD.[183] As health systems move towards offering prenatal FASTS universally, an increasing number of women will have to manage the psychosocial consequences of a higher risk status.[183]

Ethnicity, cultural beliefs and social norms. Several studies[182,186-189] have documented the impact of ethnicity, culture, and social norms as determinants of participation and non-participation in prenatal screening. These factors are main contributors to explain differences in knowledge and attitudes regarding fetal aneuploidy and ONTD. There is evidence that women from certain ethnic groups may be less likely to be offered prenatal testing for certain conditions and certain women may be less likely to take up screening when offered.[189] A systematic review of studies examining the frequency of prenatal testing use for trisomy 21 and ONTD reported that screening use was significantly lower in Asian women than in Caucasian women (risk ratios of screening utilization of Asian versus Caucasian women ranging from 0.24 to 0.6).[189] Another systematic review of studies on prenatal screening for trisomy 21 found that ethnic groups varied in their participation in prenatal screening in the United Kingdom (UK), with Caucasian women having higher uptake rates compared to women from non-Caucasian ethnic minorities.[186] This finding was attributed to ethnic differences in knowledge of trisomy 21, attitudes towards having a child with trisomy 21, influence of the partner, family and healthcare providers, socioeconomic factors and differences in the offer of prenatal screening.[186] Knowledge of prenatal screening has been reported to be higher in Caucasian women than in non-Caucasian women.[184] Caucasian women in the UK had significantly better knowledge of trisomy 21 than Asian women.[187] Factors affecting knowledge included the quality of spoken English, knowing a child with the condition, parity, and religion.

Religious convictions and beliefs are significantly related to declining prenatal screening tests.[182,186] Analysis of studies conducted in the United States showed that African–American women who were less likely to undergo prenatal screening were significantly more religious, had a more fatalistic attitude towards trisomy 21, and had less desire of knowing the test results.[188] Alternatively, Caucasian women assigned higher values to the birth of child without the condition compared to African–American, Hispanic, and Asian women. However, Asians and Pacific Islanders appeared to feel more negatively about having a child with trisomy 21 than other women.[186] Spanish-speaking women in the United States with low levels of acculturation are significantly more likely than more acculturized Spanish speaking women to refuse prenatal screening for trisomy 21.[186]

Ethnic differences in the availability of prenatal screening in Australia have been also reported; women of a non-English speaking background are less likely to be referred for screening than English-speaking women.[186] Beliefs directly influence women's attitude towards participating in prenatal screening. Factors such as fatalism, faith, fear of having a child with a chromosomal anomaly, and risk perception influence personal, family, and social beliefs about trisomy 21. Beliefs about prenatal screening are influenced by attitudes towards termination of pregnancy and miscarriage risk.[186] Finally, subjective norms are relevant in women's decision to participate or not in prenatal screening programs. Determinants of subjective norms identified in studies using qualitative methodologies include the influence of a gynaecologist or midwife, perceived expectations of society, and influences and support of the partner and the family.[186]

Socio-demographic and socio-economic factors. One systematic review[189] assessed how social inequalities influenced the provision, utilization, or uptake of prenatal screening for trisomy 21 and ONTD. The frequency of prenatal testing was examined according to women's social class and level of education. The review did not find evidence of social class inequities in the offer or uptake of prenatal testing; however, given the small number of studies in this area, the reviewers caution that it would be wrong to draw any firm conclusions from their results. Education level affects the ability to retain new knowledge regarding the use of screening tests, with women having completed university or postgraduate education having a significantly higher level of knowledge after receiving information about the screening options available.[182,190,191] Highly educated women, however, are likely more reluctant to participate in the screening test offered and find the decision to undergo testing more difficult.[182]

Alongside geographic variability in the availability of FASTS services, maternal age is a key factor in the woman's decision to undergo prenatal testing. A systematic review that assessed the impact of a variety of psychosocial factors on the decision of accepting or declining available screening results found that women undergoing screening were older than those who do not (mean age 30 versus 28 years).[182] There is also evidence that older women and living in urban centres are more knowledgeable than younger women and those living in remote or rural areas regarding prenatal screening options.[182,184,190,191]

Perspective and influence of healthcare providers. Healthcare providers are an essential source of information that influences the choice of participation in prenatal screening. Analysis of data from a systematic review on access to prenatal screening showed that, when making a decision regarding prenatal screening, women that decided to undergo testing were more influenced by their doctor than untested women (75% versus 45%).[182] The healthcare provider is perceived as a very (31%) or somewhat (57%) helpful source of information that helped women to reach a decision regarding undergoing testing for fetal anomalies.[182]

Overall, health providers who offer and perform the tests are likely to have a predominantly positive attitude toward screening procedures during pregnancy that influences the women's decision to use FASTS services.[182] As pregnant women trust the healthcare system, participation in prenatal screening programs seems to be legitimized by those offering the tests. Data from individual studies reported in a systematic review that examined the reasons for accepting or declining prenatal testing indicate that only a few women question the information provided or the justification or quality of the prenatal tests offered, but rely on the healthcare system offering the tests.[182] Analysis of individual study data shows that many pregnant women (55% to 66%) are not aware of prenatal testing as an option. Ultrasound examinations, for example, are often (42% to 85%) presented as a recommended or routine test, or imposed by the providers (41%). There is evidence that a higher screening participation rate is triggered when health providers present the screening test as a routine part of prenatal care. In these circumstances, women are less affected by decisional conflicts when opting in or out for screening (approximately 94% of women offered serum screening as a routine procedure find the decision easy versus 86% of those offered as a free choice).[182] Likewise, higher participation rates have been found when screening is offered as a part of a routine visit instead of a separate visit (uptake rate: 73% versus 56%).[182]

The type of language and information content that health providers choose to communicate to pregnant women is also of pivotal importance. A comprehensive review of studies assessed the information that pregnant women receive about prenatal screening and risk for trisomy 21.[192] Overall, the review found that information delivered by health providers prior to testing, as well as information given during the screening procedure, tends to focus on practical and technical aspects of the test (when, where, and what the tests screen for), whereas the possible consequences and future perspectives once the results are obtained are described more vaguely.[192] Furthermore, the use of medical words rather than lay terms to inform pregnant women about the level of risk for fetal anomalies significantly affect how the condition or risk is perceived. Evidence summarized in the systematic review also showed that the content of information provided is unlikely to empower an informed consent on the women's part; limitations of screening tests are rarely mentioned, and how to interpret a screening result is generally not explained.

Finally, a systematic review of publications evaluating decisional needs of health providers regarding prenatal testing for trisomy 21 showed that the sources of difficulty for decision making reported by health providers are related to lack of information, length of consultation, and personal values.[185] Health providers reported important ethical dilemmas, the most frequent being the request for abortion. Some pointed out the risk of eugenic pressure and the inability of the society to appropriately provide care for disabilities.[185]

Healthcare System Capacity for the Provision of First and Second Trimester Screening Services in Alberta

FASTS service provision in Alberta

In Alberta, FTS (NT, PAPP-A, and free β-hCG) is available to women between 11 weeks and 13^{+6} weeks of pregnancy.[193] NT screening alone is also offered.[194] For second trimester screening, maternal serum screening (MSS), the quad test, is available to all pregnant women in Alberta.[195] For second trimester screening for ONTD only, AFP is also offered. Maternal age is not recommended as a screening test. It has been reported that pregnant woman over the age of 40 years may opt out of screening and go directly for invasive diagnostic testing - CVS in the first trimester or amniocentesis in the second trimester (Dr. Fiona Bamforth, personal communication; November 8, 2010).

FASTS services in the province are delivered within a variety of patterns of practice without the adoption of unified criteria or standards. Alberta Health Services (AHS) provides FASTS options through the Edmonton Early Pregnancy Risk Assessment Program and the Early Prenatal Risk Assessment (ERA) Program in Calgary. Biochemical analysis and ultrasound are performed in designated AHS facilities. Pregnant women both in the north and south of the province are typically offered either first or second trimester screening but not both (Dr. Fiona Bamforth, personal communication; November 8, 2010). One half to two-thirds of pregnant women in the North who choose to undergo first trimester screening also have a partial second trimester screening for ONTD (Dr. Fiona Bamforth, personal communication; November 8, 2010). Likewise, there are some issues around the provision of NT in the north as some women only have an NT and no further follow-up tests (Dr. Fiona Bamforth, personal communication; November 8, 2010).

Edmonton Early Pregnancy Risk Assessment Program

The Edmonton Early Pregnancy Risk Assessment Program is located at the Lois Hole Hospital for Women at the Royal Alexandra Hospital complex in Edmonton. The program is affiliated with the Women's Health Program at the Department of Obstetrics & Gynecology, Division of Medical Genetics, University of Alberta. Pregnant women who are referred by a physician are eligible for this service. They must live in the geographic area that is served by Northern and Central Alberta Maternal-Fetal Medicine Centre.[196] The program is delivered by AHS with the laboratory component provided through Edmonton Laboratory Services.

The target group of the program is pregnant females desiring an early pregnancy risk assessment. A consultation letter written by a physician with the reason for referral is required. Additional documents required include completed prenatal blood work, all previous ultrasound reports, and any other pertinent lab work or reports. Key providers in the Edmonton Early Pregnancy Risk Assessment Program include administrative assistants, bereavement counselors, genetics counselors, maternal-fetal medicine specialists, registered nurses, and psychologists.[196] FTS has limited availability in Edmonton and it is generally reserved for women who are over 35 years of age.[168]

Early Prenatal Risk Assessment Program (ERA)

The ERA Program is located at the Southern Alberta Centre for Maternal Fetal Medicine in Calgary. The program is a multidisciplinary collaborative of Elliott Fong Wallace (EFW) Radiology, Specialists in Diagnostic Imaging, Calgary Laboratory Services (CLS), and the Calgary Health Region, Departments of Obstetrics and Gynecology and Medical Genetics.[197] The laboratory component is delivered through CLS and the ultrasound component is delivered through EFW Radiology. The service began March 2006 and is delivered by AHS.[198]

According to ERA reports and presentations on program performance,[198,199] the ERA program is the only program in Alberta that will screen all pregnant women regardless of age or risk. Referrals are received from the British Columbia catchment area as well as northern Alberta.[198] The ERA program offers FTS for trisomy 21, trisomy 18, and trisomy 13 to all women pregnant with singletons or twins regardless of age. Maternal serum screening is available but infrequently used since FTS became available in March 2006. For twin pregnancies, NT alone or FTS is offered and for triplets and above, NT alone is offered. Due to capacity issues, amniocentesis is offered to all women 35 years of age or older and CVS is offered only in cases of higher risk. The program does not recommend AFP for women who have had FTS (Dr. Jo-Ann Johnson, personal communication; November 18, 2010).

The ERA program delivers FTS via two models: OSCAR (One Stop Clinic for Assessment of Risk) and modified OSCAR. OSCAR allows women to have their blood drawn and NT ultrasound in one location during one appointment.[198] Within the modified-OSCAR model, women can have their blood drawn ahead of time for FTS at any CLS Patient Service Centre.[198] The ERA program uses Astraia® software to make risk calculations (Dr. Jo-Ann Johnson, personal communication; November 18, 2010).

According to ERA reports and presentations on program performance,[198,199] the demand for FTS at ERA continues to increase albeit many women are unable to access FTS due to the limited funding as well as the existing single provider for the NT component model. (i.e., FTS available if the woman has her NT ultrasound at an EFW facility).[198] This has caused confusion among referring physicians who send women for blood tests and then to non-EFW facilities for the NT ultrasound. In these cases, the blood tests cannot be utilized and the women and physicians are left with incomplete results. This situation has created concern among ERA providers who indicate that, given the difficulty that women and care providers are having in booking FTS though the ERA program, there is the possibility that pregnant women may not receive FASTS screening that meet the SOGC guidelines.[198]

Laboratory and ultrasound services

Prenatal laboratory screening practice varies across the province. In the North, the blood work can be made at an AHS lab or DynaLIFEDx facilities in the Edmonton area, Camrose, Fort McMurray, High Level and surrounding area, Lloydminster, and Red Deer. A number of sites provide NT but the blood work is referred to the AHS Edmonton Zone Laboratory Services located at the University of Alberta Biochemistry Core Laboratory[200] (Dr. Fiona Bamforth, personal communication; November 8, 2010). The first trimester risk assessment is done by the lab using software from Astraia®.[201] Data from NT measurement, if available, as well as woman's clinical information provided on the requisition is incorporated in the software calculations. The software used in the lab for second trimester risk assessment is Benetech® Prenatal Risk Assessment (PRA) software[202] and incorporates clinical data from the requisition (Dr. Fiona Bamforth, personal communication; November 8, 2010). As an aside, it has been reported that up to 40% of requisitions are not completed in full by the physicians' offices and, therefore, information for risk assessment is often missing. The lab often has to call the physicians' offices for the clinical information (Ms. Lucille Journault from Edmonton Laboratory Services, personal communication; May 16, 2011).

As part of the ERA program, CLS offers ERA women the option of having their blood collected and analyzed at the time of their appointment at the Teaching Research and Wellness facility or having their blood drawn at any CLS collection site several days before their ultrasound appointment.[198] For the first trimester screening in Calgary, the risk assessment software is done with Astraia®.[201] The lab results are incorporated into the software program. For the second trimester, the software owner is CLS, and the lab staff inputs the data and reports the risk analysis (Ms. Heather Sereda from Calgary Laboratory Services, personal communication; January 06, 2011). Currently AHS in Calgary is partnered with EFW Radiologists to perform the NT. Canada Diagnostic Centres also do NT, but with no biochemical results (Ms. Heather Sereda from Calgary Laboratory Services, personal communication; January 06, 2011).

According to the FMF Canada,[203] there are three centres in Alberta that have met FMF NT training and annual quality assurance requirements; all of them are located in Calgary: EFW Radiology Ultrasound, Canada Diagnostic Centres, Calgary Ultrasound and Radiology Consultants Associated

Diagnostic Ultrasound. EFW Radiology Ultrasound works in partnership with the ERA program. The other two diagnostic imaging centres conduct NT alone without biochemistry.

Trends of FASTS utilization

FASTS utilization in Canada

Access and utilization of prenatal testing services varies considerably among the provinces and territories.[87] Administrative data from the BCPGSP shows that in 2010 approximately 25,000 women chose prenatal screening for trisomy 21, trisomy 18, and ONTD in British Columbia.[165] This represents approximately 55% of pregnancies per year in the province. With the implementation of more NT ultrasound sites in the province, a larger number of women 35 years and older had IPS in 2010 as opposed to SIPS when compared to 2009 data (Table S.27).[165] There has also been an increase in the utilization of SIPS with a decrease in the utilization of the quad test compared to 2009; however, the shift from quad to SIPS has not occurred consistently in all health authorities in British Columbia.[165]

Table S.27: FASTS utilization in BC

Maternal age (yr)	IPS (%)		SIPS (%)		Quad test (%)	
	2009	2010	2009	2010	2009	2010
< 35	1.0	1.9	44.6	63.7	54.4	34.4
35	3.8	12.6	53.1	64.6	43.1	22.9
36-39	9.8	43.1	53.5	39.1	36.7	17.8
40 +	54.7	65.8	26.8	19.7	18.4	14.6

Source: BCPGSP, 2011[165]

IPS = integrated prenatal screening; SIPS = serum integrated prenatal screening; yr = year(s)

A survey conducted among family physicians, general practitioners, and obstetricians in Saskatchewan during May and June 2005[204] indicated that all obstetricians and 91% of family physicians reported offering maternal serum screening to pregnant women in their practices. Of these, 87% of obstetricians and 72% of family physicians reported offering maternal serum screening to all pregnant women without consideration of age.[204]

Administrative data from the SDCL on utilization trends after the introduction of the maternal serum screening program in the province in 2002 (Table S.28) showed that serum scrum screening utilization was hither in the southern region of the province in both urban and rural areas.[160,161]

Table S.28: Maternal serum screening utilization in Saskatchewan

Number of MSS test performed (May 2001 – October 2002)		
Region	**Urban**	**Rural**
Saskatoon/North	742	284
Regina/South	1513	861

Source: Saskatchewan Ministry of Health, 2010[160]

MSS = maternal serum screening

Administrative data from the Ontario Perinatal Surveillance System showed that over 80,000 women are screened in the OMMMS program annually.[156] Among 86,550 women screened in 2007, IPS represented 57% of the screening volume, followed by the quad test (22%) and FTS (15%). Since the introduction of enhanced prenatal screening, the overall screening uptake rate has increased from 46% in 2001 to 62% in 2007.[156]

Administrative data from the Newfoundland and Labrador Medical Genetics Program showed a low uptake of maternal serum screening in the province; about 22% of pregnant women in Newfoundland and Labrador underwent maternal serum screening in 2003.[205]

Administrative data for the years 2000 to 2003 on prenatal screening utilization in the Maritimes indicate that maternal serum screening is underutilized, particularly among women younger than 35 years of age. NT utilization in the Maritimes has ranged from 24% in 2000 to 38% in 2003 for a mean proportion of 32% for the 2000 to 2003 period.[153] The proportion of maternal serum screening in the Maritimes during the 2000 to 2003 period was 29% (20% among women less than 35 years of age and 36% among women older than 35 years of age).[153] Alternatively, mid trimester ultrasound was used by more than 90% of pregnant women during the 2000 to 2003 period (85% of all pregnant women less than 35 years of age and 93% of all pregnant women older than 35 years of age).[153]

Administrative data from the Manitoba Maternal Serum Screening Program indicates that prenatal screening of pregnancies represent about 70% of the live births in Manitoba.[159]

FASTS utilization in Alberta

The use of FASTS services is not documented in AHW statistics; therefore, current utilization patterns can only be estimated based on information gleaned from AHS Laboratory Services and the two risk assessment programs in the province. Data from the Early Risk Assessment program indicates that within the current model of ERA, FTS access is limited to 7000 women per fiscal year.[198] The ERA Program has seen a yearly increase in the number of referrals for FTS (Table S.29). Reports from the ERA program indicate that the waiting list for FTS appointments (particularly for NT) are common.[198]

Table S.29: Number of referrals for first trimester screening at the Early Risk Assessment program in Calgary by year

Year	Number of referrals for FTS	Number of completed FTS
2006 – 2007	6099	5013
2007 – 2008	8035	7013
2008 – 2009	7460	6717
2009 – 2010	8316	8000

Source: Early Prenatal Risk Assessment Program; Alberta Health Services, Calgary zone, 2010[198]

FTS = first trimester combined screening

In the first year of the ERA program, 6099 pregnant women were referred for first FTS and 5013 were screened. Since then, the numbers have increased annually with 8000 singletons screened between the period of 2009 to 2010.[198] The OSCAR program typically accommodates 17 women per Monday, Tuesday, Wednesday, and Friday. Since CLS provides access to blood collection services for FTS at all of its Patient Service Centres, approximately half of all women who have their NT appointments at ERA choose to have their blood drawn ahead of time. Thus, the phlebotomist at OSCAR currently draws four to eight blood samples per day.[198] As of 2010, approximately 75% to 90% of all pregnant women visiting ERA have their blood samples collected at any CLS Patient Service Centre in days prior to their NT appointment.[198]

The age of women accessing FTS at ERA ranged from 15 to 51 years with a mean maternal age of 31 years in 2010. The proportion of women 35 years and older who consented to FTS decreased slightly over time (Table S.30).

Table S.30: Mean maternal age of pregnant women screened with first trimester combined screening at the Early Risk Assessment program in Calgary by year

Year	Mean maternal age (yr, range)	≥ 35 yr; ≥ 40 yr
2006 – 2007	32 (15 – 49)	31%, 4.6%
2007 – 2008	31.6 (15 – 48)	29.5%, 4.0%
2008 – 2009	33.5 (15 – 52)	28.2%, 3.9%
2009 – 2010	31.3 (15 – 51)	27.5%, 4.34%

Source: Early Prenatal Risk Assessment Program; Alberta Health Services, Calgary zone, 2010[198]

yr = year(s)

A performance update of the ERA program in Calgary[199] reported that between 2002 and 2006, 9971 pregnant women were provided NT-adjusted risk values at the Nuchal Translucency Screening Clinic at the Southern Alberta Centre for Maternal Fetal Medicine; 32% were older than 35 years of age.

Table S.31 summarizes the number of first trimester serum screening tests conducted by AHS-CLS in 2010. Overall, an average of 812 first trimester screening tests per month was performed at CLS during 2010. The largest proportion of first trimester screening tests was conducted in pregnant women who were Calgary residents (96.5% of all tests); specimens from pregnant women from other zones were also analyzed but less frequently. Data provided by CLS (Ms. Heather Sereda from Calgary Laboratory Services, personal communication; January 07, 2011) indicates that with current instrumentation and no staff increase, approximately 70,000 specimens per year can be analyzed.

Table S.31: First trimester serum screening tests conducted by Alberta Health Services – Calgary Laboratory Services in 2010 by zone

	Calgary	South Zone	Central Zone	Edmonton	North	Out of Province	Total
January	782	10	21	1	0	0	814
February	713	8	16	2	2	0	741
March	903	18	8	2	0	1	932
April	729	12	4	3	2	0	750
May	731	9	18	0	1	0	759
June	733	14	12	1	0	0	760
July	752	15	17	0	0	2	786
August	765	13	14	1	0	0	793
September	801	18	9	0	0	0	828
October	836	9	14	0	0	0	859
November	833	21	11	0	0	0	865
December	828	12	14	1	0	1	856
Total	**9406**	**159**	**158**	**11**	**5**	**4**	**9743**

Source: Alberta Health Services Laboratory Services (personal communication), 2011

Table S.32 summarizes the number of second trimester serum screening tests conducted by AHS-CLS in 2010. An average of 88 second trimester screening tests per month was performed at CLS during 2010. The largest proportion of first trimester screening tests was conducted in pregnant women living in Calgary (77.8% of all tests). Data provided by CLS (Ms. Heather Sereda from

Calgary Laboratory Services, personal communication; January 07, 2011) indicates that with current instrumentation and staffing there is no issue with capacity.

Table S.32: Second trimester serum screening tests conducted by Alberta Health Services – Calgary Laboratory Services in 2010 by zone

	Calgary	South Zone	Central Zone	Edmonton	North	Out of Province	Total
January	99	17	3	0	0	0	119
February	98	15	4	0	0	0	117
March	71	18	5	0	0	0	94
April	72	11	2	0	0	0	85
May	56	17	5	0	0	1	79
June	52	13	5	0	0	0	70
July	64	9	5	0	0	0	78
August	63	23	6	1	0	0	93
September	69	15	1	0	0	0	85
October	59	17	1	0	0	0	77
November	70	15	4	0	0	0	89
December	54	16	4	0	2	0	76
Total	**827**	**186**	**45**	**1**	**2**	**1**	**1062**

Source: Alberta Health Services Laboratory Services (Ms. Heather Sereda from Calgary Laboratory Services, personal communication; January 07, 2011)

Table S.33 summarizes the number of maternal AFP screening tests conducted by AHS- CLS in 2010. The numbers in Table S.33 refer to stand alone AFP tests that were conducted during the second trimester that were not part of a panel of screening tests such as the quad test. Overall, an average of 1.58 maternal AFP stand alone screening tests per month was performed at CLS during 2010. Almost all maternal AFP stand alone screening tests were conducted for women living in Calgary (94.7% of all tests).

Table S.33: Maternal AFP screening test conducted by Alberta Health Services – Calgary Laboratory Services in 2010 by zone

	Calgary	South Zone	Central Zone	North Zone	Total
January	5	0	0	0	5
February	2	0	0	0	2
March	1	0	0	0	1
April	0	0	0	0	0
May	2	0	0	1	3
June	0	0	0	0	0
July	2	0	0	0	2
August	1	0	0	0	1
September	0	0	0	0	0
October	1	0	0	0	1
November	3	0	0	0	3
December	1	0	0	0	1
Total	**18**	**0**	**0**	**1**	**19**

Source: Alberta Health Services Laboratory Services (Ms. Heather Sereda from Calgary Laboratory Services, personal communication; January 07, 2011)

Data from AHS Edmonton Zone Laboratory Services on the number of first and second trimester prenatal serum screening tests conducted per year (Ms. Lucille Journault from University of Alberta Hospital Site Edmonton Zone Laboratory Services; December 31, 2010) indicate that on average, 11,000 second trimester prenatal serum tests per year are conducted (11,000 for DIA, hCG, AFP and uE3 each). Approximately 2800 first trimester prenatal serum tests (for PAPP-A and β-hCG each) are performed every year. First trimester prenatal screening testing has increased by more than 100% since last January. First trimester prenatal serum testing is increasingly monthly and the forecast for 2011 is more than 4000 tests per year. Edmonton Zone Laboratory Services is currently running at capacity for first trimester prenatal screening. A significant increase in workload will require more staff and equipment. The second trimester screening testing would allow an increase of 20% in utilization with existing staff. Equipment for second trimester screening testing is adequate (Ms. Lucille Journault from University of Alberta Hospital Site Edmonton Zone Laboratory Services; December 31, 2010).

The 2010-2011 volume of FTS and second trimester quad screening were estimated based on data from Calgary and Edmonton zones' laboratory services: 12,543 FTS and 12,062-second trimester quad tests were conducted per year across Alberta.

Characteristics of physicians involved in referral to FASTS services

According to the 2007 National Physician Survey (NPS) conducted by the College of Family Physicians of Canada, the Canadian Medical Association and the Royal College of Physicians and Surgeons of Canada,[206] there were approximately 60,000 registered active physicians in Canada of whom 56.3% reported that they provided care to pregnant women. In Alberta, there were approximately 6,000 physicians registered in the province in 2007, with 61.8% reporting that they provide care to pregnant women.[206]

Gynaecologists and obstetricians

Estimates from the 2007 NPS indicate that there were approximately 1600 gynaecologists/ obstetricians in Canada of which 9.3% worked in Alberta. About 79.6% of them provide cared to pregnant women.[206] The majority of gynaecologists/obstetricians in Canada (60.6%) serve urban or suburban populations in their practice. The proportion of gynaecologists/obstetricians in Canada serving in other patient care settings is low: 16.2% in small towns, 10.9% in inner cities, and 4.5% in rural or geographically isolated areas. The proportion of gynaecologists/obstetricians that could not identify the primary population they served was 7.8%.[206] In a typical week, 42.9% of gynaecologists/obstetricians have between 50 and 100 patient visits per week; whereas 20.2% have between 100 and 150 patient visits per week and 18.1% have up to 50 patient visits per week. The proportion of gynaecologists/obstetricians in Canada that have more than 150 patient visits in a week is 9.1% (9.7% did not report the number of patient visits per week).[206]

Family doctors and general practitioners

Estimates from the 2007 NPS indicate that there were about 32,000 family physicians/general practitioners in Canada of which 10.4% worked in Alberta.[206] About 61.1% of them were involved in some aspect of maternity care and 10.1% provide intrapartum care.[206]

Results of the NPS 2007 survey indicate that 52.4% of family physicians/general practitioners in Canada serve urban or suburban populations in their practice. The proportion of family physicians/general practitioners serving other patient care settings is low (i.e., 17.3% in small towns, 13.5% in rural or geographically isolated areas, and 10.6% in inner cities). The proportion of family physicians/general practitioners could not identify the primary population they served was 6.2%.[206]

In a typical week, 28.6% of family physicians/general practitioners have between 50 and 100 patient visits per week; whereas 24.9% have between 100 and 150 patient visits per week and 18.5% have more than 150 patient visits in a week. The proportion of family physicians/general practitioners having up to 50 patient visits in a week is 17.7% (10.2% did not report the number of patient visits per week).[206]

How many physicians are using the various FASTS options?

Accurate estimates on the number of physicians that currently use the various FASTS options in Canada and Alberta were not identified from the sources reviewed. Evidence from a series of surveys regarding the provision of prenatal screening programs in certain Canadian provinces[150,207-209] as well as data from the 2007 National Physician Survey[206] provide some indirect estimates of the number of physicians that are likely to offer FASTS to pregnant women.

A survey among Ontario's family physicians and obstetricians indicated that, overall, 97% of respondents were offering maternal serum screening to pregnant women in their practices (100% of the obstetricians and 95% of the family physicians) and 88% were routinely offering it to all pregnant women (90% of the obstetricians and 87% of the family physicians).[207] Of the 12% who did not offer maternal serum screening to all pregnant women, 87.2% offered it mainly to women over the age of 35 years at their due date, 84.8% offered it to women with a family history of trisomy 21 or ONTD, and 74.4% offered it to women who asked to be tested.[207]

Healthcare providers in northern and rural Ontario were less likely to offer maternal serum screening routinely than those in other regions. Fewer respondents in the northwest region (71.4%) and in rural areas (81.9%) stated that they routinely offer maternal serum screening to all pregnant women in their practices compared with respondents in other regions (84.4% to 91.5%) and urban centres (90.1%).[208]

Studies conducted among family physicians in Newfoundland and Labrador in 2003 found that overall, 86.8% of respondents were offering maternal serum screening to pregnant women in their practices. Just over half the physicians (52.2%) offered maternal serum screening to all pregnant women, 34.6% offered it to some, and 13.2% did not offer maternal serum screening at all. Physicians who offered maternal serum screening to only some women targeted those women older than 35 years (36.1%), women with a family history of trisomy 21 or ONTD (36.7%), and women who requested maternal serum screening (28.5%).[150,209]

Data on the number of Alberta physicians who refer pregnant women to FASTS services are scarce. There is some evidence that 22% of Northern Alberta physicians routinely offer prenatal screening for fetal aneuploidy to all pregnant women.[210]

System support needs for the provision of the FASTS services in Alberta

The organization of screening services has three main strands: the patient journey, the associated health service functions of service provision, and service management.[142] Delivery of services for FASTS within the healthcare system should ideally provide the resources to facilitate all key aspects of the screening program (Table S.39).

Table S.39: Key aspects of a screening program

Patient	Service provision	Service management
Identify person	Maintain population register and screening diary	Coordination of individual component and overall program
Invite person	Invitation and recall; education and information	Planning and work scheduling
Screen person	Apply screening test	Quality assurance of test process
Advise on result and future action	Interpret test and determine future action	Evaluation of screening test and quality assurance of screening process
Provide diagnostic assessment and intervention as necessary	Referral protocols; investigation, treatment and follow up	Training; staff recruitment and retention; workload implications for each activity
Provide follow up as necessary	Follow up, education and information	Information for quality assurance and service monitoring
Information provision and support to individuals	Education and counselling support; program monitoring and reporting	Clinical governance and formal performance review

Source: NHS Quality Improvement Scotland[142]

The SOGC guidelines[98] and evaluations conducted abroad[142,204] on system support characteristics for the provision of prenatal screening services recommend the creation of regional program groups to assist with the development of standards, training/certification of health providers in screening techniques such as NT in the first trimester, provision of information and counselling services for pregnant women, availability of invasive diagnostic procedures, and mechanisms of follow-up. Furthermore, it is recommended[98] that prenatal screening services are implemented with resources that support informed decision making by women and healthcare providers, timely access to screening, counselling and follow up services as well as resources for administration, training, clinical audits for local performance evaluations, and data management and surveillance.

Particularly, the implementation of first trimester combined screening in Alberta has special implications on training, technical skills and resources, and the provision of adjunct services. For example, the provision of NT involves a range of practical implementation issues that include the number of referral centres currently providing NT services, the number of certified NT sonographers in the province and adherence to guidelines.[99,205]

The TOP guidelines on NT screening in Alberta[108] recommend training for sonographers in NT screening, and the implementation of quality assurance processes. Training and image audit for NT in Canada is offered through the FMF Canada;[196] which works in close collaboration with the FMF United Kingdom to provide training and certification. The sonographers receive didactic and practical course work and submit 50 NT images and measurements before they can be certified as competent to perform NT ultrasounds.[105,207,208] More than 2000 Canadian sonographers have completed the course through FMF Canada.[98] While such certification is not mandatory for sonographers conducting NT measurements in Canada, it is recommended by the SOGC.[98]

The provision of FASTS services raises a number of issues with regard to both patient and provider education. According to the SOCG guidelines, healthcare providers and pregnant women should be aware of the screening modalities available in the province.[98] Patient counseling regarding the invasive diagnostic procedures available and possible interventions after a positive screening test are also recommended.[99]

The SOGC guidelines[98] recommend that counseling should be non-directive, should respect women's' choice to accept or to refuse any or all of the testing or options offered at any point in the

process. System supports also include the facilitation of alternative education materials and information in languages other than English for pregnant women and their families.

Another area for the provision of system supports for FASTS services includes follow-up. The provision of FASTS services is aimed at identifying pregnancies at increased-risk of aneuploidy or ONTD. The provision of FASTS services require that diagnosis services are available, in this case by amniocentesis or CVS, and that follow-up systems are in place. In the case of screening for fetal aneuploidy, pregnancy termination is one of several choices after a diagnosis. These would include, in addition, preparation for the birth of a child with special needs as well as plans for diagnosis and interventions for the condition.[8]

In conclusion, efforts to improve prenatal screening should continue to emphasize the need for improved access to all aspects of prenatal care, stress the importance of provider education and the necessity for extensive patient counseling, and reinforce the role of patient education and choice and equity in service provision.[99]

Conclusion

The social and systems demographics review has summarized the evidence from the scientific literature in Canada and from worldwide and surveillance data of congenital anomalies to address: questions about the epidemiological profile of fetal aneuploidy and ONTD, the patterns of care, utilization trends and factors affecting the provision of first and second trimester screening (FASTS) services for fetal aneuploidy and ONTD. The following key findings are highlighted:

Patterns and burden of aneuploidy and open neural tube defects

- Aneuploidy occurs when the chromosomes do not separate properly resulting in an abnormal number of chromosomes in the fetus. The most common fetal aneuploidies are trisomy 21, trisomy 18, and trisomy 13.
- Advanced maternal age is an essential risk factor for the occurrence of aneuploidy in the fetus. No lifestyle or environmental factors have been definitively reported to affect aneuploidy risk. The condition has not been attributed to any particular parental behaviour before or during pregnancy, or to other lifestyle, social, or environmental factors.
- Little has been published about the economic burden of trisomy 21 to society or families and economic analyses of the effects of trisomy 18 and trisomy 13 were not identified.
- ONTD are a group of congenital malformations in which the normal closure process of the neural tube fails. They include anencephaly, encephalocele, and spina bifida.
- The development of ONTD is linked to both genetic and environmental risk factors such as folic acid deficiency, maternal obesity, gestational diabetes, maternal folic acid and vitamin deficiency, family history of anencephaly and previous ONTD pregnancies, maternal stress, and history of epileptic seizures.
- There is scientific evidence documenting the economic impact of spina bifida, but no Canadian data was identified in this analysis. Evidence on the economic impact of anencephaly and encephalocele on the society and the family was not identified.

Prevalence of fetal aneuploidy and ONTD

- The birth prevalence of aneuploidy and ONTD in Canada vary substantially among provinces and territories.

- Period birth prevalence rates for trisomy 21 in Canada between 2001 and 2004: 14.3 cases per 10,000 births.
- Period birth prevalence rates for ONTD in Canada between 2001 and 2004: 4.6 cases per 10,000 births (anencephaly and encephalocele: one case per 10,000 births and spina bifida: 3.1 cases per 10,000 births.
- Annual prevalence rates of trisomy 21 in Alberta for the period between 2003 and 2007: 17.9 cases per 10,000 in 2003 to 16.6 cases per 10,000 of total births (live and stillbirths) in 2007.
- Annual prevalence rates of trisomy 18 in Alberta for the period between 2003 and 2007: 1.2 cases per 10,000 total births in 2003 to 3.1 cases per 10,000 total births in 2007.
- Annual prevalence rates of trisomy 13 in Alberta for the period between 2003 and 2007: 1.2 cases per 10,000 total births in 2003 and 2.5 cases per 10,000 total births in 2007.
- Annual prevalence rates of anencephaly in Alberta for the period between 2003 and 2007: 2.2 cases per 10,000 total births in 2003 to 1.4 cases per 10,000 total births in 2007.
- Annual prevalence rates of encephalocele in Alberta for the period between 2003 and 2007: 0.77 cases per 10,000 total births in 2003 to 0.6 cases per 10,000 total births in 2007.
- Annual prevalence rates of spina bifida in Alberta for the period between 2003 and 2007: 2.7 cases per 10,000 total births in 2003 to 3.3 cases per 10,000 total births in 2007.

Current patterns of care

- There are currently four main components to screening for fetal aneuploidy and ONTD defects: first trimester ultrasound (NT), first-trimester biochemistry (PAPP-A and β-hCG), second-trimester ultrasound, and second trimester biochemistry (AFP, hCG, uE3 and DIA).
- First trimester screening strategies for fetal aneuploidy and ONTD include: NT measurement alone; serum combined (double test: PAPP-A and free β-hCG), and FTS (NT, PAPP-A and free β-hCG).
- Second trimester screening options include: double test (AFP and free β-hCG); triple test (AFP, uE3 and intact hCG); quad test (AFP, uE3, free β-hCG and DIA), and ultrasonography.
- Practical approaches for risk assessment combine information and tests results completed in the first trimester with information and test results completed in the second trimester:
    - Integrated approaches: results are withheld until both first and second trimester screening tests have been obtained (i.e.; integrated prenatal screening); and
    - Sequential approaches (i.e. stepwise screening and contingency screening): intermediate results are disclosed.
- Standards of care of prenatal diagnostic techniques include the use of invasive techniques such as amniocentesis in the second trimester and CVS in the first trimester of pregnancy.

First and second trimester screening patterns of care and health system capacity

- Screening practices differ across the country and provinces rely on the self-regulation of practitioners to govern the use of prenatal screening tests with different standards of care being used.
- Prenatal screening is funded provincially and offered population-wide in Manitoba, Ontario, British Colombia, Newfoundland, Saskatchewan, and Quebec and is centrally organized—though not provincially funded—in the Maritimes by the IWK Health Centre in Nova Scotia.
- Alberta does not have a provincial screening program. FASTS services in the province are delivered through a variety of patterns of practice without unified criteria.
- There are two risk assessment programs in the province: The Edmonton Early Pregnancy Risk Assessment Program and the ERA Program in Calgary.
- All pregnant women in Alberta are offered the quad test in the second trimester. There is also the option of requesting AFP to screen for ONTD. FTS has limited availability in Edmonton. The ERA program is the only program in Alberta that screens all pregnant women regardless of age or risk.
- Data on the number of physicians in Alberta that refer their pregnant patients to FASTS services is scarce. There is some evidence that 22% of northern Alberta physicians routinely offer prenatal screening for fetal aneuploidy to all pregnant women.

Factors that affect the use, access and provision of FASTS:

- Factors that can potentially affect the performance of FASTS tests include gestational dating methods and other measurement issues, maternal weight, the presence of certain clinical conditions in the mother (IDDM), multiple pregnancies, and the use of assisted reproduction.
- Factors related to the access and use of FASTS include the level of knowledge about procedural and practical aspects of the screening tests, expectations and attitudes toward prenatal screening, psychological factors (i.e., anxiety towards screen results), socio-economic and socio-demographic factors, factors related with believes, culture and social norms, health providers attitudes towards testing and patterns of referral and characteristics of the facilities involved in the provision of FASTS services.
- Prenatal screening services should be implemented with resources that support the informed decision making by patient and healthcare providers, timely access to audited screening and diagnostic laboratory and ultrasound services; counselling and follow-up services as well as resources for administration, training, clinical audit, and data management and surveillance.

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Appendices

Appendix S.A: Data sources and synthesis methods for the Social and System Demographics Analysis

Data sources

The medical literature was searched to identify relevant articles and documents published between January 2005 and October 2010 using key health and sociological information resources including PubMed/MEDLINE and Sociological Abstracts. In addition, key textbooks on congenital abnormalities were identified and Internet searches were conducted to retrieve grey literature. Reference lists of relevant articles were also browsed to identify more studies. The search results were limited to English language publications. The date restriction was applied to ensure that the evidence collected was current and clinically relevant. The literature search was focused on articles and documents providing information on the profile (definition, etiology, pathogenesis) epidemiology (incidence and prevalence) and psychosocial impact of trisomies 13, 18, 21 and ONTD. It was also aimed at retrieving documents on the patterns of care, utilization trends and factors affecting the provision of first and second trimester screening (FASTS) of aneuploidy and ONTD in Canada but also internationally. The search strategy was further focused on retrieving systematic and other types of reviews and health technology assessment studies. In addition, evidence-based clinical practice guidelines; policy papers; government technical reports, population-based cohort studies, and population surveys were also searched for via the internet and by way of reference lists. Local data was derived from consulting Alberta Health and Wellness administrative health databases.

Literature searches

The literature search was conducted by the IHE Research Librarian for publications published between 2005 and October 1, 2010. The search was further limited to human studies and to publication types. The search was developed and carried out prior to the study selection process. In addition to the strategy outlined in Table S.A.1 (which was conducted between September 1, 2010 and October 1, 2010) reference lists of retrieved articles were reviewed for potentially relevant articles. Grey literature searches were conducted to identify literature from non-indexed sources, government documents and thesis and dissertations (i.e., AMA clinical practice guidelines, CMA infobase, National Guidelines Clearinghouse, NEOS, AMICUS, LocatorPLUS, Eureth, Alberta Health and Wellness, Health Canada, Proquest Dissertations and Theses, Google).

Electronic literature searches conducted for the SSDA yielded 821 potentially relevant references. After screening of titles and abstracts, 194 references were selected to summarize information for the SSDA.

Table S.A.1: Search strategy to identify studies for the social and system demographics analysis

Database	Edition or date searched	Search Terms ††
MEDLINE (includes in-process and non-Medline citations) OVID Licensed Resource	1 January 2005 – 1 October 2010 EPI/Social Demographics	**Results** 1 Aneuploidy/9220 2 aneuploid*.tw./13669 3 exp Neural Tube Defects/21132 4 (neural tube defect* or ancephal* or encephalocele* or spina bifida.tw. 5 ((down* or patau or edwards) adj syndrome).tw./14947 6 Down syndrome/18437 7 Trisom*.tw./14120 8 Trisomy/9843 9 Congenital abnormalities/27543 10 Chromosome Disorders/16703 11 ((congenital or chromosom* or anatomic*) adj anomal*).tw.13874 12 ((chromosom* or anatomic*) adj abnormalit*).tw./13365 13 or/1-12/127351 14 (Socio-demographic* or social demographic*).tw./6639 15 exp Health Status/77556 16 Comorbidity/ or exp Mortality/ or exp Morbidity/519613 17 exp Prognosis/758896 18 (burden adj2 (illness or disease or condition or sickness)).ti./879 19 Adaptation, psychological/60887 20 ((Psychological or psychosocial or emotional) adj2 (outcome* or effect* or burden)).tw./8804 21 (economic adj2 (outcome* or effect* or burden)).ti./1212 22 Cost of illness/13265 23 exp Health Care Costs/36099 24 exp Health Expenditures/13033 25 Quality of Life/84892 26 social support/39169 27 "Activities of Daily Living"/40875 28 Motor activity/59791 29 quality-adjusted life years/4521 30 (quality of life or quality adjusted life year* or QoL or HQRL or HRQoL or QALY or self-rated health).ti./28642 31 (wellbeing or well-being or quality adjusted survival).ti./5247 32 population surveillance/36388 33 demography/46419 34 age distribution/42581 35 exp population groups/162113 36 exp american native continental ancestry group/15066 37 (incidence or prevalence).ti./121079 38 risk factors/425197 39 Socio-economic factors/0 40 Educational status/30682 41 Income/18093 42 Poverty/21046 43 Social class/26172 44 Social conditions/7644 45 exp social environment/70497 46 Minority groups/8431 47 Cultural characteristics/10801 48 Age factors/322915 49 Age distribution/42581 50 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 49/2284760 51 13 and 50/24582

		52 exp Neural Tube Defects/co, ec, ep, eh, mo, px/7437 53 Down Syndrome/co, ec, ep, eh, mo, px/6613 54 Trisomy/co, ep, mo/28 55 Congenital Abnormalities/co, ep, eh, mo, px/5777 56 Chromosome Disorders/co, ep, eh, mo, px/207 57 52 or 53 or 54 or 55 or 56/19676 58 51 or 57/36567 59 51 or 57/36567 60 limit 59 to (english language and yr="2005 - 2010")/6854 61 limit 60 to "review articles"/870 **870 results**
	Patterns of Care	1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester).sh,ti. 2 mass screening/ or genetic testing/88560 3 prenatal diagnosis/27996 4 (screen* or diagnos* or test or tests or testing).ti./657697 5 maternal age.tw./9441 6 amniocentesis/ or chorionic villi sampling/ or ultrasonography, prenatal 7 (ultrasound* or ultrason* or sonogra*).tw./219734 8 (amniocentes* or chorionic vill* or cvs).tw./13239 9 Nuchal Translucency Measurement/542 10 nuchal translucency.tw./1314 11 (maternal serum or serum marker*).tw./9441 12 biological markers/106645 13 ((biochemical or serum or soft) adj marker*).tw./12751 14 Chorionic Gonadotropin/ or Chorionic Gonadotropin, beta Subunit,Human/26514 15 ((chorionic adj2 gonadotrop*) or hcg).tw./25804 16 PAPP A.tw./835 17 Pregnancy-Associated Plasma Protein-A/968 18 alpha-Fetoproteins/12737 19 (afp or alpha fetoprotein*).tw./14277 20 exp Estriol/5570 21 (uE3 or estriol).tw./3539 22 inhibin*.mp./6349 23 or/2-22/1075736 24 Aneuploidy/9269 25 aneuploid*.tw./13731 26 exp Neural Tube Defects/21191 27 (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw 28 ((down* or patau or edwards) adj syndrome).tw./14986 29 Down syndrome/18489 30 Trisom*.tw./14162 31 Trisomy/9857 32 congenital abnormalities/27577 33 Chromosome Disorders/16725 34 ((congenital or chromosom* or anatomic*) adj anomal*).tw.13942 35 ((chromosom* or anatomic*) adj abnormalit*).tw./13417 36 or/24-35/127689 37 1 and 23 and 36/15354 38 standard* of care.ti./1665 39 Practice Guideline/14729 40 (health services needs and demands).mp./783 41 Ethnic Groups/35980 42 exp Socioeconomic Factors/277556 43 exp Educational Status/30876 44 Income/18173 45 Poverty/21160 46 Social Conditions/7651 47 exp Social Environment/70948 48 (Socio-demographic* or social demographic*).mp./6712 49 Minority Groups/8494

		50 social support/39431 51 ((patient or population or key or important or cultural or ethic or psychological or linguistic or economic or socioeconomic or psychosocial or policy or financial or lifestyle or emotional or psychological) adj2 (disparities or factor* or barrier* or consideration* or implication* or concern* or effect* or issue* or characteristic*)).tw. 52 Cultural Characteristics/10847 53 Age Factors/324106 54 exp Psychology/52834 55 Cultural Competency/1150 56 exp Cross-Cultural Comparison/17926 57 cultural diversity/7859 58 Health services accessibility/38240 59 (barrier* adj3 (implement* or utili?ation or "use")).tw./3917 60 (access not access-port).ti./20938 61 (system* adj2 support*).tw./10970 62 exp population characteristics/1130374 63 Population Surveillance/36598 64 age distribution/42846 65 ethnic groups/35980 66 exp american native continental ancestry group/15150 67 "Patient Acceptance of Health Care"/24022 68 (implication* or issue* or adverse effect*).ti./137613 69 adverse effect*.tw./75382 70 or/38-69/1927247 71 37 and 70/2228 72 Prenatal Diagnosis/ae, hi, is, mo, px, st, sn, td, ut/1918 73 71 or 72/3956 74 limit 73 to (english language and yr="2000 - 2011")/1740 75 limit 74 to "review articles"/ **209 results**
Sociological Abstracts	2000 – September 1, 2010	(((down* or patau or edwards) NEAR syndrome) or (spina bifida) or Trisom*) or (aneuploid* or ((congenital or chromosom* or anatomic*) NEAR anomal*) or ((chromosom* or anatomic*) NEAR abnormalit*)) or (neural tube defect*) **279 results**
Clinical Practice Guidelines		
AMA Clinical Practice Guidelines http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines.html	April 8, 2010	Browsed lists of guidelines **2 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	April 8, 2010	Browsed lists of guidelines **5 results**
National Guideline Clearinghouse http://www.ngc.gov	April 7, 2010	Prenatal or antenatal or trimester or fetal or maternal or pregnancy AND Diagnosis or Screening **11 results**
NICE Guidance http://guidance.nice.org.uk	April 7, 2010	Browsed lists of guidelines **No results**

Health Regulatory Sites		
Alberta Health and Wellness http://www.health.gov.ab.ca	September 22, 2010	Browsed list of publications **7 results**
CDC – Centers for Disease Control and Prevention http://www.cdc.gov/obesity/index.html	September 22, 2010	Browsed topics list **11 results**
Aetna Clinical Policy Bulletins http://www.aetna.com/about/cov_det_policies.htm	September 22, 2010	Browsed topics list **4 results**
MHRA http://www.mhra.gov.uk/index.htm		NA
Library Catalogues		
NEOS (Cenral Alberta Library Consortium) http://www.library.ualberta.ca/catalogue	September 22, 2010	"neural tube defect*" OR Any field "down* syndrome" OR Any field "aneuploid* or trisom*" OR Any field "prenatal screening" OR Any field "prenatal diagnosis" OR Any field "(antenatal screening) or (antenatal diagnosis)" **291 results**
AMICUS http://www.nlc-bnc.ca/amicus (Command search interface)		NA
LocatorPLUS (National Library Medicine US) http://locatorplus.gov/		NA
Theses Canada Portal http://www.nlc-bnc.ca/thesescanada		NA
Proquest Dissertations and Theses Full Text Licensed Resource (Proquest Interface)	September 22, 2010	neural tube defect* or down* syndrome or aneuploid* or spina bifida) OR (trisom* or "prenatal screening" or "prenatal diagnosis" or "antenatal screening" or "antenatal diagnosis" or trimester screen or trimester screening or trimester testing or "prenatal testing") OR (amniocentes* or chorionic vill* sampling or "maternal serum" or "nuchal translucency") AND PDN(>10/4/2000) or congenital abnormalit* or chromosomal abnormalit* or congenital anomal* or chromosomal anomal* or chromosome disorder*) AND PDN(>10/4/2000) **1000 results**
Internet Search Engine		
Google http://www.google.ca	Oct 20, 2010	1. down's-syndrome OR down-syndrome 2. aneuploidy OR aneuploidies OR spina-bifida OR 3. neural-tube-defects or trisomy 4. congenital-abnormality OR congenital-abnormalities OR chromosomal-abnormality OR chromosomal-abnormalities OR congenital-anomaly OR congenital-anomalies OR chromosomal-anomaly OR chromosomal-anomalies OR chromosome-disorder OR chromosome-disorders 5. prenatal-screening OR prenatal-diagnosis OR antenatal-screening OR

		antenatal-diagnosis OR trimester-screen OR trimester-screening OR trimester-testing OR prenatal-testing 6. amniocenteses OR amniocentesis OR chorionic-villi-sampling OR chorionic-villus-sampling OR maternal-serum OR nuchal-translucency *6 separate searches **42 results**
Grey Literature Sources		
Intute http://www.intute.ac.uk/healthandlifesciences/nursing/	September 20, 2010	Browsed lists of publications under MESH headings : prenatal diagnosis, down syndrome, Amniocentesis, Chronic villi sampling, chromosome aberrations **8 relevant results**
Centre for Health Economics and Policy Analysis http://www.chepa.org	October 1, 2010	Prenatal or antenatal or trimester or amniocentesis or chorionic or maternal or downs syndrome or spina bifida or neural tube or congenital or chromosomal or chromosome or aneuploidy or nuchal **2 results**
NLH (National Library for Health) http://www.library.nhs.uk/Default. aspx	September 22, 2010	pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester OR (((down* or patau or edwards) NEAR syndrome) or (spina bifida) or Trisom*) or (aneuploid* or ((congenital or chromosom* or anatomic*) NEAR anomal*) or ((chromosom* or anatomic*) NEAR abnormalit*)) or (neural tube defect*) OR Amniocentesis or chorionic vill* sampling or maternal serum or nuchal translucency In title **12 results**
AETMIS: http://www.aetmis.gouv.qc.ca/site/ home.phtml	October 1, 2010	Browsed list of publications **2 results**
CADTH: http://www.cadth.ca	October 1, 2010	Prenatal or antenatal or trimester or amniocentesis or chorionic or maternal or downs syndrome or spina bifida or neural tube or congenital or chromosomal or chromosome or aneuploidy or nuchal **2 results**
Health Technology Assessment Unit at McGill: http://www.mcgill.ca/tau	October 1, 2010	Browsed list of publications **No results**
Institute for Clinical and Evaluative Sciences (ICES) http://www.ices.on.ca	October 1, 2010	Browsed list of publications **2 results**
EuroScan: http://www.euroscan.bham.ac.uk	October 1, 2010	Browsed list of publications **3 results**
ASERNIP-S: http://www.surgeons.org/asernip-s	October 1, 2010	Browsed list of publications **0 results**
Society of Obstetricians and Gynaecologists of Canada	October 1, 2010	Browsed list of publications **2 results**

Note: †† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word

Alberta Administrative Health Databases

The Public Health Surveillance and Environmental Health Branch of Alberta Health and Wellness provided epidemiological (morbidity and mortality) and health utilization data for fetal aneuploidy

and ONTD from Alberta administrative health databases. Data from reports published by the Alberta Congenital Anomalies Surveillance System (ACASS) were also obtained.

Data analysis and synthesis

A population health approach was used to describe the data on the patterns of fetal aneuploidy and ONTD and the FASTS options for these conditions. The overview of the social and system demographics situation around fetal aneuploidy (trisomies, 21, 18 and 13) and ONTD as well as the overview of the FASTS services and patterns of utilization and practice considered the international, national and provincial contexts. Table S.A.2 provides a description of the conditions for which the following categories of data were included as part of the socio-demographic analysis:

- Definition, clinical characteristics and comorbidities
- Risk factors
- Progression and effects
- Population dynamics (epidemiological data)

Table S.A.2: Fetal aneuploidy types and open neural tube defects considered in the social and system demographics analysis

Condition	Types
Fetal aneuploidy	Trisomy 13 (also known as Patau syndrome or Trisomy D syndrome)
	Trisomy 18 (also known as Edwards syndrome or Trisomy E)
	Trisomy 21 (also known as Down syndrome)
Open neural tube defects	Anencephaly
	Encephalocele
	Spina bifida

Table S.A.3 provides a description of the FASTS options for which the following categories of data were reported:

- History and characteristics of FASTS
- Standards of care (available options and reference standard)
- Utilization trends in Alberta and Canada
- Factors that affect access and use of the various FASTS options
- System capacity for the provision of FASTS options in Alberta.
- System support needs for the provision of FASTS options.
- Patient and population characteristics that affect the capacity of the system to provide FASTS options.

Table S.A.3: First and second trimester screening options considered in the social and system demographics analysis

Screening options	Markers
FIRST TRIMESTER (day of last menstrual period to week 13 +6 days)	
Maternal age (MA)	MA
Nuchal translucency	NT
Double test*	PAPP-A, hCG
	MA
FTS	NT
	free ß-hCG and PAPP-A
	MA
SECOND TRIMESTER (week 14 to week 27+6 days)	
MA*	MA
Dual screening	AFP, free ß-hCG
	MA
Triple screening*	AFP, uE3, intact hCG
	MA
Quad test	AFP, uE3, free ß-hCG, DIA
	MA
Ultrasonography	
FIRST AND SECOND TRIMESTER	
IPS	MA
	NT and PAPP-A
	AFP, uE3, free ß-hCG/intact hCG and DIA (quad test)
IPS without DIA	MA
	NT and PAPP-A
	AFP, uE3, intact hCG (triple test)
Serum IPS	PAPP-A
	AFP, uE3, free ß-hCG/intact hCG, DIA (quad test)
Contingent screening	MA
	NT, PAPP-A, ± free ß-hCG/total hCG
	Intermediate risk woman¶: AFP, uE3, free β-hCG/intact hCG and DIA (Quad test) or AFP, uE3, intact hCG (triple test)
Sequential screening	MA
	NT, PAPP-A, ± free ß-hCG/intact hCG
	Low risk woman#: AFP, uE3, free ß-hCG/intact hCG and DIA (quad test) or AFP, uE3, intact hCG (triple test)

AFP: Alpha-fetoprotein; DIA = dimeric inhibin A; d: day(s); FT: first trimester; FTS: first trimester combined screening; hCG: human chorionic gonadotropin; IPS: integrated prenatal screening; MA: maternal age; NT: nuchal translucency; PAPP-A: pregnancy-associated plasma protein A; ST: second trimester; uE3: unconjugated estriol

Appendix S.B: International epidemiological data for fetal aneuploidy and open neural tube defects

Fetal aneuploidy

Table S.B.1: Birth prevalence of trisomy 13, trisomy 18 and trisomy 21 from international birth defects surveillance registries; year 2006

Programme/ registry*	Population data				Trisomy 13				Trisomy 18				Trisomy 21			
					Number of cases			Rates/ 10,000	Number of cases			Rates/ 10,000	Number of cases			Rates/ 10,000
	Total LB	Total SB	Total births	Total ToP	LB	SB	ToP	Total rate	LB	SB	ToP	Total rate	LB	SB	ToP	Total rate
VBDR (Australia)	69,230	626	69,856	360	6	6	17	4.15	3	12	37	7.44	67	13	135	30.78
Australia: WABDR	28,455	208	28,663	203	0	0	7	2.44	2	4	20	9.07	25	1	49	26.17
Canada ACASS	44,659	297	44,956	72	4	4	4	2.67	3	10	9	4.89	47	13	27	19.35
Canada: BCHSR	41,673	335	42,008	NR	3	3	NR	1.43	9	10	NR	4.52	53	27	NR	19.04
Chile: RRMCSSM	12,871	88	12,959	NA	2	0	NA	1.54	1	1	NA	1.54	25	0	NA	19.29
China: CBDMN	535,584	7149	542,733	NR	0	0	NR	0.00	1	4	NR	0.09	81	13	NR	1.73
Cuba: RECUMAC	109,124	2031	111,155	980	6	1	12	1.71	4	1	17	1.98	96	1	42	12.51
Czech Republic	105,831	299	106,130	663	8	1	19	2.64	4	0	52	5.28	37	0	167	19.22
England and Wales: NCAS	294,288	1542	295,830	881	5	0	23	0.95	31	14	52	3.28	284	24	187	16.73
Finland	58,840	193	59,033	312	7	1	9	2.88	2	4	29	5.93	81	3	98	30.83
France: REMERA	47,394	477	47,871	372	0	1	18	3.97	3	1	17	4.39	33	0	118	31.54
France: Paris	26,500	250	26,750	298	2	0	9	4.11	0	1	30	11.59	17	2	106	46.73
France: Strasbourg	13,826	121	13,947	83	0	1	2	2.15	0	0	9	6.45	9	1	20	21.51
Germany: Saxony Anhalt	16,927	57	16,984	94	0	0	4	2.36	0	0	4	2.36	17	0	17	20.02
Hungary	97,496	506	98,002	257	1	1	5	0.71	3	0	14	1.73	82	0	60	14.49
Iran: TROCA	21,114	232	21,346	3	NR	NR	NR	NR	1	NR	NR	0.47	8	NR	NR	3.75
Ireland; Dublin EUROCAT	22,520	101	22,621	NA	3	1	NA	1.77	3	2	NA	2.21	51	5	NA	24.76
Israel: IBDSP	37,463	321	37,784	13	1	0	0	0.26	1	0	0	0.26	27	0	1	7.41
Italy: BDRCam	62,279	154	62,433	264	1	0	2	0.48	1	0	11	1.92	66	0	62	20.50

Italy: IMER	39,741	106	39,847	186	1	0	2	0.75	4	0	21	6.27	20	0	48	17.07
Italy: North East	41,392	115	41,507	130	1	0	4	1.20	1	0	3	0.96	43	0	24	16.14
Italy: Tuscany	30,029	86	30,115	108	1	0	7	2.66	1	0	5	1.99	13	1	37	16.94
Japan: JAOG	75,817	505	76,322	NR	9	6	NR	1.97	37	21	NR	7.60	69	3	NR	9.43
Malta: MCAR	3380	11	3891	NA	0	0	0	0.00	1	0	0	2.57	8	0	0	20.56
Mexico: RYVEMCE	19,986	307	20,293	NA	6	0	NA	2.96	4	0	NA	11.83	24	0	NA	11.83
New Zealand	59,193	370	59,563	NR	7	NR	NR	1.18	11	NR	NR	1.85	63	NR	NR	10.58
Northern Netherland: EUROCAT	18,084	90	18,174	40	0	0	1	0.55	2	3	4	4.95	16	0	11	14.86
Norway: MBRN	59,030	433	59,463	239	5	1	9	2.52	5	4	21	5.05	81	3	35	20.01
Russia: MRRCM	55,843	308	56,151	167	0	0	1	0.18	1	0	2	0.53	68	0	5	13.00
Slovak Republic	53,904	218	54,122	37	2	0	0	0.37	2	0	0	0.37	40	0	6	8.50
South America: ECLAMC	162,690	2122	164,812	NA	8	1	NA	0.55	21	9	NA	1.82	271	11	NA	17.11
Spain: ECEMC	101,614	346	101,960	NR	1	0	NR	0.10	5	1	NR	0.59	64	1	NR	6.38
Sweden	105,913	319	106,232	497	7	1	24	3.01	16	2	79	9.13	169	1	124	27.68
Ukraine: OMNI-Net	29,038	148	29,186	NR	1	0	NR	0.34	0	0	NR	0.00	43	1	NR	15.08
USA: Atlanta MACDP	55,689	474	56,163	NR	2	1	4	1.25	5	3	9	3.03	58	3	8	12.29
USA: Texas BDES (2005)	385,548	2292	387,840	162	22	4	8	0.88	52	23	20	2.45	451	13	14	12.32
USA: Utah UBDN	53,475	245	53,270	43	9	2	6	3.16	9	8	5	4.10	61	3	5	12.84
Wales: CARIS	33,628	172	33,800	158	0	0	<5	0.00	5	1	8	4.14	33	1	36	20.71
Median (IQR)								1.43				2.8				17.00
IQR								0.5, 2.6				1.7, 5.2				12.3, 20.5

Source: International Clearing House for Birth Defects Surveillance and Research annual report;[89] IQR = interquartile range; LB = live births; NA = not applicable (termination of pregnancy is not permitted); NR = not reported; SB = stillbirths; ToP = terminations of pregnancy for birth defects

*In some instances, countries have more than one birth defect surveillance database contributing to the international database, or birth defect cases are registered on a regional basis (e.g. South America). Therefore, the international epidemiological data presented here should be interpreted with caution as the prevalence rates are not necessarily reported per country but for the catchment area covered by the registry.

Table S.B.2: Birth prevalence of trisomy 13, trisomy 18 and trisomy 21 from international birth defects surveillance registries; 1997-2006

Programme/registries**	1997-2001				2002-2006				Δ		
	Total births	T13 rate	T18 rate	T21 rate	Total births	T13 rate	T18 rate	T21 rate	T13 rate	T18 rate	T21 rate
Australia: VBDR	311,791	1.95	4.71	3.4	326,886	1.71	4.14	1.75	0.24	0.57	1.65
Australia: WABDR	126,876	2.03	5.79	22.9	130,651	2.75	7.31	26.31	-0.72	-1.52	-3.41
Canada Alberta	186,930	0.13	0.06	11.37	205,458	0.7	0.62	11.52	-0.57	-0.56	-0.15
Canada: BCHSR	211,365	0.85	3.08	16.26	204,627	1.47	2.87	16.32	-0.62	0.21	-0.06
Chile: RRMCSSM	NR	0.46	3.2	15.09	65,317	0.52	5.67	23.19	-0.06	-2.47	-8.1
China: CBDMN	1,574,814	2.79	6.35	25.18	2,062,012	3.4	8.66	29.34	-0.61	-2.31	-4.16
Cuba: RECUMAC	269,593	NR	NR	NR	625,257	NR	NR	NR	NA	NA	NA
Czech Republic	453,680	1	4.72	1.63	493,651	1.68	8.18	1.18	-0.68	-3.46	0.45
England and Wales: NCAS	NR	0.65	0.93	9.3	NR	0.39	1.17	9.75	0.26	-0.24	-0.45
Finland	288,062	1.24	2.28	12.57	287,481	1.09	2.32	12.46	0.15	-0.04	0.11
France: REMERA	NR	2.73	4.22	19.36	NR	1.74	5.1	20.59	0.99	-0.88	-1.23
France: Paris	191,478	1.48	3.38	15.12	183,099	1.91	3.52	15.05	-0.43	-0.14	0.07
France: Strasbourg	68,364	0.94	2.05	18.84	68,085	0.76	1.83	19.02	0.18	0.22	-0.18
Germany: Saxony Anhalt	68,295	0.89	3.38	15.31	86,294	1.25	5.82	16.31	-0.36	-2.44	-1
Hungary	489,535	1.9	1.9	17.42	484,121	0.93	3.71	15.64	0.97	-1.81	1.78
Iran: TROCA	NR	2.36	6.78	21.52	NR	3.29	7.58	27.17	-0.93	-0.8	-5.65
Ireland; Dublin EUROCAT	104,688	0.47	0.67	9.8	115,569	0.36	0.61	7.35	0.11	0.06	2.45
Israel: IBDSP	107,578	1.47	3.55	17.55	153,922	1.42	4.06	17.25	0.05	-0.51	0.3
Italy: BDRCam	NR	0.89	2.19	14.38	NR	1.17	3.59	18.76	-0.28	-1.4	-4.38
Italy: IMER	118,338	0.93	3.55	18.76	158,836	1.76	4.85	18.45	-0.83	-1.3	0.31
Italy: North East	281,208	3.15	3.82	21.78	273,353	2.16	3.89	21.55	0.99	-0.07	0.23
Italy: Tuscany	129,743	NR	NR	NR	142,768	NR	NR	NR	NA	NA	NA
Japan: JAOG	472,208	NR	NR	2.01	399,683	0.03	0.08	2.19	NA	NA	-0.18
Malta: MCAR	21,869	0.22	0.67	12.86	19,404	0.18	0.25	12.51	0.04	0.42	0.35
Mexico: RYVEMCE	154,798	1.01	3.15	15.45	129,291	2.13	4.98	18.52	-1.12	-1.83	-3.07

New Zealand	283,638	0.52	0.33	7.68	288,243	1.06	1.01	10.49	-0.54	-0.68	-2.81
Northern Netherland: EUROCAT	100,583	0.37	1.04	10.05	96,266	0.81	1.69	14.15	-0.44	-0.65	-4.1
Norway: MBRN	296,344	0.42	1.09	11.88	289,989	0.59	1.28	10.96	-0.17	-0.19	0.92
Russia: MRRCM	45,092*	1.61	4.53	23.99	274,894	2.94	6.9	26.29	-1.33	-2.37	-2.3
Slovak Republic	280,410	NR	NR	NR	265,670	1.53	0.92	22.51	NA	NA	NA
South America: ECLAMC	832,415	0.96	2.52	16.68	981,311	1.17	1.76	15.29	-0.21	0.76	1.39
Spain: ECEMC	509,009	1.71	4.49	17.6	526,739	2.19	4.82	21.32	-0.48	-0.33	-3.72
Sweden	271,123*	0.2	0.59	10.83	504,823	0.38	0.23	13.5	-0.18	0.36	-2.67
Ukraine: OMNI-Net	50,771*	NR	NR	NR	132,575	NR	NR	NR	NA	NA	NA
USA: Atlanta MACDP	235,616	NR	NR	NR	263,359	NR	NR	NR	NA	NA	NA
USA: Texas BDES (2005)	1,565,355	1.84	6.21	3.81	1,525,859	2.19	6.54	13.4	-0.35	-0.33	-9.59
USA: Utah UBDN	142,188*	3.81	9.28	36.56	255,878	4.64	13.6	42.27	-0.83	-4.32	-5.71
Wales: CARIS	128,106*	0.32	0.32	9.59	160,771	0.38	0.64	10.01	-0.06	-0.32	-0.42
Median		0.98	3.17	15.1		1.3	3.6	15.9	-0.3	-0.5	-0.4
IQR		0.5, 1.8	1.0, 4.5	10, 18.7		0.7, 2	1.2, 5.5	11.7, 21.1	-0.6, 0	-1.5, -0.06	-3.4, 0.3

Source: International Clearing House for Birth Defects Surveillance and Research annual report;[89] *Data include less than 5 years; birth prevalence rates: (live births + stillbirths + termination of pregnancy) per 10,000. IQR = interquartile range; NA = not available; NR = not reported; T13 = trisomy 13; T18 = trisomy 18; T21 = trisomy 21

**In some instances, countries have more than one birth defect surveillance database contributing to the international database, or birth defect cases are registered on a regional basis (e.g. South America). Therefore, the international epidemiological data presented here should be interpreted with caution as the prevalence rates are not necessarily reported per country but for the catchment area covered by the registry.

Table S.B.3: Birth prevalence of trisomy 21, trisomy 18, and trisomy 13 in the European Union (2004-2008)

Chromosomal abnormality	Number of cases (n)			Rates per 10,000		
	LB	FD	ToP	LB rate	LB + FD rate	Total rate
Trisomy 13	195	30	612	0.35	0.40	1.49
Trisomy 18	434	160	1571	0.77	1.06	3.85
Trisomy 21	5310	153	4704	9.48	9.71	18.06

Source: EUROCAT, 2010;[86] LB = live births; FD = fetal deaths; include stillbirths and spontaneous abortions from 20 weeks gestation; ToP = termination of pregnancy for fetal anomaly following prenatal diagnosis; birth prevalence rates: (live births + fetal deaths + termination of pregnancy) per 10,000

Table S.B.4: International birth prevalence of trisomy 13, trisomy 18 and trisomy 21 (2004-2008)

		Trisomy 13				Trisomy 18				Trisomy 21			
Year	Total births	LB	FD	ToP	Rate	LB	FD	ToPFA	Rate	LB	FD	ToPFA	Rate
2004	1328748	37	4	133	1.31	101	30	362	3.71	1321	38	1142	18.82
2005	1152218	44	6	99	1.29	89	42	305	3.78	1168	31	897	18.19
2006	1217008	40	7	145	1.58	92	28	319	3.61	1086	26	1060	17.85
2007	1220060	47	9	131	1.53	93	31	355	3.96	1078	31	972	17.06
2008	710726	27	4	104	1.90	59	29	230	4.47	657	27	633	18.53
Total	5628760	195	30	612	1.49	434	160	1571	3.85	5310	153	4704	18.06

Source: EUROCAT, 2010;[86] LB = live births; FD = fetal deaths; include stillbirths and spontaneous abortions from 20 weeks gestation; ToP = termination of pregnancy for fetal anomaly following prenatal diagnosis; birth prevalence rates: (live births + fetal deaths + termination of pregnancy) per 10,000

Open neural tube defects

Table S.B.5: Birth prevalence of anencephaly, encephalocele and spina bifida from international birth defects surveillance registries; year 2006

Programme/ registry*	Population data				Ancencephaly				Encephalocele				Spina bifida			
					Number of cases			Rates/ 10,000	Number of cases			Rates/ 10,000	Number of cases			Rates/ 10,000
	Total LB	Total SB	Total births	Total ToP	LB	SB	ToP	Total rate	LB	SB	ToP	Total rate	LB	SB	ToP	Total rate
Australia: VBDR	69,230	626	69,856	360	3	5	32	5.73	4	1	3	1.15	13	16	13	6.01
Australia: WABDR	28,455	208	28,663	203	0	0	12	4.19	1	0	2	1.05	4	1	16	7.33
Canada Alberta	44,659	297	44,956	72	1	6	2	2.00	2	0	0	0.44	16	9	1	5.78
Canada: BCHSR	41,673	335	42,008	NR	0	4	NR	0.95	0	0	NR	0.00	6	4	NR	2.38
Chile: RRMCSSM	12,871	88	12,959	NA	1	1	NA	1.54	0	2	NR	1.54	1	0	NA	0.77
China: CBDMN	535,584	7149	542,733	NR	14	106	NR	2.21	29	49	NR	1.44	91	181	NR	5.01
Cuba: RECUMAC	109,124	2031	111,155	980	0	0	70	6.30	3	0	27	2.70	8	0	32	3.60
Czech Republic	105,831	299	106,130	663	3	0	22	2.36	9	0	11	1.88	1	0	37	3.58
England and Wales: NCAS	294,288	1542	295,830	881	5	5	82	3.11	2	2	20	0.81	30	1	45	2.57
Finland	58,840	193	59,033	312	0	1	15	2.71	1	0	14	2.54	7	1	15	3.90
France: REMERA	47,394	477	47,871	372	1	0	15	3.34	1	0	2	0.63	7	2	38	9.82
France: Paris	26,500	250	26,750	298	0	0	8	2.99	1	2	4	2.62	4	0	8	4.49
France: Strasbourg	13,826	121	13,947	83	0	0	3	2.15	0	0	2	1.43	0	0	9	6.45
Germany: Saxony Anhalt	16,927	57	16,984	94	0	0	1	0.59	0	0	0	0.00	5	0	6	6.48
Hungary	97,496	506	98,002	257	3	0	10	1.33	1	0	0	0.10	18	0	16	3.47
Iran: TROCA	21,114	232	21,346	3	6	1	NR	3.28	NR	5	2	3.28	1	NR	NR	0.47
Ireland; Dublin EUROCAT	22,520	101	22,621	NA	4	3	NA	3.09	0	0	NA	0.00	3	0	NA	1.33
Israel: IBDSP	37,463	321	37,784	13	4	0	1	1.32	2	0	0	0.53	6	0	1	1.85
Italy: BDRCam	62,279	154	62,433	264	1	0	21	3.52	0	0	2	0.32	12	0	13	4.00

Italy: IMER	39,741	106	39,847	186	0	1	5	1.51	0	0	1	0.25	2	1	8	2.76
Italy: North East	41,392	115	41,507	130	1	1	3	1.20	0	0	1	0.24	4	0	4	1.93
Italy: Tuscany	30,029	86	30,115	108	1	1	9	3.65	1	0	0	0.33	1	0	1	0.66
Japan: JAOG	75,817	505	76,322	NR	2	2	NR	0.52	3	1	NR	0.52	36	1	NR	4.85
Malta: MCAR	3,380	11	3,891	NA	0	0	0	0.00	1	0	0	2.57	3	0	0	7.71
Mexico: RYVEMCE	19,986	307	20,293	NA	2	10	NA	5.91	3	0	NA	1.48	15	1	NA	7.88
New Zealand	59,193	370	59,563	NR	6	NR	NR	1.01	0	NR	NR	0.00	13	NR	NR	2.18
Northern Netherland: EUROCAT	18,084	90	18,174	40	0	0	3	1.65	0	0	1	0.55	5	2	1	4.40
Norway: MBRN	59,030	433	59,463	239	0	1	20	3.53	5	0	2	1.18	11	0	18	4.88
Russia: MRRCM	55,843	308	56,151	167	0	1	20	3.74	1	1	3	0.89	11	0	4	2.67
Slovak Republic	53,904	218	54,122	37	0	0	5	0.92	2	0	1	0.55	8	0	3	2.03
South America: ECLAMC	162,690	2122	164,812	NA	35	29	NA	3.88	31	9	NA	2.43	128	8	NA	8.25
Spain: ECEMC	101,614	346	101,960	NR	0	1	NR	0.10	1	0	NR	0.10	9	0	NR	0.88
Sweden	105,913	319	106,232	497	5	0	37	3.95	2	0	10	1.13	18	0	26	4.14
Ukraine: OMNI-Net	29,038	148	29,186	NR	0	2	19	7.20	1	1	4	2.06	8	3	19	10.28
USA: Atlanta MACDP	55,689	474	56,163	NR	2	1	4	1.25	0	0	0	0.00	13	0	5	3.20
USA: Texas BDES (2005)	385,548	2292	387,840	162	27	28	31	2.22	22	1	7	0.77	126	6	8	3.61
USA: Utah UBDN	53,475	245	53,270	43	3	3	8	2.61	3	2	0	0.93	18	3	2	4.28
Wales: CARIS	33,628	172	33,800	158	0	0	15	4.44	1	0	5	1.78	6	0	21	7.99

Source: International Clearing House for Birth Defects Surveillance and Research annual report;[89] IQR = interquartile range; LB = live births; NA = not applicable (termination of pregnancy is not permitted); NR = not reported; SB = stillbirths; ToP = terminations of pregnancy for birth defects.

*In some instances, countries have more than one birth defect surveillance database contributing to the international database, or birth defect cases are registered on a regional basis (e.g. South America). Therefore, the international epidemiological data presented here should be interpreted with caution as the prevalence rates are not necessarily reported per country but for the catchment area covered by the registry.

Table S.B.6: Birth prevalence of anencephaly, encephalocele and spina bifida from international birth defects surveillance registries; 1997-2006

Programme/ registries**	1997-2001				2002-2006				Δ		
	Total births	Ane. rate	Enc. rate	SB rate	Total births	Ane. rate	Enc.rate	SB rate	Ane.	Enc.	SB
Australia: VBDR	311,791	5.61	1.73	7.25	326,886	5.84	1.41	6.24	-0.23	0.32	1.01
Australia: WABDR	126,876	6.78	1.42	6.70	130,651	5.43	1.22	7.50	1.35	0.2	-0.8
Canada Alberta	186,930	3.10	1.23	3.64	205,458	2.29	1.31	3.65	0.81	-0.08	-0.01
Canada: BCHSR	211,365	1.70	0.52	4.64	204,627	1.47	0.44	3.13	0.23	0.08	1.51
Chile: RRMCSSM	NR	NR	NR	NR	65,317	2.76	1.22	2.60	NR	NR	NR
China: CBDMN	1,574,814	4.73	1.78	7.48	2,062,012	2.89	1.50	5.75	1.84	0.28	1.73
Cuba: RECUMAC	269,593	0.07	0.22	1.78	625,257	4.81	1.17	4.83	NA	NA	NA
Czech Republic	453,680	3.04	0.88	4.01	493,651	2.53	1.42	3.73	0.51	-0.54	0.28
England and Wales: NCAS	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Finland	288,062	3.23	1.56	4.86	287,481	2.92	2.16	4.49	0.31	-0.6	0.37
France: REMERA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
France: Paris	191,478	5.48	2.14	4.95	183,099	6.17	2.02	4.48	-0.69	0.12	0.47
France: Strasbourg	68,364	4.24	1.90	7.02	68,085	5.58	1.18	5.73	-1.34	0.72	1.29
Germany: Saxony Anhalt	68,295	1.76	2.49	6.30	86,294	2.67	1.16	6.14	-0.91	1.33	0.16
Hungary	489,535	1.84	0.63	3.29	484,121	1.55	0.45	3.10	0.29	0.18	0.19
Iran: TROCA	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ireland; Dublin EUROCAT	104,688	3.44	1.62	5.06	115,569	2.77	0.95	3.20	0.67	0.67	1.86
Israel: IBDSP	107,578	0.84	0.28	3.16	153,922	2.14	0.39	3.18	-1.3	-0.11	-0.02
Italy: BDRCam	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Italy: IMER	118,338	2.11	0.85	3.89	158,836	1.89	0.69	3.78	0.22	0.16	0.11
Italy: North East	281,208	1.78	0.75	3.56	273,353	1.06	0.40	2.78	0.72	0.35	0.78
Italy: Tuscany	129,743	2.31	0.62	3.47	142,768	1.68	0.42	2.52	NA	NA	NA
Japan: JAOG	472,208	4.17	0.83	0.83	399,683	5.28	0.78	0.78	NA	NA	0.05
Malta: MCAR	21,869	3.20	2.74	5.03	19,404	2.06	2.06	5.67	1.14	0.68	-0.64
Mexico: RYVEMCE	154,798	10.98	2.33	13.11	129,291	5.41	1.39	7.19	5.57	0.94	5.92

New Zealand	283,638	0.42	0.39	2.71	288,243	0.45	0.42	2.12	-0.03	-0.03	0.59
Northern Netherland: EUROCAT	100,583	2.78	0.70	5.07	96,266	1.87	0.73	4.47	0.91	-0.03	0.6
Norway: MBRN	296,344	3.17	0.64	5.13	289,989	4.86	1.28	5.14	-1.69	-0.64	-0.01
Russia: MRRCM	45,092*	3.99	0.44	7.10	274,894	3.20	0.65	3.35	0.79	-0.21	3.75
Slovak Republic	280,410	0.68	1.21	3.46	265,670	0.72	0.90	2.75	NA	NA	NA
South America: ECLAMC	832,415	7.03	2.86	10.56	981,311	6.08	2.77	9.54	0.95	0.09	1.02
Spain: ECEMC	509,009	0.37	0.20	1.91	526,739	0.15	0.21	1.08	0.22	-0.01	0.83
Sweden	271,123*	3.47	1.00	5.09	504,823	3.82	1.09	4.22	-0.35	-0.09	0.87
Ukraine: OMNI-Net	50,771*	8.47	2.36	9.85	132,575	8.75	2.04	11.54	NA	NA	NA
USA: Atlanta MACDP	235,616	3.40	1.53	3.95	263,359	1.75	1.14	3.80	NA	NA	NA
USA: Texas BDES (2005)	1,565,355	3.03	1.00	4.01	1,525,859	2.42	0.75	3.62	0.61	0.25	0.39
USA: Utah UBDN	142,188*	2.18	0.91	3.31	255,878	2.31	0.94	4.34	-0.13	-0.03	-1.03
Wales: CARIS	128,106*	7.26	2.34	8.74	160,771	6.10	1.80	7.22	1.16	0.54	1.52
Median		3.1	1	4.8		2.7	1.1	4.0	0.3	0.1	0.5
IQR		1.8, 4.2	0.6, 1.7	3.4, 6.7		1.8, 5.1	0.7, 1.4	3.1, 5.7	-0.18, 0.8	-0.05, 0.03	0.09, 1.08

Source: International Clearing House for Birth Defects Surveillance and Research annual report;[89] *Data include less than 5 years; Birth prevalence rates: (live births + stillbirths + termination of pregnancy) per 10,000. Ane = anencephaly; Enc = encephalocele; IQR = interquartile range; NA = not available; NR = not reported; SB = spina bifida

**In some instances, countries have more than one birth defect surveillance database contributing to the international database, or birth defect cases are registered on a regional basis (e.g. South America). Therefore, the international epidemiological data presented here should be interpreted with caution as the prevalence rates are not necessarily reported per country but for the catchment area covered by the registry.

Table S.B.7: Birth prevalence of anencephaly, encephalocele and spina bifida in the European Union (2004-2008)

	Number of cases (n)			Rates per 10,000		
	LB	FD	ToP	LB rate	LB + FD rate	Total rate
Anencephaly	186	117	1223	0.33	0.54	2.71
Encephalocele	212	20	359	0.38	0.41	1.05
Spina bifida	1265	66	1203	2.26	2.36	4.50

Source: EUROCAT, 2010;[86] LB = live births; FD = fetal deaths; include stillbirths and spontaneous abortions from 20 weeks gestation; ToP = termination of pregnancy for fetal anomaly following prenatal diagnosis; birth prevalence rates: (LB + FD + ToPFA) per 10,000

Table S.B.8: International birth prevalence of anencephaly, encephalocele and spina bifida 2004-2008

Year	Total births	Anencephaly				Encephalocele				Spina bifida			
		LB	FD	ToPFA	Rate	LB	FD	ToP	Rate	LB	FD	ToPFA	Rate
2004	1328748	51	27	279	2.69	59	5	77	1.06	319	23	268	4.59
2005	1152218	43	31	256	2.86	40	5	62	0.93	292	10	228	4.6
2006	1217008	41	24	258	2.65	44	4	67	0.94	281	16	265	4.62
2007	1220060	29	24	239	2.39	54	3	99	1.28	258	14	278	4.51
2008	710726	22	11	191	3.15	15	3	54	1.01	115	3	164	3.97
Total	**5628760**	**186**	**117**	**1223**	**2.71**	**212**	**20**	**359**	**1.05**	**1265**	**66**	**1203**	**4.50**

Source: EUROCAT, 2010;[86] LB = live births; FD = fetal deaths; include stillbirths and spontaneous abortions from 20 weeks gestation; ToP = termination of pregnancy for fetal anomaly following prenatal diagnosis; birth prevalence rates: (LB + FD + ToPFA) per 10,000

Results

1 Aneuploidy/9220
2 aneuploid*.tw./13669
3 exp Neural Tube Defects/21132
4 (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw./10014
5 ((down* or patau or edwards) adj syndrome).tw./14947
6 Down syndrome/18437
7 Trisom*.tw./14120
8 Trisomy/9843
9 Congenital abnormalities/27543
10 Chromosome Disorders/16703
11 ((congenital or chromosom* or anatomic*) adj anomal*).tw./13874
12 ((chromosom* or anatomic*) adj abnormalit*).tw./13365
13 or/1-12/127351
14 (Socio-demographic* or social demographic*).tw./6639
15 exp Health Status/77556
16 Comorbidity/ or exp Mortality/ or exp Morbidity/519613
17 exp Prognosis/758896
18 (burden adj2 (illness or disease or condition or sickness)).ti./879
19 Adaptation, psychological/60887
20 ((Psychological or psychosocial or emotional) adj2 (outcome* or effect* or burden)).tw./8804
21 (economic adj2 (outcome* or effect* or burden)).ti./1212
22 Cost of illness/13265
23 exp Health Care Costs/36099
24 exp Health Expenditures/13033
25 Quality of Life/84892
26 social support/39169
27 "Activities of Daily Living"/40875
28 Motor activity/59791
29 quality-adjusted life years/4521
30 (quality of life or quality adjusted life year* or QoL or HQRL or HRQoL or QALY or self-rated health).ti./28642
31 (wellbeing or well-being or quality adjusted survival).ti./5247
32 population surveillance/36388
33 demography/46419
34 age distribution/42581
35 exp population groups/162113
36 exp american native continental ancestry group/15066
37 (incidence or prevalence).ti./121079
38 risk factors/425197
39 Socio-economic factors/0
40 Educational status/30682
41 Income/18093
42 Poverty/21046
43 Social class/26172
44 Social conditions/7644

45 exp social environment/70497
46 Minority groups/8431
47 Cultural characteristics/10801
48 Age factors/322915
49 Age distribution/42581
50 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49/2284760
51 13 and 50/24582
52 exp Neural Tube Defects/co, ec, ep, eh, mo, px/7437
53 Down Syndrome/co, ec, ep, eh, mo, px/6613
54 Trisomy/co, ep, mo/28
55 Congenital Abnormalities/co, ep, eh, mo, px/5777
56 Chromosome Disorders/co, ep, eh, mo, px/207
57 52 or 53 or 54 or 55 or 56/19676
58 51 or 57/36567
59 51 or 57/36567
60 limit 59 to (english language and yr="2005 - 2010")/6854
61 limit 60 to "review articles"/870
870 Results

1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester).sh,ti.
2 mass screening/ or genetic testing/88560
3 prenatal diagnosis/27996
4 (screen* or diagnos* or test or tests or testing).ti./657697
5 maternal age.tw./9441
6 amniocentesis/ or chorionic villi sampling/ or ultrasonography, prenatal/27663
7 (ultrasound* or ultrason* or sonogra*).tw./219734
8 (amniocentes* or chorionic vill* or cvs).tw./13239
9 Nuchal Translucency Measurement/542
10 nuchal translucency.tw./1314
11 (maternal serum or serum marker*).tw./9441
12 biological markers/106645
13 ((biochemical or serum or soft) adj marker*).tw./12751
14 Chorionic Gonadotropin/ or Chorionic Gonadotropin, beta Subunit,Human/26514
15 ((chorionic adj2 gonadotrop*) or hcg).tw./25804
16 PAPP A.tw./835
17 Pregnancy-Associated Plasma Protein-A/968
18 alpha-Fetoproteins/12737
19 (afp or alpha fetoprotein*).tw./14277
20 exp Estriol/5570
21 (uE3 or estriol).tw./3539
22 inhibin*.mp./6349
23 or/2-22/1075736
24 Aneuploidy/9269
25 aneuploid*.tw./13731
26 exp Neural Tube Defects/21191
27 (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw./10043
28 ((down* or patau or edwards) adj syndrome).tw./14986
29 Down syndrome/18489
30 Trisom*.tw./14162
31 Trisomy/9857
32 congenital abnormalities/27577
33 Chromosome Disorders/16725
34 ((congenital or chromosom* or anatomic*) adj anomal*).tw./13942
35 ((chromosom* or anatomic*) adj abnormalit*).tw./13417
36 or/24-35/127689
37 1 and 23 and 36/15354
38 standard* of care.ti./1665
39 Practice Guideline/14729
40 (health services needs and demands).mp./783
41 Ethnic Groups/35980
42 exp Socioeconomic Factors/277556
43 exp Educational Status/30876
44 Income/18173

45 Poverty/21160
46 Social Conditions/7651
47 exp Social Environment/70948
48 (Socio-demographic* or social demographic*).mp./6712
49 Minority Groups/8494
50 social support/39431
51 ((patient or population or key or important or cultural or ethnic or psychological or linguistic or economic or socioeconomic or psychosocial or policy or financial or lifestyle or emotional or psychological) adj2 (disparities or factor* or barrier* or consideration* or implication* or concern* or effect* or issue* or characteristic*)).tw.
52 Cultural Characteristics/10847
53 Age Factors/324106
54 exp Psychology/52834
55 Cultural Competency/1150
56 exp Cross-Cultural Comparison/17926
57 cultural diversity/7859
58 Health services accessibility/38240
59 (barrier* adj3 (implement* or utili?ation or "use")).tw./3917
60 (access not access-port).ti./20938
61 (system* adj2 support*).tw./10970
62 exp population characteristics/1130374
63 Population Surveillance/36598
64 age distribution/42846
65 ethnic groups/35980
66 exp american native continental ancestry group/15150
67 "Patient Acceptance of Health Care"/24022
68 (implication* or issue* or adverse effect*).ti./137613
69 adverse effect*.tw./75382
70 or/38-69/1927247
71 37 and 70/2228
72 Prenatal Diagnosis/ae, hi, is, mo, px, st, sn, td, ut/1918
73 71 or 72/3956
74 limit 73 to (english language and yr="2000 - 2011")/1740
75 limit 74 to "review articles"/
209 results

SECTION TWO: TECHNOLOGY EFFECTS AND EFFECTIVENESS ANALYSIS

Ken Bond, BAH, BEd, MA, Carmen Moga, MD, MSc, Christa Harstall, MHSA

Introduction

This health technology assessment report has been produced in response to a request from Alberta Health and Wellness (AHW) as part of the Alberta Health Technologies Decision Process (AHTDP) to perform an evaluation of the scientific evidence on the performance of available first and second trimester screening tests (FASTS) for trisomy 21, 18, 13, and open neural tube defects (specifically, spina bifida, anencephaly, encephalocele, and hereafter referred to collectively as ONTDs).

Objective and Scope

To perform a systematic review and critical appraisal of the published primary and secondary research concerning the comparative efficacy, effectiveness and safety of first and second trimester screening tests for trisomy 21, 18, and 13 (Down syndrome) and open neural tube defects (spina bifida, anencephaly, encephalocele).

Research questions

The **T**echnology (**T**) section of the report attempts to address the following overall questions:

- What is the comparative efficacy, effectiveness and safety of the FASTS options for the identified conditions?

This section will address a set of more detailed questions from Alberta Health and Wellness in terms of condition, screening test, effects and effectiveness, and program context.

Effects and effectiveness

- Screening test performance (detection rates, false positive rates, positive predictive values, and positive and negative likelihood ratios):
    - What are the expected benefits of various FASTS options for affected individuals?
    - What are the potential risks, side effects (including adverse events) for affected individuals of all options?
    - Are there factors that affect the outcomes of the various options (e.g., patient characteristics, training/experience of service provider, equipment)?
    - Describe the available evidence of safety, efficacy and effectiveness with respect to key outcomes.
- What level of available evidence currently exists?
- What are the gaps in current evidence with respect to:
    - Measurement and indicators of outcomes (benefits, risks, side effects)?
    - Dependence of outcomes of specific screening procedures on:
        - Patient characteristics (e.g., age)?

- Specific training or experience of the providers?
- Other factors?

Context for provision

- What, if any, wider program of intervention is needed for the appropriate use of the technologies?
- Is there a requirement for other technologies for appropriate use of FASTS options or is there any ability to use equipment already in use for publicly funded procedures?
- What follow up or related procedures may be required for the various FASTS options?
- What are the potential effects on the related or follow-up procedures that would be required by FASTS options?

To answer these questions, the methodological approach for this study (developed a priori) included a systematic review and critical appraisal of the primary (screening accuracy studies) and secondary (i.e. systematic reviews) scientific research on the use of any of first or second trimester tests (including integrated or sequential tests that combined the use of first and second trimester screens) to assess the risk of fetal trisomy 21, 18, 13, or ONTDs for the purpose of offering further diagnostic testing. This review did not assess the use of first trimester ultrasound for determining gestational age or the use of second trimester ultrasound for a variety of other structural anomalies that can be detected at that stage using ultrasound technology. More details on the methodology and results for this systematic review are provided in Appendices T.A–T.D. Appendix T.A describes the literature search strategy and summarizes the methodological approach used for study selection, data extraction, data analysis and quality assessment. Appendix T.B lists the excluded research studies and the reasons for their exclusion. Appendix T.C provides detailed descriptions of the characteristics of the included studies, and Appendix T.D provides the results for assessment of methodological quality for individual studies. Appendix T.E contains the likelihood ratios for individual studies by test.

Background

Project scope

The scope of the **T** section of the report was defined as follows:

Population: Women in their first or second trimester of pregnancy

Intervention: Any one of the first or second trimester screening tests or two-step tests (see Table T.1 below)

Reference standard: The ideal reference standard is karyotype based on samples obtained by chorionic villi sampling or amniocentesis or on samples obtained via autopsy in the case of aborted fetuses; however, clinical examination upon birth was also used as a reference standard, especially for those pregnancies considered at low risk of fetal anomaly.

Outcome measures: The main outcomes were diagnostic performance measures including detection rate (DR), false positive rate (FPR), positive predictive value, and positive and negative likelihood ratios (LR+ and LR-).

Description of technology

Screening programs are implemented to identify people with no known signs or symptoms of a disease or condition who may be at high risk of developing the disease or condition. The assumption is that early intervention may lead to improved health outcomes, that is, they are more likely to be helped than harmed by further tests or treatments.[1] The distinguishing features of genetic screening are that it is offered to all members of a population or population subgroup rather than to individuals who have specifically sought clinical care or advice; its ability to identify the risk of heritable or genetic conditions; and the notion that it is a program comprising not only the tests themselves, but also ancillary services such as counseling and follow-up diagnostics.[2]

The specific aim of prenatal screening for aneuploidy and open neural tube defects (ONTDs) is to ascertain the risk of a pregnant woman having a fetus with trisomy 13, 18, and 21 and, in second trimester screening, an ONTD, and to determine the appropriateness of offering further genetic counselling and invasive prenatal diagnostic testing (chorionic villus sampling in the first trimester or amniocentesis in the second trimester) with which results individual women or couples can plan their families. A number of conditions are detected through prenatal screening, but the majority are trisomy 21 as open neural tube defects have a greatly reduced prevalence in Canada since the inclusion of folic acid in cereal and grain products.[3] The primary purpose of screening has been to provide women with accurate information about the fetal risk of chromosomal aneuploidy or neural tube defects that women can then use in making a decision about whether to pursue diagnosis based on their understanding of the options open to them in the event of a positive diagnosis.

Prior to the development of maternal serum screening tests, maternal age, and its associated risk of fetal trisomy and ONTD, was the main screening criterion used. This was because the risks of a fetus having trisomy 21 or ONTD when a woman was above a particular age threshold (historically 35 years of age and then increased to 40 years) were greater than the risks of potential harm to the mother and fetus (including spontaneous abortion) attributable to the use of amniocentesis. With the advent of maternal serum testing, the combinations of maternal age, ultrasonography, and maternal serum tests became accepted as providing a more accurate estimate of the risk of trisomy 21 and ONTDs than did maternal age alone. As a result, because these combinations of tests carry very low risks, it is possible to offer pregnant women, regardless of age, a non-invasive screen to assess the risk of having a fetus with trisomy 13, 18, 21, and ONTD and to consider the appropriateness of invasive diagnostic testing based on this risk assessment. The major drawback of amniocentesis is that results can take up to four weeks to become available, as late as 24 to 26 weeks gestation; too late for the complex decision-making involved with termination of pregnancy or preparation for having an affected baby. As a result, first trimester risk assessments have been developed to provide women with an earlier risk assessment. Regardless of the test used, current best practice recommends the use of a second trimester ultrasound to detect other structural anomalies and other potentially important indicators of adverse fetal health.

Positive test thresholds

Prenatal screening for chromosomal anomalies and open NTD comprises the use of multiple markers that include maternal age, biochemical markers in maternal blood or ultrasonography of the fetus during the first and/or second trimester of pregnancy to produce a single result for the risk of carrying a fetus with these conditions.[4,5] Biochemical marker screening results are expressed in terms of the multiples of the median (MoM), which is the observed value of a specific marker divided by the median value for that marker in a specified population (usually pregnancies of the same gestational age). The expected value of the MoM is 1.0. A value of 2.0 in the MoM is interpreted as

having the concentration levels as twice as high as expected.[4] The MoM is used to calculate a likelihood ratio which is then multiplied by the prevalence of the condition for the mother's age to obtain an estimate of the individual risk, expressed as 1:N, for each woman (e.g., 1:250). The positive test threshold (risk threshold at or above which women will be offered invasive diagnostic testing), or risk cut-off, is established based upon an acceptable balance between the DR and the FPR.[6] A risk estimates that falls at or above the cut-off point is not a definite indication of the presence of fetal aneuploidy or neural tube defects, rather it expresses the probability of the condition being present in the fetus at term or at mid-trimester,[8] and is suggestive of the need for diagnostic testing.[4] There is no mandated risk cut-off, but the SOGC[8] recommends that first trimester screens have a minimum DR of 75% at an FPR of 3% and that second trimester screens have a minimum DR of 75% at an FPR of 5%.

Table T.1: Screening tests considered in review

Test	Description	Conditions for which risk estimate is generated	
		Trisomies	ONTD
First trimester	Tests conducted between 7 and 13^{+6} weeks' gestation		
Nuchal translucency (NT)	ultrasound measurement	Yes	No
Double serum	PAPP-A, hCG serum tests	Yes	No
Combined	NT and PAPP-A, hCG serum test	Yes	No
Second trimester	Tests conducted between 14 and 22 weeks' gestation		
Dual serum	AFP, hCG serum tests	Yes	Yes
Triple serum	AFP, hCG, uE3 serum tests	Yes	Yes
Quadruple serum	AFP, hCG, uE3, inhibin-A serum tests	Yes	Yes
Ultrasound	Ultrasound detection of open neural tube defects	Not assessed	Yes
Two-step screens	Uses first and second trimester screens to provide sequential risk assessment and a final risk based on the combination of first and second trimester screens		
Full integrated	NT, PAPP-A + quadruple screen	Yes	Yes
Integrated – inhibin A	NT, PAPP-A + triple screen	Yes	Yes
Integrated serum	PAPP-A, hCG serum test + quadruple screen	Yes	Yes
Sequential	NT, PAPP-A + quadruple or triple screen Women are divided into high and low risk groups based on first trimester screen. High risk group offered diagnostic test and low risk group offered second trimester screen.	Yes	Yes
Contingent	NT, PAPP-A + quadruple or triple screen Women are divided into high, medium and low risk groups based on first trimester screen. High risk group offered diagnostic test and medium risk group offered second trimester screen. Low risk group not offered further testing.	Yes	Yes
Repeated measures 1	PAAP-A and uE3 measured in first and second trimester	Yes	No
Repeated measures 2	NT + PAAP-A and uE3 measured in first trimester and PAAP-A and uE3 in second trimester	Yes	No

Local/Current Context

While traditionally limited to pregnant women considered to be at "high risk", the Society of Obstetricians and Gynaecologists of Canada (SOGC) considers screening a part of general prenatal care offered to all Canadian women and recommended in its 2011 practice guideline[8] that prenatal screening be offered to all pregnant women regardless of age, disease history, or risk status. Though practices vary across Alberta with respect to the group targeted for screening, one prenatal screening program has already been implemented in southern Alberta (the Early Risk Assessment Program) with the expressed purpose of offering the first-trimester combined test to all pregnant woman regardless of age or risk (the program also receives referrals from British Columbia and Northern Alberta).[7] A maternal serum screening test (the second trimester quadruple serum test) is currently in use in Northern Alberta (www.healthlinkalberta.ca). See the section on social and system demographics for further description of the current local context of provision for prenatal screening.

Methodology

Literature search

A comprehensive literature search was conducted to identify the most recent systematic reviews and primary diagnostic accuracy studies that examined first and second trimester screening strategies. A detailed description of the literature search strategy, including sources, dates searched, and search terms used, is provided in Appendix T.A.

Selection of literature

Eligibility of key studies (i.e., systematic reviews/HTAs of RCTs) was determined according to the pre-specified inclusion/exclusion criteria outlined in Appendix T.A.

Quality assessment

Methodological quality of the included studies was appraised by two independent reviewers using the QUADAS quality appraisal tool[8] for diagnostic accuracy studies. The quality assessment tool and the quality assessment results are presented in Appendix T.C.

Data extraction

Information on the characteristics of the primary studies was extracted according to a pre-developed data extraction form (see Appendix T.A). Data extracted from each of the studies are summarized in Appendix T.D.

Data analysis and synthesis

Data extracted from the included studies were described and integrated using a narrative approach and summarized graphically in forest plots and receiver operating characteristic (ROC) curves when appropriate.

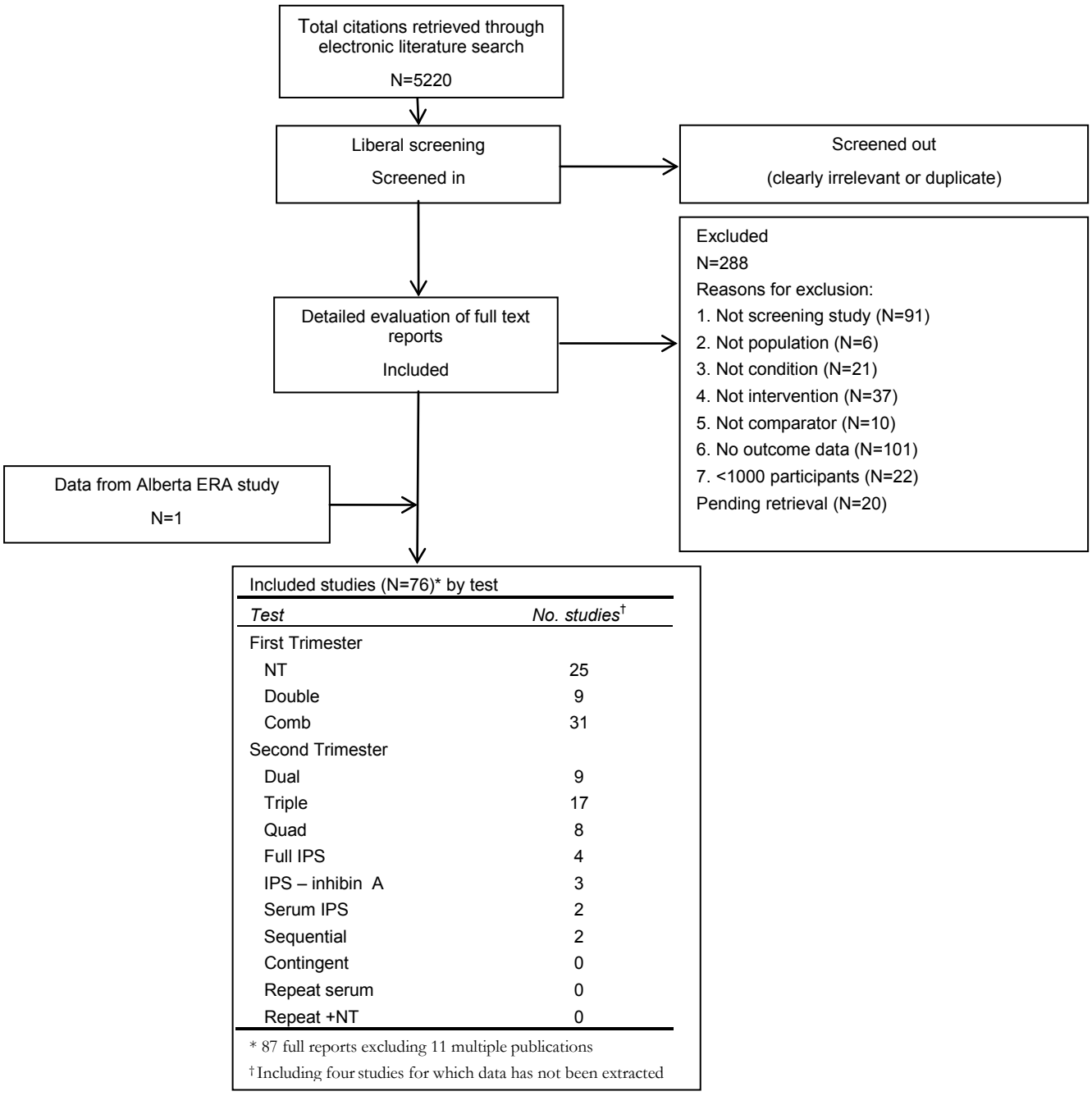
Results

Literature search and selection

The literature search for the diagnostic performance studies published between 2000 and 2010 of the 14 prenatal screening tests identified 5220 citations from electronic databases. One additional report[9] provided data on the performance of the combined test in southern Alberta. Initial broad screening identified 395 potentially relevant citations and a total 288 reports were excluded based on the detailed inclusion/exclusion criteria. Main reasons for exclusion were 1) not being primary research on screening accuracy (91 studies); 2) not containing a population of pregnant women (six studies); 3) not examining at least one of the six conditions of interest (T21, 18, 13, spina bifida, anencephaly, or encephalocele)(21 studies); 4) not examining at least one of the screening methods or tests (37 studies); 5) not using one of the established reference standards of diagnosis (10 studies); 6) not providing outcome data sufficient to calculate test accuracy (101 studies); and 7) having fewer than 1000 study subjects (22 studies). At the time of review, 20 studies had not been retrieved and evaluated for relevance and were considered pending evaluation. See Appendix T.B for the list of excluded studies with reasons for exclusion.

There were 87 reports[7,9-94] included in the review providing data from 76 unique studies. Data from four studies[91-94] that had been assessed as relevant were not extracted due to time constraints; however, their inclusion was judged unlikely to change the overall results or conclusions of the review (see Limitations). Seven primary studies[7,25,26,42,56,80,81] were each associated with a single corresponding multiple publication;[18,20,27,43,59,77,79] that is, cases in which the same study was published more than once or part of data from an original report was republished. Two studies[48,51] were each associated with two multiple publications.[36,37,89,90] The multiple publications were not considered to be unique studies and any information that they provided was included with the data reported in the main study. Either the report that was published first or that was considered most complete (in the case of the publication of a final data set) was regarded as the main study (Figure T.1).

Figure T.1: Flow diagram of literature selection for systematic review



Included studies (N=76)* by test

Test	*No. studies*†
First Trimester	
NT	25
Double	9
Comb	31
Second Trimester	
Dual	9
Triple	17
Quad	8
Full IPS	4
IPS – inhibin A	3
Serum IPS	2
Sequential	2
Contingent	0
Repeat serum	0
Repeat +NT	0

* 87 full reports excluding 11 multiple publications

† Including four studies for which data has not been extracted

Description of included studies

Publication

The 72 included unique studies for which data were analyzed were published between 2000 and 2010 (median year of publication 2005, IQR: 2002, 2007).

Study designs and timing

In terms of study timing, 62% (45/72) were prospectively designed cross-sectional diagnostic accuracy studies, 36% (26/72) were retrospective, and two studies[50,65] combined retrospectively and

prospectively collected data. In almost all studies (97%, 71/72), the populations were assembled as cohorts, e.g. as participants in a screening program. Two studies[13,30] assembled the study population using cases and controls.

Location and setting

The studies were conducted in 24 countries: Australia (five studies), Belgium (one study), Canada (four studies), Chile (one study), China (one study), Croatia (one study), Denmark (two studies), Finland (two studies), France (five studies), Germany (four studies, one of which included centres from Germany, Switzerland , and Austria), Hong Kong (two studies), Hungary (one study), Israel (two studies), Italy (one study), Japan (two studies), Netherlands (three studies), Slovenia (one study), Spain (two studies), Taiwan (five studies), Thailand (two studies), Turkey (one study), United Kingdom (13 studies), United States (10 studies, one of which is US and Canada), and Venezuela (one study). The screening programs were conducted in a variety of settings including academic/research hospitals, community hospitals, and maternity clinics.

Study population

The populations are described in detail for each test and condition in the results below and in Appendix T.C. Individual study data, rather than overall summary data, is provided regarding population and study characteristics such as maternal and gestational age at time of testing, pregnancy type, positive test threshold, and condition prevalence within the study population.

Outcomes

Most studies examined test performance in singleton pregnancies with some studies examining singleton and doubleton pregnancies combined or unselected pregnancies. No empirical studies were found that have examined the performance of contingent screening, or either of the repeated measures screening methods. Twenty studies provided information on potential accuracy modifiers: maternal age (12 studies),[10,14,26,27,33,35,38,41,57,60,73,81] gestational age (four studies),[14,39,74,80] and risk cut-off (six studies).[21,31,33,34,80,84] No studies were identified that examined the impact of ethnicity or sonographer training on test performance. No more detailed summary has been produced of the results of these studies.

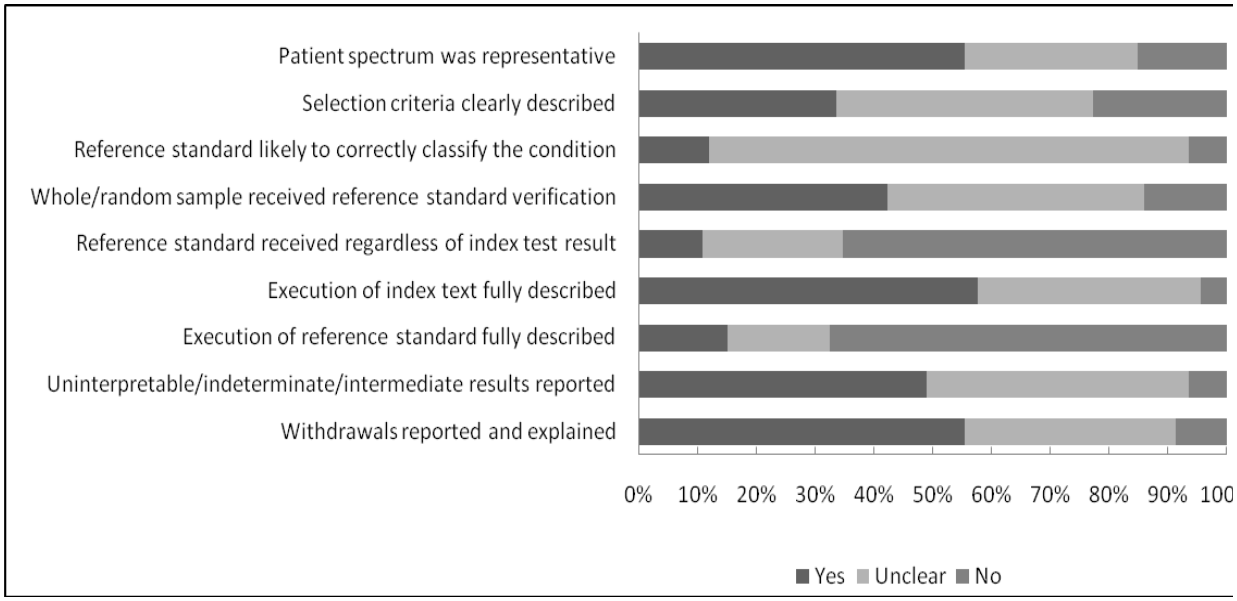
Methodological quality

Overall, the potential threats to the validity of the study results varied across studies, with all studies subject to more than one source of potential bias. The single source of bias affecting over four-fifths of the studies (86%) was the ability of the various reference standards to correctly classify the specific condition because the gold standard for diagnosis (karyotyping) was usually only applied to those in whom the screening results were positive. In general, just over half of the studies (52%) were considered to have included an adequate spectrum of patients, to have adequately described the execution of the screening test being evaluated (60%), and to have adequately described and explained any withdrawals and dropouts (52%). Fewer than half of the studies were considered to have adequately described the selection criteria for study participants (32%), to have applied the reference standard to the whole or a random sample of the study participants (45%), or to have adequately reported on uninterpretable or indeterminate results (47%). Two-thirds of the studies (67%) were considered not to have provided an adequate description of the reference standard (e.g. karyotype, physician examination, or parental contact), and over four-fifths of the studies (88%) used different reference standards according to the results of the index test.

A summary of the results of the studies by component is provided in Figure T.2. Studies indicating "yes" were considered to have been conducted in such a way that they have minimized the bias

associated with the particular domain being assessed. The methodological quality of the individual studies for each screening test is provided in Appendix T.D.

Figure T.2: Methodological quality of included studies



Results by test and condition

Test results are reported by test and condition. For each test, the visual display of the study results are ordered by detection rate in terms of decreasing performance.

First Trimester Screening Tests

Nuchal translucency (ultrasound)

Trisomy 21

Study characteristics

Twenty-three studies,[11,12,22,25,28,40,44,47,48,50,52,56,58,63,64,67,68,70,72,75,82,83,85] published between 2001 and 2009 and including a total of 171,103 pregnancies (756 T21, 170,347 no T21) provided data on the use of the nuchal translucency screen for trisomy 21 (Table T.2). All studies recruited the study participants in clinical cohorts. Fourteen studies reported results for singleton pregnancies only, three reported on unselected pregnancies, and the remaining six studies did not specify the pregnancy type. The within study prevalence of trisomy 21 ranged from 0.14 to 2.41%. A variety of positive test thresholds were used: 1:250 (six studies), 1:300 (eight studies), 1:320 (one study), percentiles based on NT measurement, e.g., > 99th percentile for gestational age (three studies), and NT measures: ≥2.5 mm (two studies) and ≥3 mm (three studies).

Table T.2: Study characteristics for nuchal translucency for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Audibert 2001[11] France	Cohort (prospective)	30.1 (mean) (16–37)	12–13	Singleton	0.29
Babbur 2005[12] United Kingdom	Cohort (prospective)	37 (19–46)	11–14	Singleton	0.78
Chasen 2003[22] USA	Cohort (retrospective)	33 (IQR: 31, 36)	11–14	Unselected	0.53
Gasiorek-Weins 2001[25] Germany, Switzerland, Austria	Cohort (prospective)	33 (15–49) 36%≥35	12 (12–14)	Singleton	0.96
Has 2006[28] Turkey	Cohort (prospective)	28.2±5.3 (mean±SD) (15–47)	11–14	ND	0.44
Lam 2002[40] Hong Kong	Cohort (prospective)	30.5 (mean)	12.4 (mean)	ND	0.23
MacRae 2008[44] United Kingdom	Cohort (retrospective)	ND	$10–13^{+6}$	ND	0.20
Michailidis 2001[47] UK	Cohort (retrospective)	30.1 (mean) (13–50)	12^{+5} (mean)	Unselected	0.31
Monni 2005[48] Italy	Cohort (retrospective)	32 (14–49)	11–14	Singleton	0.58
Muller 2003[50] France	Cohort (ambispective)*	ND	11–14	Singleton	0.46
Neimimaa 2001[52] Finland	Cohort (prospective)	17.5%≥35	10–13	ND	0.31
O'Leary 2006[56] Australia	Cohort (retrospective)	31 (14–47)	12^{+3} (8.9–14.4)	Singleton	0.27
Panburana 2001[58] Thailand	Cohort (prospective)	28.7±0.13 (mean±SD)	11.9 wk ±1.07 (mean±SD)	ND	0.08
Sau 2001[63] United Kingdom	Cohort (retrospective)	27.5±5.1 (mean±SD)	ND	ND	0.26
Schaelike 2009[64] Germany	Cohort (prospective)	3≥35 yr	$11^{+0}–13^{+6}$ wk	Singleton	0.56
Scott 2004[67] Australia	Cohort (prospective)	32 (15–44)	11–14	Singleton	0.24
Sepulveda 2007[68] Chile	Cohort (prospective)	33 (14–47) 35%≥35	12 (12–14)	Singleton	2.41
Soergel 2006[70] Germany	Cohort (prospective)	32.5 (16–44)	11–14	Singleton	0.44
Strah 2008[72] Slovenia	Cohort (retrospective)	28.6 (15–42)	12^{+4} ($10^{+5}–13^{+6}$)	Singleton	0.17
Tsai 2001[75] Taiwan	Cohort (retrospective)	ND	10–13	Singleton	0.66
Wayda 2001[82] Hungary	Cohort (prospective)	31 (16–46)	10–12	Unselected	0.25

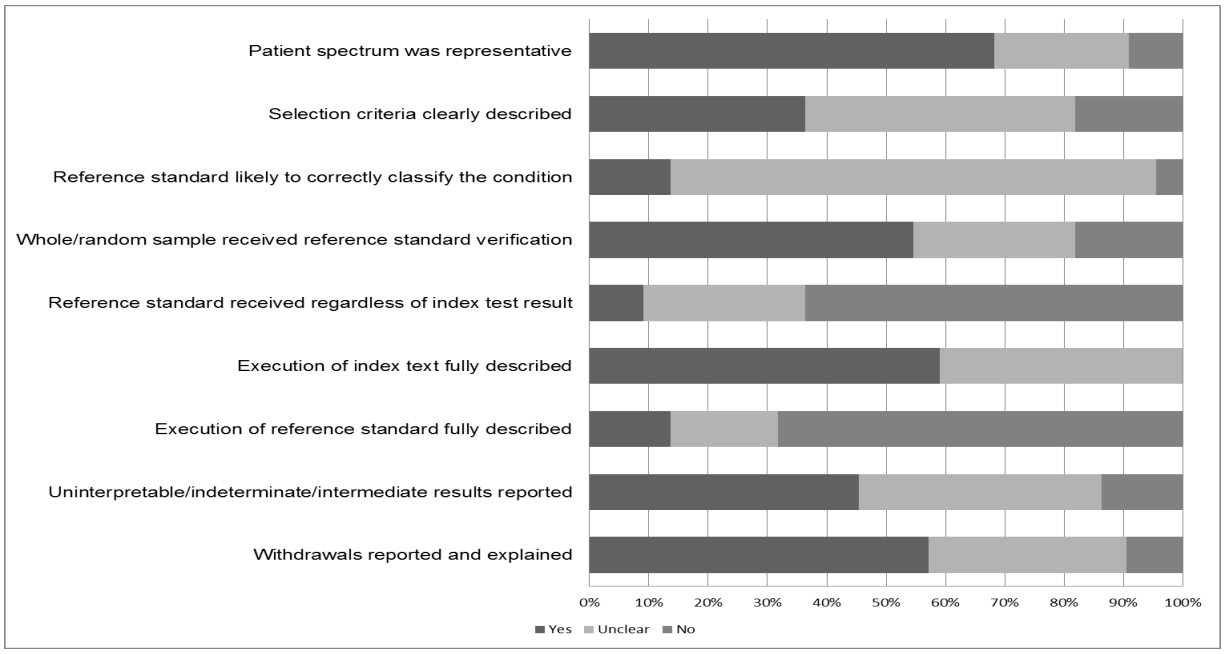
Weingertner 2006[83] France	Cohort (prospective)	32 (16–47)	12.9 (10.9–14)	Singleton	1.47
Wøjdemann 2005[85] Denmark	Cohort (prospective)	29.3 (mean) 10.8%≥35	10^{+3}–13^{+6}	Singleton	0.14

**Ambispective* refers to the combination of retrospective and prospective data

Methodological quality

Sixteen of the studies[12,22,25,28,40,47,48,50,52,56,63,64,67,68,83,85] used appropriate methods of patient enrollment and included a spectrum of patients representative of those who are likely to be seen in practice. Ten studies[11,12,28,44,47,48,56,64,67,72] provided a clear definition of both the inclusion and exclusion criteria for entry into the studies. All but three[25,72,85] of the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Twelve of the studies[11,40,47,48,58,63,64,67,70,82,83,85] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All but two[28,64] of the studies were potentially affected by differential verification bias as some of the test index results were verified by a different reference standard. Fourteen studies[12,22,25,28,50,56,64,67,68,70,75,82,83,85] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for prenatal trisomy 21 risk calculation and the cut-off level of risk for invasive testing. Four of the studies[44,64,68,75] provided a complete description of the execution of the reference standard. Eleven studies[11,22,25,40,56,64,67,70,82,83,85] accounted for intermediate/indeterminate results in the analysis of data and thirteen described withdrawals and dropouts (Figure T.3).[11,22,25,40,44,47,56,64,67,70,82,83,85]

Figure T.3: Methodological quality of nuchal translucency for trisomy 21



Quantitative results

The median DR was 75% (range: 40 to 100) and the median FPR was 5% (range: 1 to 23) (Figure T.4). The study result with the least uncertainty (Gasiorek-Weinset al.[25]) had a DR of 88% (95% CI: 82 to 92) and FPR of 14% (95% CI: 14 to 14). The PPV ranged from 1.59 to 5.52%. The LR+

ranged from 3.78 to 47.35; the LR- ranged from 0.06 to 0.45 (Appendix T.E, Table 1). The corresponding ROC curve is presented in Figure T.5. Symbols representing studies are scaled by the size of the study population (i.e. larger boxes represent larger studies).

Figure T.4: Nuchal tranlucency for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Sau 2001	7	52	0	2624	99%	1.00 [0.59, 1.00]	0.98 [0.97, 0.99]
Panburana 2001	2	63	0	2288	≥2.5 mm	1.00 [0.16, 1.00]	0.97 [0.97, 0.98]
Wayda 2001	17	292	0	6533	≥2.5 mm	1.00 [0.80, 1.00]	0.96 [0.95, 0.96]
Scott 2004	5	112	0	1936	1:300	1.00 [0.48, 1.00]	0.95 [0.93, 0.95]
Sepulveda 2007	28	82	3	1174	99%	0.90 [0.74, 0.98]	0.93 [0.92, 0.95]
Gasiorek-Wiens 2001	184	3039	26	18710	1:300	0.88 [0.82, 0.92]	0.86 [0.86, 0.86]
Michailidis 2001	20	371	3	7053	1:250	0.87 [0.66, 0.97]	0.95 [0.94, 0.95]
Weingertner 2006	26	463	4	1551	1:250	0.87 [0.69, 0.96]	0.77 [0.75, 0.79]
Chasen 2003	10	185	2	2051	1:300	0.83 [0.52, 0.98]	0.92 [0.91, 0.93]
Soergel 2006	9	128	2	2358	1:300	0.82 [0.48, 0.98]	0.95 [0.94, 0.96]
Wojdemann 2005	9	154	3	8496	1:250	0.75 [0.43, 0.95]	0.98 [0.98, 0.98]
Strah 2008	9	162	3	6922	1:300	0.75 [0.43, 0.95]	0.98 [0.97, 0.98]
Monni 2005	72	744	24	15769	99%	0.75 [0.65, 0.83]	0.95 [0.95, 0.96]
Has 2006	14	200	5	4146	1:300	0.74 [0.49, 0.91]	0.95 [0.95, 0.96]
O'Leary 2006	44	1902	16	20318	1:300	0.73 [0.60, 0.84]	0.91 [0.91, 0.92]
MacRae 2008	26	606	11	18322	1:300	0.70 [0.53, 0.84]	0.97 [0.97, 0.97]
Lam 2002	24	761	11	14457	1:320	0.69 [0.51, 0.83]	0.95 [0.95, 0.95]
Audibert 2001	8	178	4	3940	1:250	0.67 [0.35, 0.90]	0.96 [0.95, 0.96]
Babbur 2005	16	57	9	3106	≥3 mm	0.64 [0.43, 0.82]	0.98 [0.98, 0.99]
Muller 2003	16	281	10	5298	1:250	0.62 [0.41, 0.80]	0.95 [0.94, 0.96]
Niemimaa 2001	3	186	2	1411	1:250	0.60 [0.15, 0.95]	0.88 [0.87, 0.90]
Schaelike 2009 (NT)	33	546	26	10013	≥3 mm	0.56 [0.42, 0.69]	0.95 [0.94, 0.95]
Tsai 2001 (NT)	4	13	6	1491	≥3 mm	0.40 [0.12, 0.74]	0.99 [0.99, 1.00]

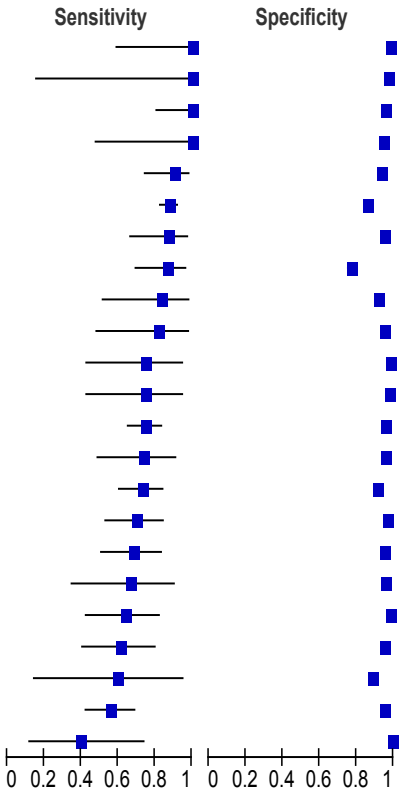
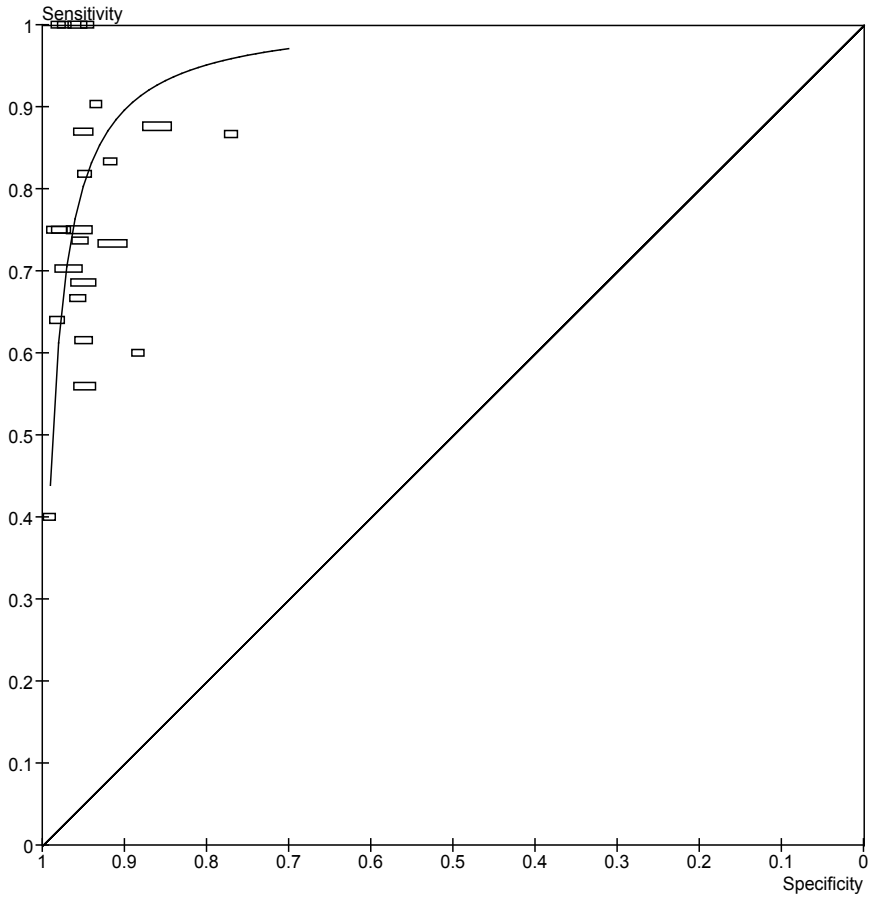


Figure T.5: ROC curve for nuchal translucency for trisomy 21



Trisomy 18

Study characteristics

Seven studies,[22,25,28,44,58,63,82] published between 2001 and 2008 and including a total of 59,414 pregnancies (145 T18, 59,269 no T18), provided data on the use of nuchal translucency to screen for trisomy 18 (Table T.3). All studies recruited the study participants in clinical cohorts. One study reported results for singleton pregnancies only, two reported on unselected pregnancies, and the remaining four studies did not specify the pregnancy type. The within study prevalence of trisomy 18 ranged from 0.03 to 0.51%. A variety of positive test thresholds were used: 1:300 (four studies), NT measurement ≥2.5 mm (two studies), and NT measurement > 95th percentile for gestational age (one study).

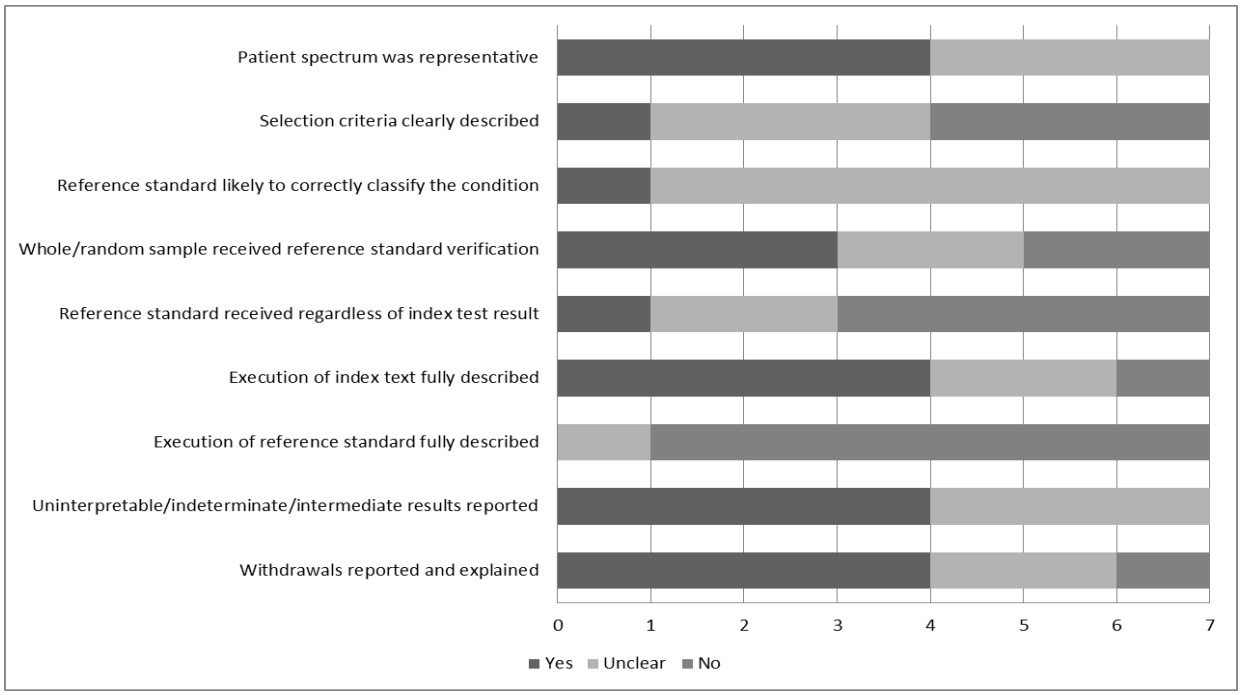
Table T.3: Study characteristics for nuchal translucency for trisomy 18

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Chasen 2003[22] USA	Cohort (retrospective)	33 (IQR: 31, 36)	11–14	Unselected	0.44
Gasiorek-Weins 2001[25] Germany, Switzerland, Austria	Cohort (prospective)	33 (15–49) 36%≥35	12 (median) 12–14	Singleton	0.51
Has 2006[28] Turkey	Cohort (prospective)	28.2±5.3 (mean±SD) 15–47	11–14	ND	0.11
MacRae 2008[44] United Kingdom	Cohort (retrospective)	ND	$10–13^{+6}$	ND	0.03
Panburana 2001[58] Thailand	Cohort (prospective)	28.7±0.13 (mean±SD)	11.9±1.07 (mean±SD)	ND	0.08
Sau 2001[63] United Kingdom	Cohort (retrospective)	27.5±5.1 (mean±SD)	ND	ND	0.11
Wayda 2001[82] Hungary	Cohort (prospective)	31 (16–46)	10–12	Unselected	0.12

Methodological quality

Four of the studies[22,25,28,63] used appropriate methods of patient enrollment and included a spectrum of patients representative of those who are likely to be seen in practice. One study[28] provided a clear definition of both the inclusion and exclusion criteria for entry into the study. All but one[25] of the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Three of the studies[58,63,82] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All but one[25] of the studies were potentially affected by differential verification bias as some of the test index results were verified by a different reference standard. None of the studies provided a complete description of the execution of the reference standard. Four studies[22,25,28,82] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for prenatal trisomy 21 risk calculation and the cut-off level of risk for invasive testing. Four studies[22,25,44,82] accounted for intermediate/indeterminate results in the analysis of data and described withdrawals and dropouts (Figure T.6).

Figure T.6: Methodological quality for nuchal translucency for trisomy 18



Quantitative results

The median DR was 90% (range: 67 to 100) and the median FPR was 4% (range: 2 to 14) (Figure T.7). The study with the least uncertainty (Gasiorek-Weins et al.[25]) had a DR of 94% (95% CI: 88 to 97) and an FPR of 14% (95% CI: 14 to 15). The PPV ranged from 0.63 to 4.62%. The LR+ ranged from 6.71 to 33.5; the LR- ranged from 0.06 to 0.34 (Appendix T.E, Table T.E.2). The corresponding ROC curve is presented in Figure T.8. Symbols representing studies are scaled by the size of the study population (i.e. larger boxes represent larger studies).

Figure T.7: Nuchal translucency for trisomy 18

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Panburana 2001	2	63	0	2288	≥2.5 mm	1.00 [0.16, 1.00]	0.97 [0.97, 0.98]
Wayda 2001	8	301	0	6532	≥2.5 mm	1.00 [0.63, 1.00]	0.96 [0.95, 0.96]
Gasiorek-Wiens 2001	105	3118	7	18729	1:300	0.94 [0.88, 0.97]	0.86 [0.85, 0.86]
Chasen 2003	9	186	1	2052	1:300	0.90 [0.55, 1.00]	0.92 [0.90, 0.93]
MacRae 2008	4	628	1	18332	1:300	0.80 [0.28, 0.99]	0.97 [0.96, 0.97]
Has 2006	4	210	1	4150	1:300	0.80 [0.28, 0.99]	0.95 [0.95, 0.96]
Sau 2001	2	57	1	2623	>95%	0.67 [0.09, 0.99]	0.98 [0.97, 0.98]

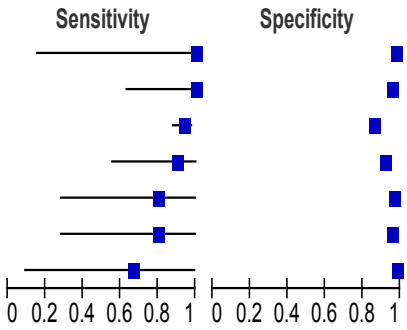
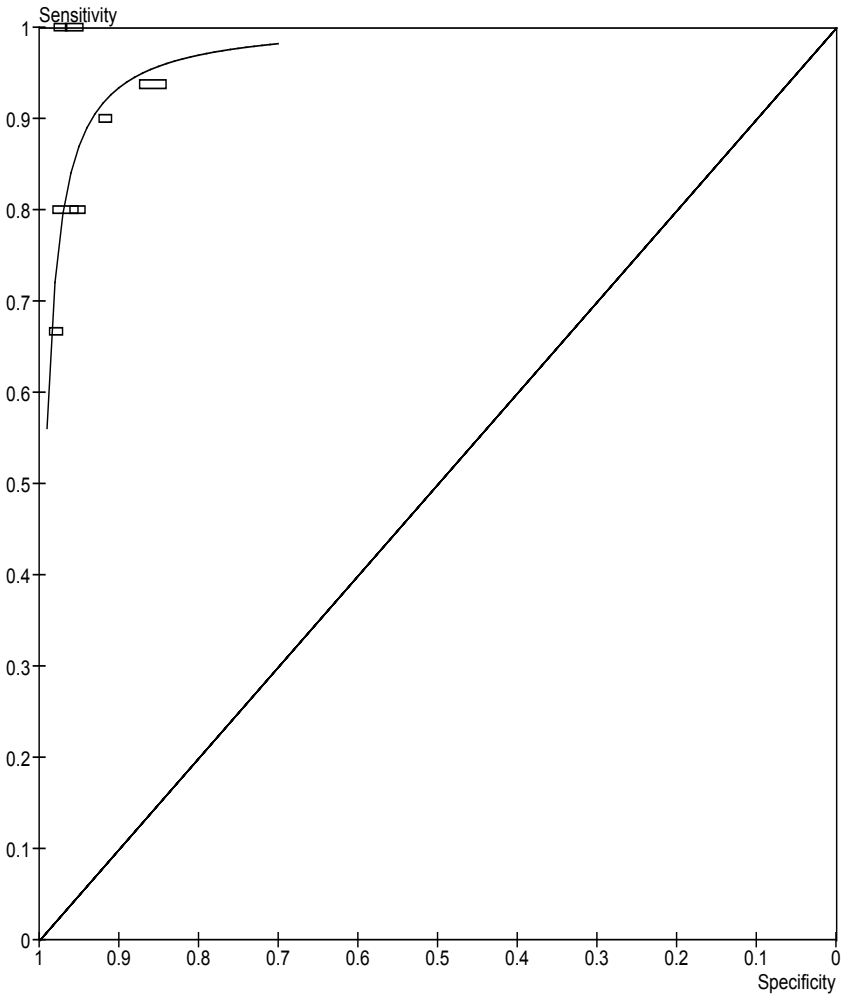


Figure T.8: ROC curve for nuchal translucency for trisomy 18



Trisomy 13

Study characteristics

Five studies,[25,44,58,63,82] four published in 2001 and one in 2008 and including a total of 52,801 pregnancies (39 T13, 52,762 no T13), provided data on the use of nuchal translucency to screen for trisomy 13 (Table T.4). All studies recruited the study participants in clinical cohorts. One study reported results for singleton pregnancies only, one reported on unselected pregnancies, and the remaining three studies did not specify the pregnancy type. The within study prevalence of trisomy 13 ranged from 0.02 to 0.13%. A variety of positive test thresholds were used: 1:300 (two studies), NT measurement ≥ 2.5 mm (two studies), and NT measurement > 95th percentile for gestational age (one study).

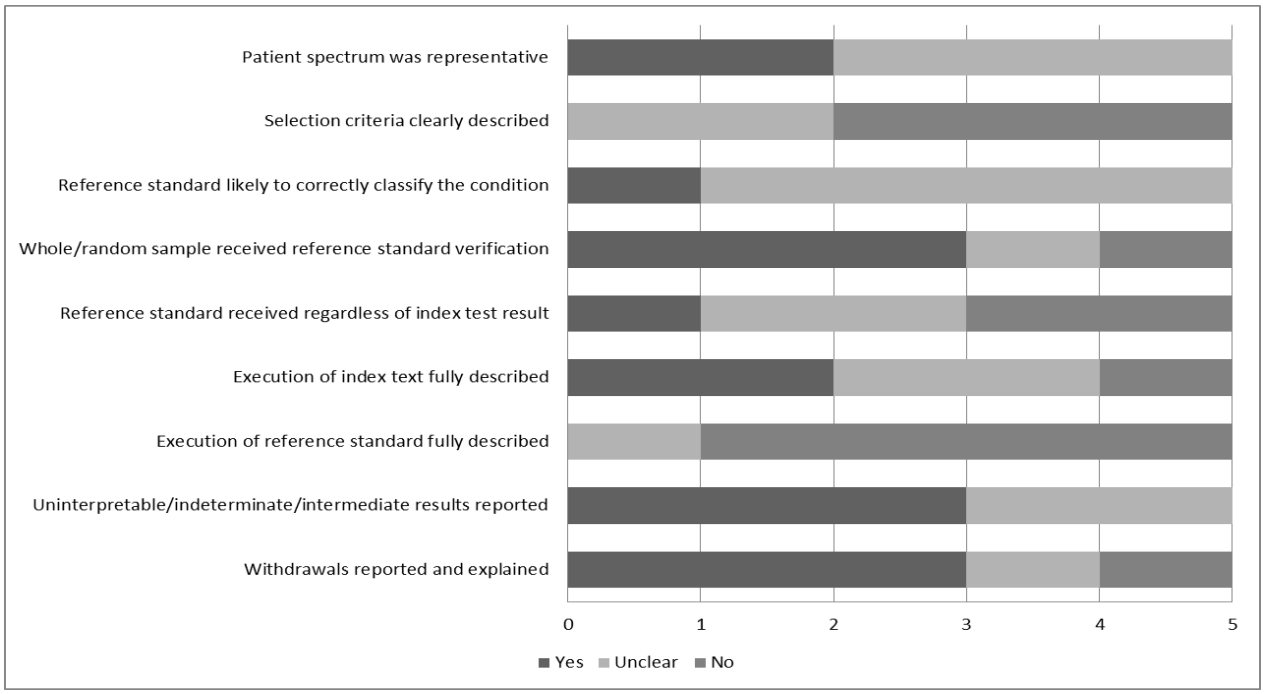
Table T.4: Study characteristics for nuchal translucency for trisomy 13

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Gasiorek-Weins 2001[25] Germany, Switzerland, Austria	Cohort (prospective)	33 (15–49) 36%≥35 yr	12 (median) 12–14	Singleton	0.13
MacRae 2008[44] United Kingdom	Cohort (retrospective)	ND	10–13+6	ND	0.02
Panburana 2001[58] Thailand	Cohort (prospective)	28.7±0.13 (mean±SD)	11.9 ±1.07 (mean±SD)	ND	0.04
Sau 2001[63] United Kingdom	Cohort (retrospective)	27.5±5.1 (mean±SD)	ND	ND	0.07
Wayda 2001[82] Hungary	Cohort (prospective)	31 (16–46)	10–12	Unselected	0.06

Methodological quality

Two of the studies[25,63] used appropriate methods of patient enrollment and included a spectrum of patients representative of those who are likely to be seen in practice. No study provided a clear definition of both the inclusion and exclusion criteria for entry into the study. All but one[25] of the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Three of the studies[58,63,82] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All but one[25] of the studies were potentially affected by differential verification bias as some of the test index results were verified by a different reference standard. Two studies[25,82] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for prenatal trisomy 21 risk calculation, and the cut-off level of risk for invasive testing. None of the studies provided a complete description of the execution of the reference standard. Three studies[25,44,82] accounted for intermediate/ indeterminate results in the analysis of data and described withdrawals and dropouts (Figure T.9).

Figure T.9: Methodological quality for nuchal translucency for trisomy 13



Quantitative results

The median DR was 97% (range: 33 to 100) and the median FPR was 3% (range: 2 to 15) (Figure T.10). The study with the least uncertainty (Gasiorek-Weins et al.[25]) had a DR of 97% (95% CI: 82 to 100) and and FPR of 15% (95% CI: 14 to 15). PPV ranged from 0.16 to 1.69%. The LR+ ranged from 6.47 to 27.37; the LR- ranged from 0.04 to 0.69 (Appendix T.E, Table T.E.3). The corresponding ROC curve is presented in Figure T.11. Symbols representing studies are scaled by the size of the study population (i.e. larger boxes represent larger studies).

Figure T.10: Nuchal translucency for trisomy 13

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Wayda 2001	4	305	0	6532	≥2.5 mm	1.00 [0.40, 1.00]	0.96 [0.95, 0.96]
Panburana 2001	1	64	0	2288	≥2.5 mm	1.00 [0.03, 1.00]	0.97 [0.97, 0.98]
Gasiorek-Wiens 2001	28	3195	1	18735	1:300	0.97 [0.82, 1.00]	0.85 [0.85, 0.86]
Sau 2001	1	58	1	2623	NT value	0.50 [0.01, 0.99]	0.98 [0.97, 0.98]
MacRae 2008	1	631	2	18331	1:300	0.33 [0.01, 0.91]	0.97 [0.96, 0.97]

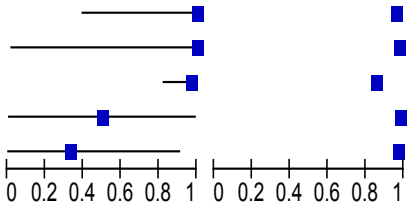
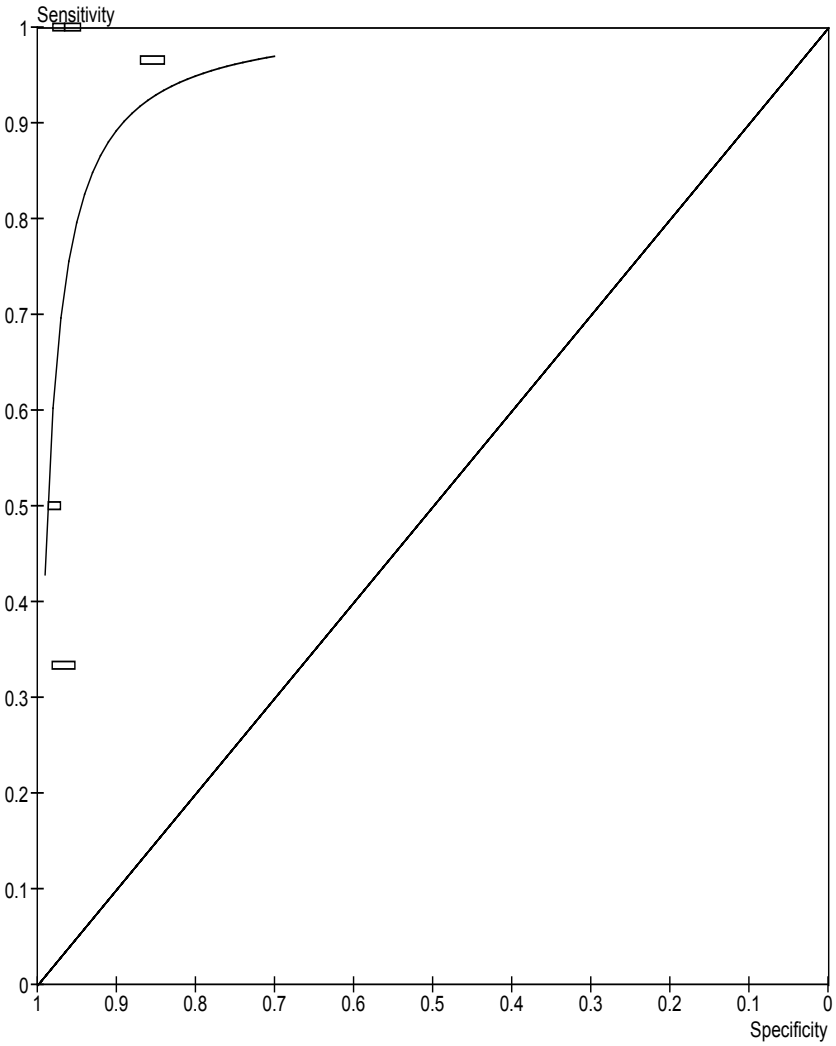


Figure T.11: ROC curve for nuchal translucency for trisomy 13



Double serum test (PAPP-A + free-β hCG)

Trisomy 21

Study characteristics

Nine studies,[27,50,52,56,64,67,70,76,85] published between 2001 and 2009 and including a total of 66,349 pregnancies (220 T21, 66,129 no T21), provided data on the use of the first trimester double serum test (PAPP-A, free-β hCG*)* for assessing the risk of fetal trisomy 21 (Table T.12). All studies recruited the study participants in clinical cohorts. Seven studies reported results for singleton pregnancies and two studies did not specify the pregnancy type. The within study prevalence of trisomy 21 ranged from 0.17 to 0.56%. Four of the seven studies used a positive test threshold of 1:250, four studies used a threshold of 1:300 and one study a threshold of 1:85.

Table T.5: Study characteristics on double test for trisomy 21

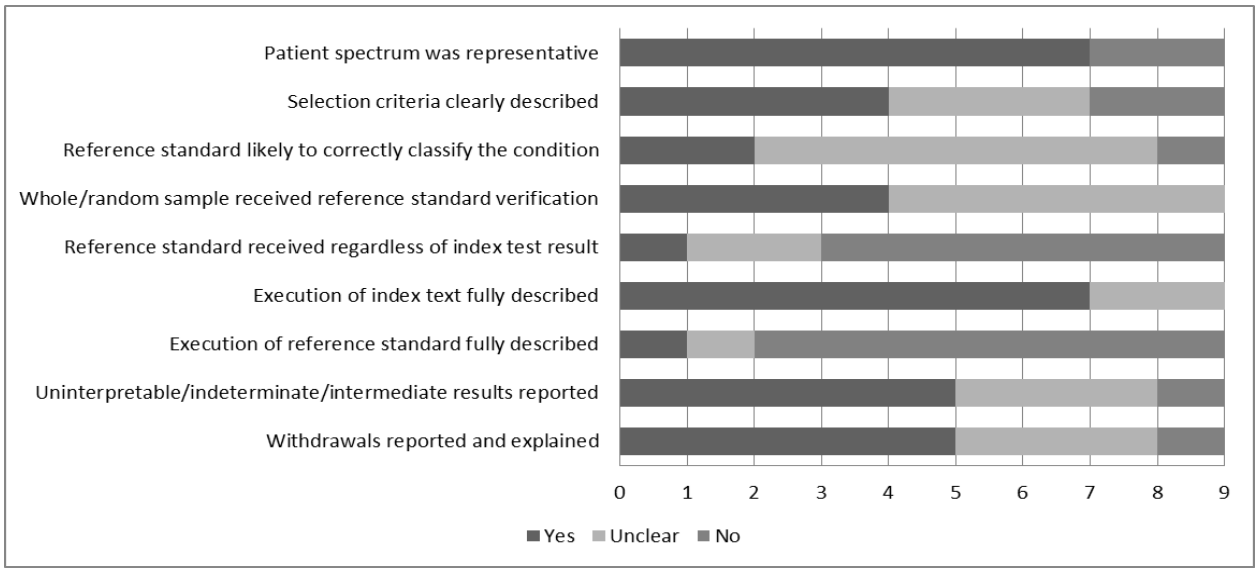
Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Gysaelers 2004[27] Belgium	Cohort (retrospective)	8.6%≥35	ND	ND	0.18
Muller 2003[50] France	Cohort (ambispective)*	ND	11–14	Singleton	0.46
Niemimaa 2001[52] Finland	Cohort (prospective)	17.5%≥35	10–13	ND	0.32
O'Leary 2006[56] Australia	Cohort (retrospective)	31 (14–47)	12^{+3} (median) (8.9–14.4)	Singleton	0.27
Schaelike 2009[64] Germany	Cohort (prospective)	31%≥35 yr	11^{+0}–13^{+6} wk	Singleton	0.56
Scott 2004[67] Australia	Cohort (prospective)	32 (15–44)	11–14	Singleton	0.24
Soergel 2006[70] Germany	Cohort (prospective)	32.5 (16–44)	11–14	Singleton	0.36
Valinen 2007[76] Finland	Cohort (retrospective)	29.6 (mean) 18.6%>35	10–12^{+6}	Singleton	0.40
Wøjdemann 2005[85] Denmark	Cohort (prospective)	29.8 (mean) 10.8%≥35	10^{+3}–3^{+6}	Singleton	0.17

**Ambispective* refers to the combination of retrospective and prospective data. In the case of Muller et al.[50], the NT data was collected retrospectively and the biochemical data prospectively

Methodological quality

Seven of the studies[50,52,56,64,67,76,85] used appropriate methods of patient enrollment and included a spectrum of patients representative of those who are likely to be seen in practice. Four studies[56,64,67,76] provided a clear definition of both the inclusion and exclusion criteria for entry into the studies. All but two[64,85] of the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Four of the studies[64,67,70,85] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All but one[64] of the studies was likely affected by differential verification bias as some of the test index results were verified by a different reference standard. Seven studies[50,56,64,67,70,76,85] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for prenatal trisomy 21 risk calculation and the cut-off level of risk for invasive testing. One[64] of the studies provided a complete description of the execution of the reference standard. Five studies[56,64,67,70,85] accounted for intermediate/indeterminate results in the analysis of data and described withdrawals and dropouts (Table T.6).

Table T.6: Methodological quality for double serum test for trisomy 21



Quantitative results

The median DR was 76% (range: 62 to 88) and the median FPR was 9% (range: 5 to 19) (Figure T.12). The study result with the least uncertainty (O'Leary et al.[56]) had a DR of 85% (95% CI: 73 to 93) and an FPR of 12% (95% CI: 11 to 12) . The PPV ranged from 1.02 to 6.01%. The LR+ ranged from 4.21 to 15.40; the LR- ranged from 0.17 to 0.40 (Appendix T.E, Table T.E.4). The corresponding ROC curve is presented in Figure T.13.

Figure T.12: Double serum test for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Soergel 2006	7	336	1	1852	1:300	0.88 [0.47, 1.00]	0.85 [0.83, 0.86]
O'Leary 2006	51	2560	9	19660	1:300	0.85 [0.73, 0.93]	0.88 [0.88, 0.89]
Schaelike 2009	48	1730	11	8829	1:300	0.81 [0.69, 0.90]	0.84 [0.83, 0.84]
Scott 2004	4	390	1	1658	1:300	0.80 [0.28, 0.99]	0.81 [0.79, 0.83]
Valinen 2007	23	360	7	7144	1:250	0.77 [0.58, 0.90]	0.95 [0.95, 0.96]
Niemimaa 2001	6	243	2	2264	1:250	0.75 [0.35, 0.97]	0.90 [0.89, 0.91]
Wojdemann 2005	8	564	3	5866	1:250	0.73 [0.39, 0.94]	0.91 [0.91, 0.92]
Muller 2003	18	451	8	5156	1:250	0.69 [0.48, 0.86]	0.92 [0.91, 0.93]
Gyselaers 2004	8	352	5	6714	1:85	0.62 [0.32, 0.86]	0.95 [0.94, 0.96]

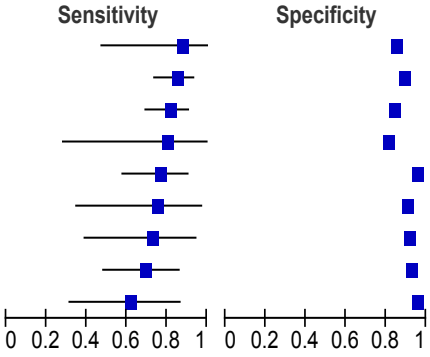
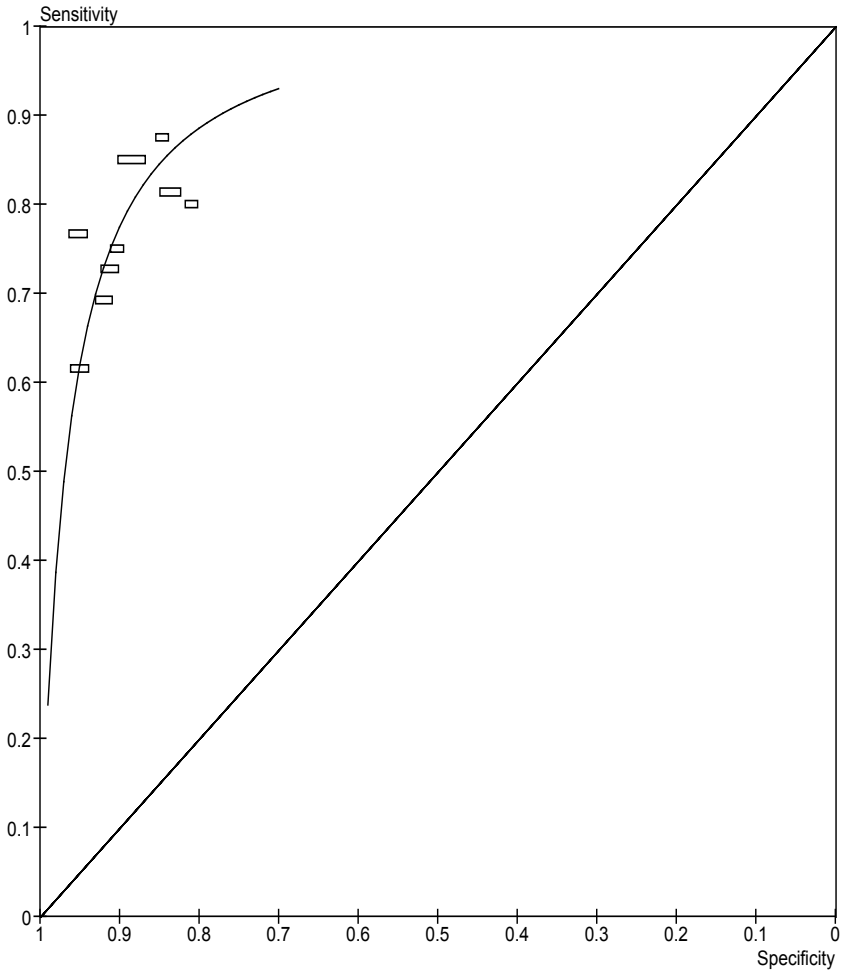


Figure T.13: ROC curve for double test for trisomy 21



Combined test (NT, PAPP-A, free-β hCG)

Trisomy 21

Study characteristics

Thirty studies[7,9,15,19,23,32,42,46,49-53,55,56,62,64-67,70,71,74-77,80,81,85,87] including 397,021 pregnancies (1706 T21, 395,315 no T21) and published between 2001 and 2010 provided data on the use of the first trimester combined test (NT, PAPP-A, free-β hCG*)* for the detection of trisomy 21 (Table T.7). All studies recruited the study participants in clinical cohorts. Twenty-five studies reported results for singleton pregnancies, one study reported on combined singleton and doubleton pregnancies, one on unselected pregnancies, and the remaining four studies did not describe the pregnancy type. The within study prevalence of trisomy 21 ranged from 0.15 to 3.56%. The high prevalence (3.56%) reported by Tørring et al.[74] may be a function of the large proportion of women aged ≥ 35 years; however, the authors did not describe the proportion of women in the study who fell within this category. The median maternal age and range reported in this study was similar to that reported in other studies with much lower prevalence rates. Fourteen studies used a positive test threshold of 1:250. Other positive test thresholds were 1:300 (eleven studies), 1:270 (two studies), 1:200 (one study), 1:380 (one study), and 1:400 (one study).

Table T.7: Study characteristics on combined test for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Alberta Health Services 2010[9] Canada	Cohort (prospective)	32 (mean) (15–52)	$11–13^{+6}$	Singleton	0.58
Avgidou 2005[7] UK	Cohort (prospective)	34 (15–49)	$11–13^{+6}$	ND	0.64
Benn 2007[15] USA	Cohort (retrospective)	36.2	ND	Singleton	0.44
Borrell 2004[19] Spain	Cohort (prospective)	31 (mean) (14–45)	7–12	Singleton	0.29
Cocclione 2008[23] Australia	Cohort (prospective)	31.3	12^{+2}	ND	0.35
Jaques 2007[32] Australia	Cohort (retrospective)	33 (16–51)	$11^{+3}–13^{+6}$	Unselected	0.39
Leung 2009[42] Hong Kong	Cohort (prospective)	32 (IQR: 30, 35)	$11–13^{+6}$	Singleton and doubleton	0.34
Malone 2005[46] USA	Cohort (prospective)	21.6%≥35	$10^{+3}–13^{+6}$	Singleton	0.25
Montalvo 2005[49] Spain	Cohort (prospective)	31.08±5.13 (mean±SD)	11^{+5}±0.9 (mean±SD)	Singleton	0.42
Muller 2003[50] France	Cohort (ambispective)	ND	11–13	Singleton	0.46
Neimimaa 2001[52] Finland	Cohort (prospective)	17.5%≥35	10–13	ND	0.31
Nicolaides 2005[51] UK	Cohort (prospective)	31 (13–49)	12 ($11^{+0}–13^{+6}$)	Singleton	0.43
Ochshorn 2001[53] Israel	Cohort (prospective)	ND	10–13	Singleton	0.15
Okun 2008[55] Canada	Cohort (prospective)	34	12.5 (mean)	Singleton	0.43
O'Leary 2006[56] Australia	Cohort (retrospective)	31 (14–47)	12^{+3} (8.8–14.4)	Singleton	0.27
Rozenberg 2006[62] France	Cohort (prospective)	30.7 (28.0–33.9)	12^{+3} (IQR: 12^{+0}, 12^{+6})	Singleton	0.38
Schaelike 2009[64] Germany	Cohort (prospective)	31%≥35 yr	$11^{+0}–13^{+6}$ wk	Singleton	0.56
Schmidt 2008[66] Germany	Cohort (retrospective)	31.3 (mean) (16–43)	$11^{+0}–13^{+6}$	Singleton	0.54
Schielen 2006[65] Netherlands	Cohort (ambispective)*	36.5 (18–47)	11.5 (8.0–13.6)	Singleton	0.52
Scott 2004[67] Australia	Cohort (prospective)	32 (15–44)	11–14	Singleton	0.24
Soergel 2006[70] Germany	Cohort (prospective)	32.5 (16—44) 26.4%≥35	11–14	Singleton	0.36
Stenhouse 2004[71] UK	Cohort (prospective)	31.5 (14–45)	93% 11–14	ND	0.30

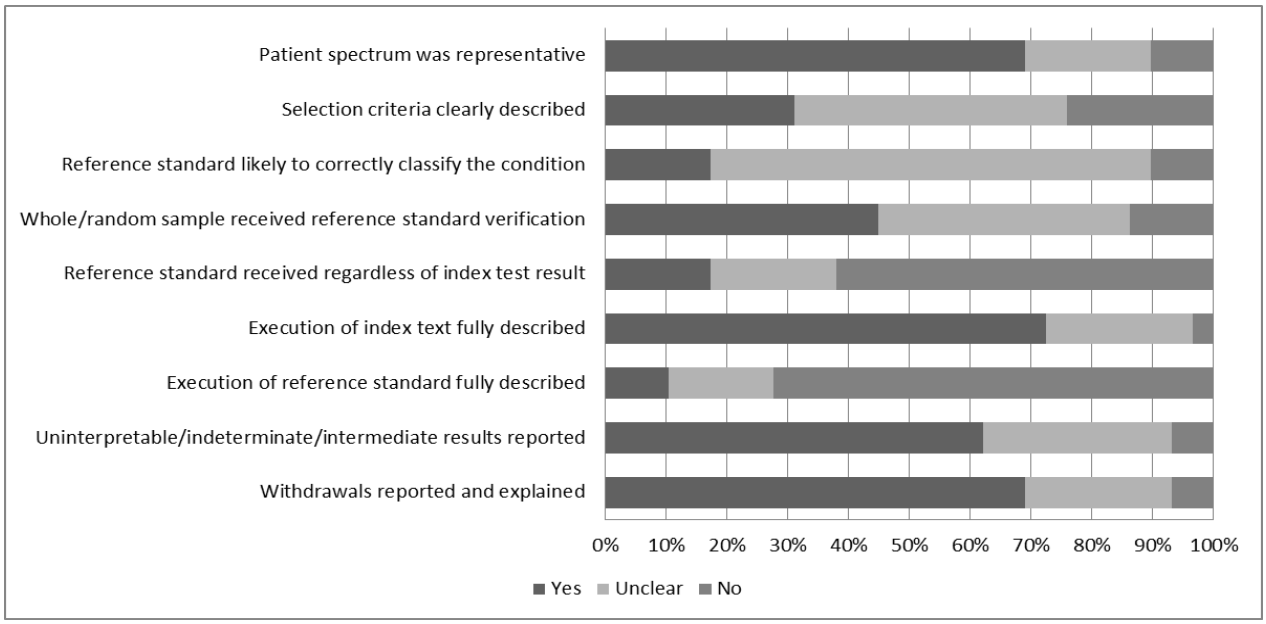
Tørring 2009[74] Denmark	Cohort (retrospective)	35 (mean)	7^{+5}–13^{+6} (biochemical) 11^{+3}–13^{+6} (NT)	Singleton	3.56
Tsai 2001[75] Taiwan	Cohort (retrospective)	ND	10–13	Singleton	0.66
Valinen 2007[76] Finland	Cohort (retrospective)	29.6 (mean) 18.6%>35	10–12^{+6}	Singleton	0.5
von Kaisenberg 2002[77] Germany	Cohort (prospective)	33 (15–46) 35.8%≥35	12 (11–14)	Singleton	0.53
Wald 2003 (SURUSS)[80] UK	Cohort (prospective)	ND	10–13	Singleton	0.21
Wapner 2003[81] USA and Canada	Cohort (prospective)	34.5±4.6 (mean±SD)	12.2±0.81 (mean±SD)	Singleton	0.74
Wøjdemann 2005[85] Denmark	Cohort (prospective)	29.3 (mean) 10.8%≥35	10^{+3}–13^{+6}	Singleton	0.17
Wortelboer 2009[87] Netherlands	Cohort (prospective)	34.3 (patients seen in last year of study)	8–13^{+6}	Singleton	0.43

**Ambispective* refers to the combination of retrospective and prospective data. In the case of Schielen et al.[65], the NT data was collected retrospectively and the biochemical data prospectively

Methodological quality

Twenty-one of the studies[7,15,19,32,42,46,50-52,55,56,62,64,67,71,74,76,77,80,81,85] used appropriate methods of patient enrollment and included a spectrum of patients representative of those who are likely to be seen in practice. Nine studies[32,46,51,56,62,64,67,76,81] provided a clear definition of both the inclusion and exclusion criteria for entry into the studies. All but five[7,15,23,64,77] of the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Fifteen of the studies[7,15,19,23,32,46,51,64,65,67,70,81,85,87,95] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All but five of the studies[7,15,23,64,77] were likely affected by differential verification bias as some of the test index results were verified by a different reference standard. Twenty-two studies[7,15,19,46,49,50,53,55,56,64,66,67,70,71,74-77,80,81,85,87] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for prenatal trisomy 21 risk calculation, and the cut-off level of risk for invasive testing. Four of the studies[7,55,64,75] provided a complete description of the execution of the reference standard. Twenty studies[7,19,32,42,46,51,53,55,56,62,64-67,70,71,77,81,85,87] accounted for intermediate/indeterminate results in the analysis of data and twenty-one studies described withdrawals and dropouts (Table T.8).[7,19,32,42,46,51,53,55,56,62,64-67,70,71,77,81,85,87]

Table T.8: Methodological quality for combined test for trisomy 21



Quantitative results

The median DR was 88% (range: 50 to 100) and the median FPR was 5% (range: 1 to 9) (Figure T.14). The two study results (Avgidou et al.[7] and Nicolaideset al.[51]) with the least uncertainty had DRs of, respectively, 93% (95% CI: 89 to 96) and 93% (95% CI: 89 to 95) and FPRs of, respectively, 8% (95% CI: 8 to 8) and 5% (95% CI: 5 to 6). PPV ranged from 1.96 to 82.4%. The LR+ and LR- ranged from 7.14 to 90 and 0.07 to 0.54, respectively (Appendix T.E, Table T.E.5). The corresponding ROC curve is presented in Figure T.15). Benn et al.[15] reported a DR much lower than the next lowest (50% vs 71%), and there was great uncertainty around the DR (95% CI: 19 to 81). The FPR was consistent with those reported in other studies (i.e. < 10%). As the condition prevalence, positive test threshold, and other characteristics of the study were similar to those of other studies (with the exception of gestational age which was not described), it is unclear what may have produced this lower detection rate. The study reports an overall detection rate of 60% for all chromosome abnormalities.

Figure T.14: Combined test for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Scott 2004	5	145	0	1903	1:300	1.00 [0.48, 1.00]	0.93 [0.92, 0.94]
Ochshorn 2001	2	100	0	1196	1:380	1.00 [0.16, 1.00]	0.92 [0.91, 0.94]
Avgidou 2005	183	2382	13	27986	1:300	0.93 [0.89, 0.96]	0.92 [0.92, 0.92]
Stenhouse 2004	14	283	1	4702	1:250	0.93 [0.68, 1.00]	0.94 [0.94, 0.95]
Nicolaides 2005	301	4100	24	71396	1:300	0.93 [0.89, 0.95]	0.95 [0.94, 0.95]
Leung 2009	31	582	3	9478	1:250	0.91 [0.76, 0.98]	0.94 [0.94, 0.95]
Wojdemann 2005	10	138	1	6292	1:250	0.91 [0.59, 1.00]	0.98 [0.97, 0.98]
Cocciolone 2008	60	866	6	17969	1:250	0.91 [0.81, 0.97]	0.95 [0.95, 0.96]
AHS 2010	98	1107	10	17414	1:250	0.91 [0.84, 0.95]	0.94 [0.94, 0.94]
Jaques 2007	57	626	6	15314	1:300	0.90 [0.80, 0.96]	0.96 [0.96, 0.96]
Torring 2009	108	23	12	3227	1:300	0.90 [0.83, 0.95]	0.99 [0.99, 1.00]
Tsai 2001	9	88	1	1416	1:400	0.90 [0.55, 1.00]	0.94 [0.93, 0.95]
Schaelike 2009	52	517	7	10042	1:300	0.88 [0.77, 0.95]	0.95 [0.95, 0.96]
Soergel 2006	7	87	1	2101	1:300	0.88 [0.47, 1.00]	0.96 [0.95, 0.97]
Valinen 2007	21	232	3	4509	1:250	0.88 [0.68, 0.97]	0.95 [0.94, 0.96]
Borrell 2004	7	92	1	2680	1:250	0.88 [0.47, 1.00]	0.97 [0.96, 0.97]
Schmidt 2008	47	656	7	9307	1:300	0.87 [0.75, 0.95]	0.93 [0.93, 0.94]
Wapner 2003	52	770	9	7385	1:250	0.85 [0.74, 0.93]	0.91 [0.90, 0.91]
von Kaisenberg 2002	16	269	3	3299	1:300	0.84 [0.60, 0.97]	0.92 [0.92, 0.93]
Okun 2008	52	573	10	13852	1:200	0.84 [0.72, 0.92]	0.96 [0.96, 0.96]
Wald 2003 (SURUSS)	71	2015	14	38287	1:250	0.84 [0.74, 0.91]	0.95 [0.95, 0.95]
O'Leary 2006	50	827	10	21383	1:300	0.83 [0.71, 0.92]	0.96 [0.96, 0.97]
Malone 2005	75	2028	17	34186	1:300	0.82 [0.72, 0.89]	0.94 [0.94, 0.95]
Rozenberg 2006	41	370	10	12963	1:250	0.80 [0.67, 0.90]	0.97 [0.97, 0.97]
Niemimaa 2001	4	132	1	1465	1:250	0.80 [0.28, 0.99]	0.92 [0.90, 0.93]
Wortelboer 2009	66	677	21	19529	1:250	0.76 [0.65, 0.84]	0.97 [0.96, 0.97]
Montalvo 2005	14	183	5	4336	1:270	0.74 [0.49, 0.91]	0.96 [0.95, 0.97]
Muller 2003	19	263	7	5309	1:250	0.73 [0.52, 0.88]	0.95 [0.95, 0.96]
Schielen 2006	15	190	6	3822	1:300	0.71 [0.48, 0.89]	0.95 [0.95, 0.96]
Benn 2007	5	166	5	2080	1:270	0.50 [0.19, 0.81]	0.93 [0.91, 0.94]

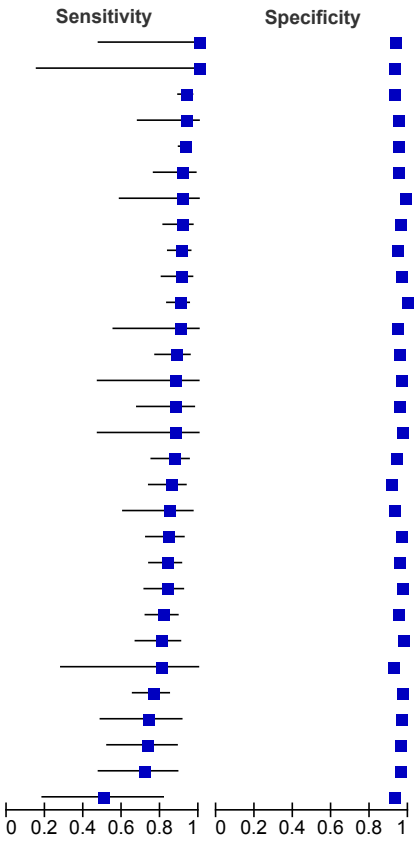
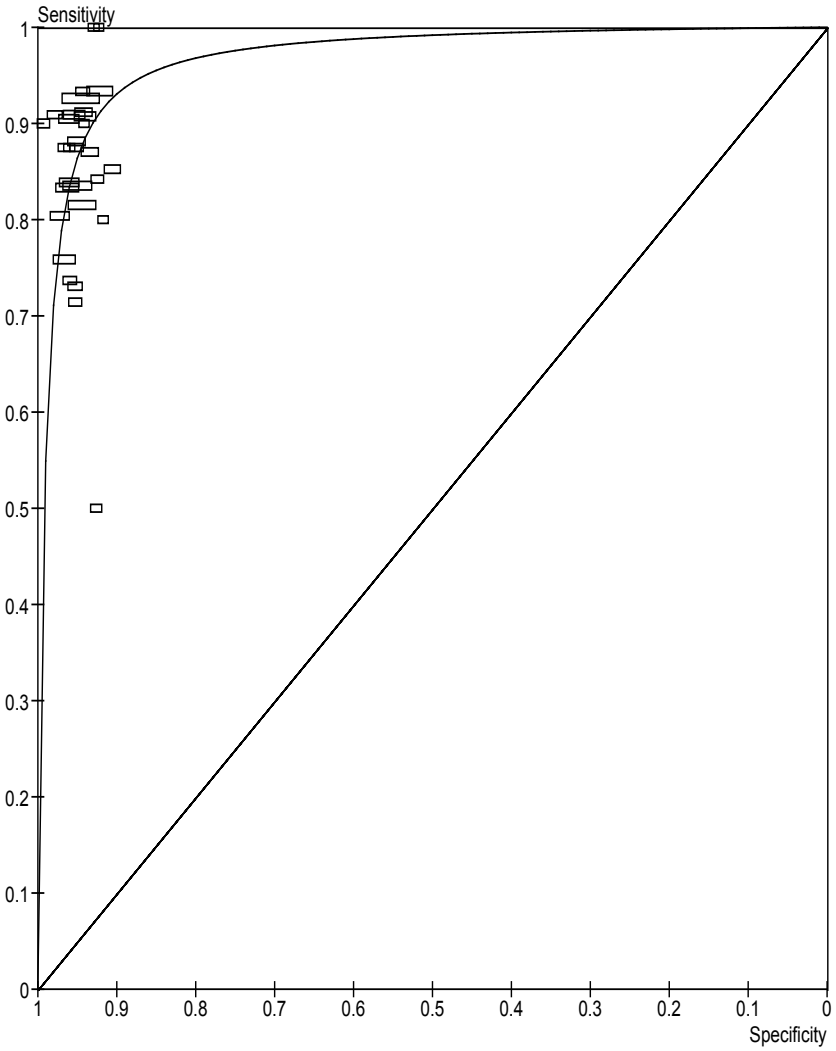


Figure T.15: ROC curve for combined test for trisomy 21



Trisomy 18

Study characteristics

Nine studies,[7,15,19,32,42,49,53,77,81] published between 2001 and 2009 and including a total of 79,300 women (119 T18, 79,181 no T18), provided data on the use of the first trimester combined test (NT, PAPP-A, free-β hCG) for the detection of trisomy 18 (Table T.9). All studies recruited participants in clinical cohorts. Six studies reported results for singleton pregnancies only, one reported on the results of a combination of singleton and doubleton pregnancies, and one did not specify the pregnancy type. The within study prevalence of T18 ranged from 0.09 to 0.31%. Four studies used a positive test threshold of 1:250 and two studies used a threshold of 1:300. Other positive test thresholds used in single studies were 1:100, 1:270, and 1:380.

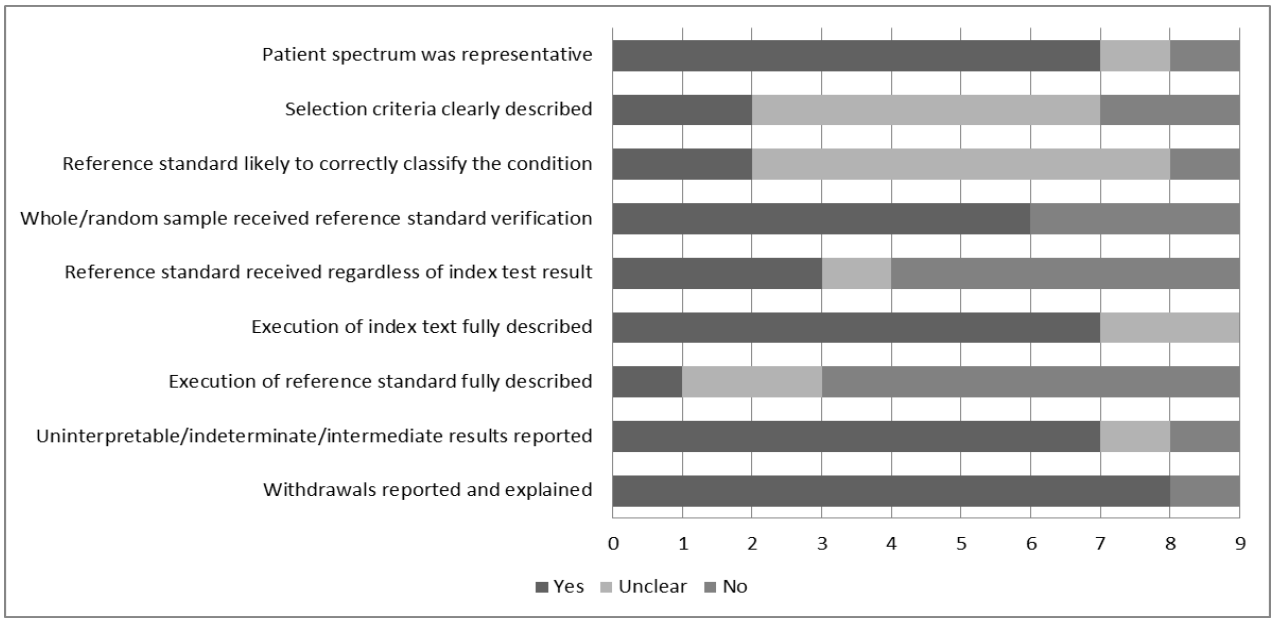
Table T.9: Study characteristics for combined test for trisomy 18

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Avgidou 2005[7] UK	Cohort (prospective)	34 (15–49)	11–13^{+6}	ND	0.17
Benn 2007[15] USA	Cohort (retrospective)	36.2	ND	Singleton	0.13
Borrell 2004[19] Spain	Cohort (prospective)	31 (mean) (14–45)	7–12	Singleton	0.14
Jaques 2007[32] Australia	Cohort (retrospective)	33 (16–51)	11^{+3}–13^{+6}	Unselected	0.09
Leung 2009[42] Hong Kong	Cohort (prospective)	32 (IQR: 30, 35)	11–13^{+6}	Singleton and doubleton	0.15
Montalvo 2005[49] Spain	Cohort (prospective)	31.1±5.13 (mean±SD)	11^{+5}±0.94 (mean±SD)	Singleton	0.11
Ochshorn 2001[53] Israel	Cohort (prospective)	ND	10–13	Singleton	0.31
von Kaisenberg 2002[77] Germany	Cohort (prospective)	33 (15–46) 35.8%≥35	12 (11–14)	Singleton	0.12.
Wapner 2003[81] USA/Canada	Cohort (prospective)	34.5±4.6 (mean±SD)	12±0.81 (mean±SD)	Singleton	0.13

Methodological quality

Seven[7,15,19,32,42,77,81] of the nine studies used appropriate methods of patient enrollment and included a spectrum of patients representative of those who are likely to be seen in practice. Only two studies[32,81] provided a clear definition of both the inclusion and exclusion criteria for entry into the studies. All but two[15,77] of the studies were likely to have used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Six[7,15,19,32,42,81] studies accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All but three of the studies[7,15,77] were likely affected by differential verification bias as some of the test index results were verified by a different reference standard. Seven studies[7,15,19,49,53,77,81] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for risk calculation, and the positive test threshold. One study[7] provided a complete description of the execution of the reference standard. Seven studies accounted for intermediate/indeterminate results in the analysis of data and eight studies,[7,15,19,32,42,53,77,81] described withdrawals and dropouts (Table T.10).

Table T.10: Methodological quality of combined test for trisomy 18



Quantitative results

The median DR was 90% (range: 33 to 100) and the median FPR was 6% (range: 0 to 8) (Figure T.16). The study result with the least uncertainty (Avgidouet al.[7]) had a DR of 92% (95% CI: 81 to 98) and an FPR of 8% (95% CI: 8 to 9). PPV ranged from 0.58 to 15.15%. The LR+ and LR- ranged, respectively, from 4.13 to 191.43 and 0.07 to 0.73 (Appendix T.E, Table T.E.6). The corresponding ROC curve is presented in Figure T.17. Benn et al.[15] reported a very low DR (33%), and there was tremendous uncertainty around the estimate (95% CI: 1 to 91). The FPR was consistent with those reported in other studies (i.e. < 10%). As the condition prevalence, positive test threshold, and other characteristics of the study were similar to those of other studies, it is unclear what may have produced this lower detection rate.

Figure T.16: Combined test for trisomy 18

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Montalvo 2005	5	192	0	4341	1:270	1.00 [0.48, 1.00]	0.96 [0.95, 0.96]
Leung 2009	14	599	1	9480	1:250	0.93 [0.68, 1.00]	0.94 [0.94, 0.95]
Avgidou 2005	48	2517	4	27995	1:300	0.92 [0.81, 0.98]	0.92 [0.91, 0.92]
Wapner 2003	10	154	1	8051	1:250	0.91 [0.59, 1.00]	0.98 [0.98, 0.98]
von Kaisenberg 2002	9	264	1	3277	1:300	0.90 [0.55, 1.00]	0.93 [0.92, 0.93]
Borrell 2004	3	92	1	2684	1:250	0.75 [0.19, 0.99]	0.97 [0.96, 0.97]
Jaques 2007 (T18)	10	56	5	15932	1:250	0.67 [0.38, 0.88]	1.00 [1.00, 1.00]
Ochshorn 2001	2	100	2	1194	1:380	0.50 [0.07, 0.93]	0.92 [0.91, 0.94]
Benn 2007 (T18)	1	170	2	2083	1:100	0.33 [0.01, 0.91]	0.92 [0.91, 0.94]

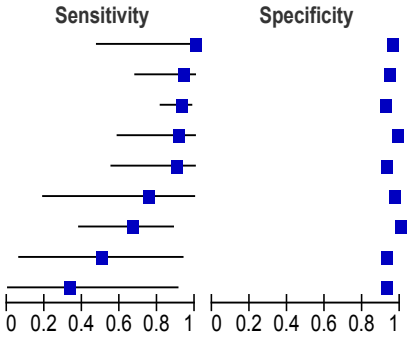
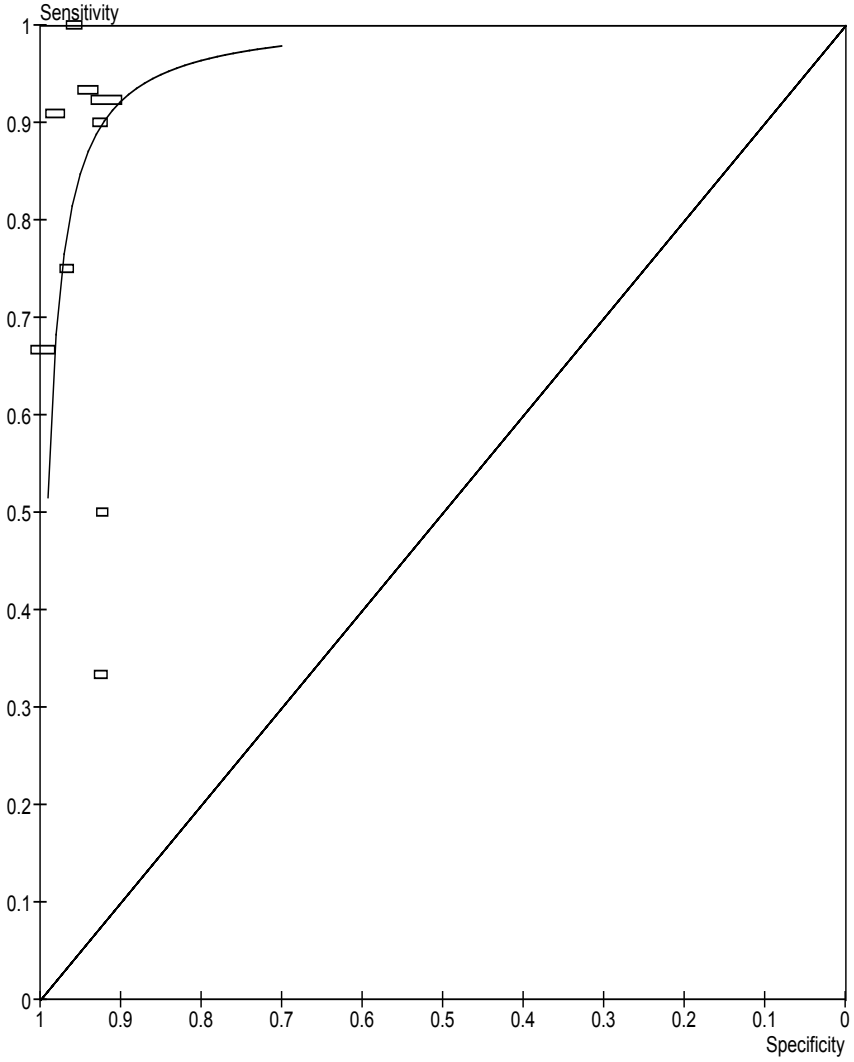


Figure T.17: ROC curve for combined test for T21



Trisomy 13

Study characteristics

Four studies,[7,49,53,77] published between 2001 and 2005 and including a total of 30,951 pregnancies (41 T13, 39,910 no T13), provided data on the first trimester combined test for assessing the risk of trisomy 13 (Table T.11). All studies recruited participants in clinical cohorts. Three studies reported results for singleton births only and one did not describe pregnancy type. The within study prevalence of T13 ranged from 0.09 to 0.23%. The positive test thresholds varied: 1:270 (one study), 1:300 (two studies), and 1:380 (one study).

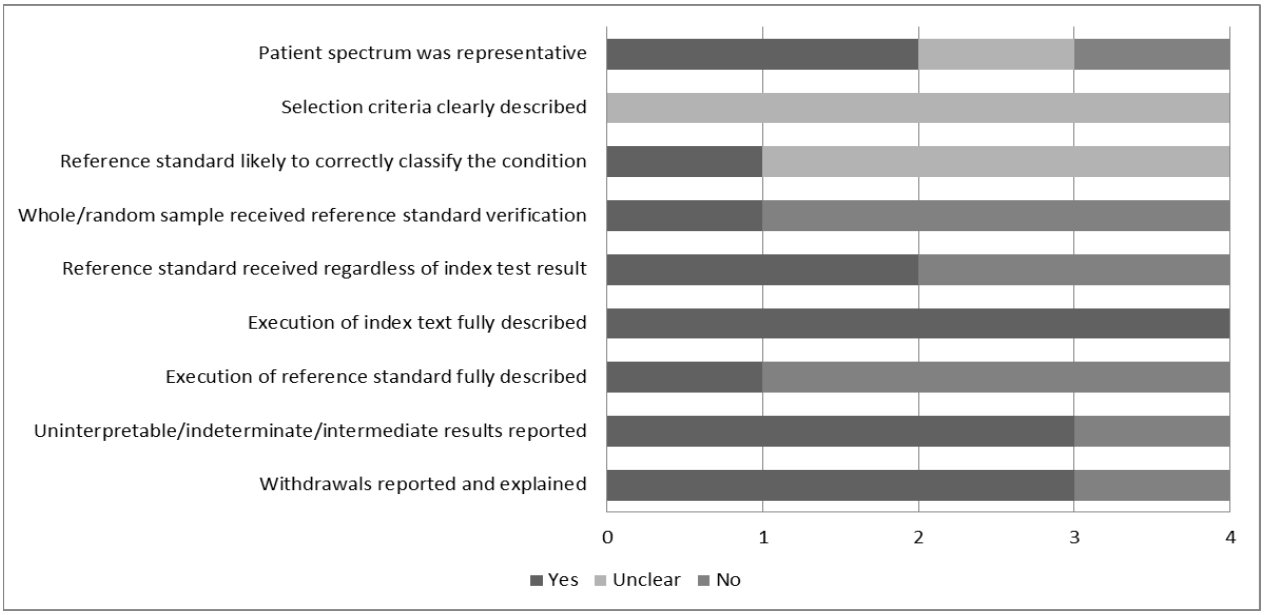
Table T.11: Study characteristics for combined test for trisomy 13

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Avgidou 2005[7] UK	Cohort (prospective)	34 (15–49)	11–13^{+6}	ND	0.09
Montalvo 2005[49] Spain	Cohort (prospective)	31.1±5.13 (mean±SD)	11^{+5}±0.94 (mean±SD)	Singleton	0.15
Ochshorn 2001[53] Israel	Cohort (prospective)	ND	10–13	Singleton	0.23
von Kaisenberg 2002[77] Germany	Cohort (Prospective)	33 (15–46) 35.8%≥35	12 (11–14)	Singleton	0.11

Methodological quality

Two studies[7,77] included a spectrum of patients representative of those who are likely to be seen in practice; however, no studies provided definitions for the exclusion and exclusion criteria that were applied to enroll participants. All studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. One study[7] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. In two studies[7,77] the index test results were verified by the same reference standard and, therefore, it is likely that the accuracy results were not affected by differential verification bias. The four studies provided a complete description of both the execution of the index test (including the characteristics of the technology, the software that was used for prenatal trisomy 13 risk calculation and the cut-off level of risk for invasive testing), but only one study[7] provided a full description of the execution of the reference standard. Three studies[7,53,77] accounted for intermediate/indeterminate results and patient withdrawals in the analysis of data (Figure T.18).

Figure T.18: Methodological quality of combined test for trisomy 13

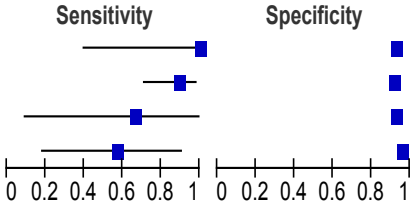


Quantitative results

The median DR was 78% (range: 57 to 100) and the median FPR was 8% (range: 4 to 8) (Figure T.19). The study result with the least uncertainty (Avgidou[7]) reported a DR of 89% (95% CI: 71 to 98). The PPV ranged from 0.94 to 2.03%. The LR+ ranged from 8.38 to 14.25 and LR- from 0.11 to 0.45 (Appendix T.E, Table T.E.6).

Figure T.19: Combined test for trisomy 13

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
von Kaisenberg 2002	4	269	0	3278	1:300	1.00 [0.40, 1.00]	0.92 [0.91, 0.93]
Avgidou 2005	24	2541	3	27996	1:300	0.89 [0.71, 0.98]	0.92 [0.91, 0.92]
Ochshorn 2001	2	100	1	1195	1:380	0.67 [0.09, 0.99]	0.92 [0.91, 0.94]
Montalvo 2005	4	193	3	4338	1:270	0.57 [0.18, 0.90]	0.96 [0.95, 0.96]



Second Trimester Screening Tests

Dual serum test (AFP, free-β hCG)

Trisomy 21

Study characteristics

Eight studies,[11,14,24,30,35,40,47,60] published between 2000 and 2008 and including a total of 223,015 women (423 T21, 222,592 no T21), provided data on the use of the dual serum test (AFP, free-β hCG) for screening for trisomy 21 (Table T.12). Seven studies recruited the study participants in cohorts and one (Hsieh et al.[30]) used cases and controls. Two studies reported results for singleton pregnancies, one study[24] also reported test accuracy results for twin pregnancies, one study reported on unselected pregnancies, and the remaining five studies did not specify the pregnancy type. The within study prevalence of trisomy 21 ranged from 0.08 to 0.81%. Six of the eight studies used a positive test threshold of 1:250; other positive test thresholds were 1:270 (one study) and 1:320 (one study).

Table T.12: Study characteristics for dual serum test for trisomy 21

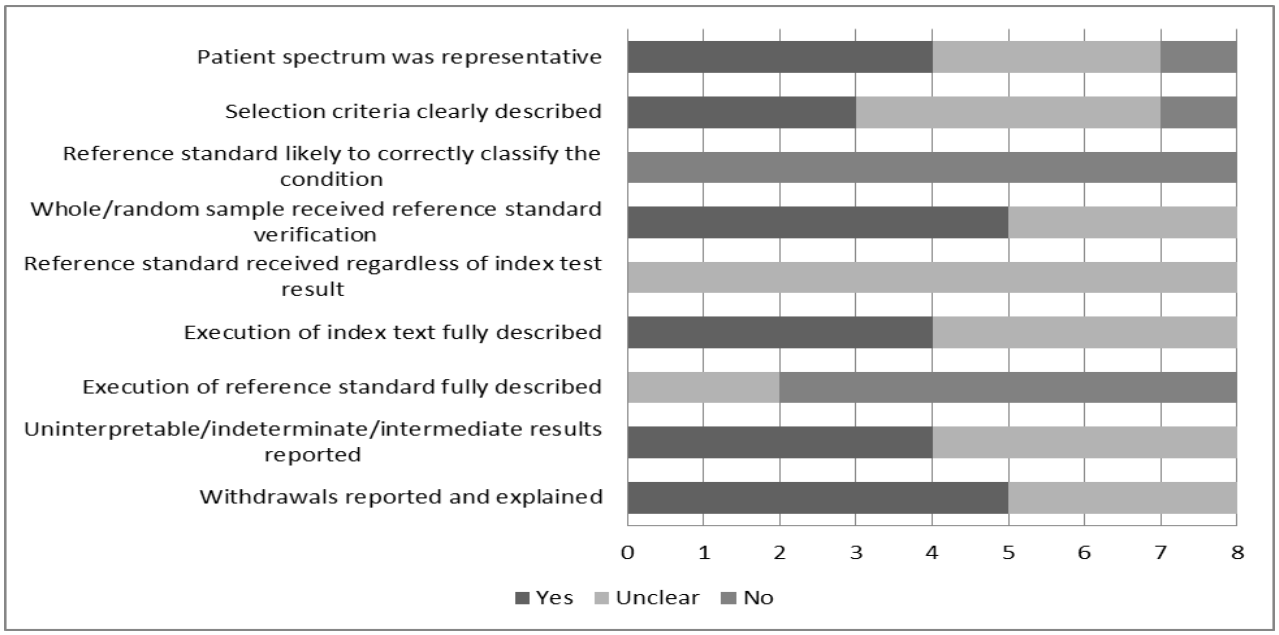
Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Gestational age (wk) (range)	Pregnancy type	Study prevalence %
Audibert 2001[11] France	Cohort (prospective)	30.1 (mean) (16–37)	14–17+6	Singleton	0.26
Beaman 2008[14] United Kingdom	Cohort (prospective)	ND	15–20	ND	0.16
Garchet-Beaudron 2008[24] France	Cohort (prospective)	T21: 35 (17–43); no T21: 29 (13—49)	ND	Singleton	0.13
		T21: 35.5 (18–44); no T21: 30 (15–46)	ND	Twin	0.24
Hsieh 2007[30] Taiwan	Case-control (retrospective)	33.1±4.7 (cases), 29.4±3.5 (controls) (mean±SD)	17.9±5.2 (cases), 16.8±1.6 (controls) (mean±SD)	ND	0.81
Jou 2000[35] Taiwan	Cohort (prospective)	29 (15–45)	17 (median) (14–22)	ND	0.09
Lam 2002[40] Hong Kong	Cohort (prospective)	30.5 (mean)	16 (mean)	ND	0.22

Michailidis 2001[47] United Kingdom	Cohort (retrospective)	30.1 (mean) (13–50)	12^{+5} (mean)	Unselected	0.08
Roberts 2000[60] United Kingdom	Cohort (retrospective)	27 (mean) (14–55)	15–20	ND	0.16

Methodological quality

Four studies[35,40,47,60] included a spectrum of patients representative of those who are likely to be seen in practice. Three studies[11,35,47] provided a clear definition of both the inclusion and exclusion criteria for entry into the studies. All eight studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Five studies[11,35,40,47,60] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All studies were likely affected by differential verification bias as some of the test index results were verified by a different reference standard. Four studies[14,24,30,35] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for risk calculation, and the positive test threshold. None of the studies provided a complete description of the execution of the reference standard. Four studies[11,35,40,60] accounted for intermediate/indeterminate results in the analysis of data whereas five[11,35,40,47,60] described withdrawals and dropouts (Figure T.20).

Figure T.20: Methodological quality of studies on dual serum test for trisomy 21



Quantitative results

The median DR was 65% (ranged: 50 to 76) and the median FPR was 6% (range: 3 to 11) (Figure T.21). The studies with the least uncertainty (Garchet-Beaudron et al.[24] and Beaman et al.[14]) had DRs, respectively, of 74% (95% CI: 64 to 83) and 67% (95% CI: 57 to 75) and FPRs, respectively, of 10% (95% CI: 10 to 11) and 6% (95% CI: 6 to 6). The PPV ranged from 0.47 to 7.67%. The LR+ ranged from 5.56 to 20; the LR- ranged from 0.27 to 0.55 (Appendix T.E, Table T.E.8). The corresponding ROC curve is presented in Figure T.22. The boxes representing the studies are proportional to the sample size for individual studies.

Figure T.21: Dual serum test for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Roberts 2000	31	1323	10	24716	1:250	0.76 [0.60, 0.88]	0.95 [0.95, 0.95]
Garchet-B. 2008 (sing)	64	6682	22	58047	1:250	0.74 [0.64, 0.83]	0.90 [0.89, 0.90]
Lam 2002	26	810	9	15392	1:320	0.74 [0.57, 0.88]	0.95 [0.95, 0.95]
Beaman 2008	72	3858	36	62665	1:250	0.67 [0.57, 0.75]	0.94 [0.94, 0.94]
Garchet-B. 2008 (twin)	17	1199	10	9814	1:250	0.63 [0.42, 0.81]	0.89 [0.89, 0.90]
Hsieh 2007	60	727	36	10993	1:250	0.63 [0.52, 0.72]	0.94 [0.93, 0.94]
Jou 2000	10	1143	6	16583	1:270	0.63 [0.35, 0.85]	0.94 [0.93, 0.94]
Audibert 2001	6	124	4	3656	1:250	0.60 [0.26, 0.88]	0.97 [0.96, 0.97]
Michailidis 2001	2	423	2	4437	1:250	0.50 [0.07, 0.93]	0.91 [0.90, 0.92]

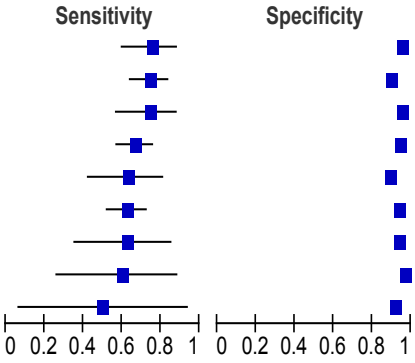
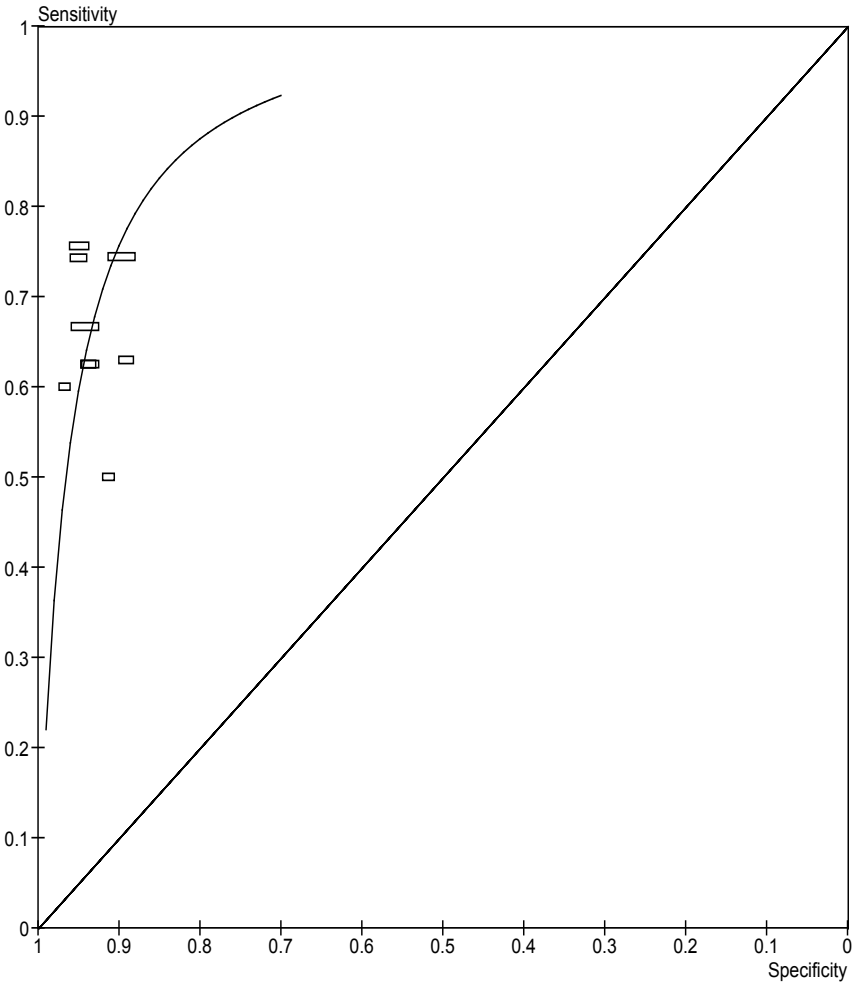


Figure T.22: ROC curve for dual test for trisomy 21



Trisomy 18

Study characteristics

One study[34] including a total of 25,530 women (9 T18, 25,521 no T18) provided data on the use of the dual serum test (AFP + free-β hCG) for the detection of trisomy 18. The study was published in

2002. The study was prospective and recruited participants in cohorts. The study did not describe pregnancy type. The within study prevalence of T18 was 0.04%. The study used a positive test threshold of MoM of AFP≤0.75, hCG≤0.55.

Table T.13: Study characteristics for dual serum test for trisomy 18

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Gestational age (wk) (range)	Pregnancy type	Study prevalence %
Jou 2002[34] Taiwan	Cohort (prospective)	29.6 (16–45)	Median 17.1 (15–22)	ND	0.04

Methodological quality

It is unclear whether the study included a spectrum of patients representative of those who are likely to be seen in practice. The study did not provide a description of the participant inclusion and exclusion criteria. The study used a combination of different reference standards to correctly classify trisomy 18 cases and accounted for problems related to partial verification bias. The index test results were verified by a different reference standard and therefore it is likely that the accuracy results were affected by differential verification bias. The study failed to provide a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for risk calculation, and the positive test threshold. The study did not provide a full description of the execution of the reference standard. It is unclear whether the study accounted for intermediate/indeterminate results or patient withdrawals in the analysis of data.

Quantitative results

The DR was 89% (95% CI: 52 to 100); the FPR was 3% (95% CI: 3 to 4); PPV was 0.90%. The LR+ was 29.67 and the LR- was 0.11.

Trisomy 13

No studies provided outcome data on the use of the dual serum test for trisomy 13.

Triple serum test

Trisomy 21

Study characteristics

Fourteen studies,[10,13,23,26,31,38,41,54,57,61,73,80,86,88] published between 2000 and 2008 and including a total of 632,428 women (1268 T21, 631,160 no T21), provided data on the use of the triple serum test (AFP, free-β hCG, uE3) for screening for trisomy 21 (Table T.14). Thirteen of the studies recruited the study population in cohorts and one recruited cases and controls. Nine studies reported results for singleton births only; the remaining four studies did not describe the pregnancy type. The within study prevalence of trisomy 21 ranged from 0.10 to 1.92%. A variety of positive test thresholds were used: 1:84 (one study), 1:250 (six studies), 1:295 (one study), 1:299 (one study), 1:300 (one study), 1:380 (one study), 1:384 (one study), 1:385 (one study). One study[86] did not report the threshold used.

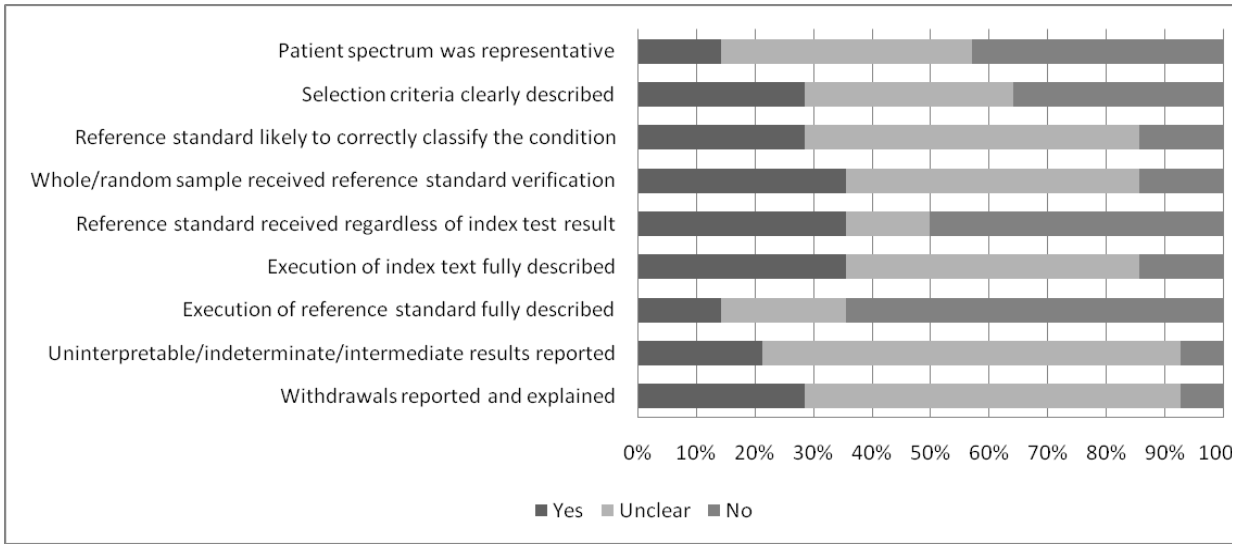
Table T.14: Study characteristics for triple serum test for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Alvarez-Nava 2008[10] Venezuela	Cohort (prospective)	ND	15–20	Singleton	0.93
Cocciolone 2008[23] Australia	Cohort (prospective)	29.5	16[+1]	ND	0.16
Bahado-Singh 2000[13] USA	Case-control (retrospective)	38.0 (T21) (17.0–44.4) 35.0 (no T21) (14.0–46.0)	14.0–24.0 (no T21), 15.0–21.6 (T21)	Singleton	1.92
Gyselaers 2004[26] Belgium	Cohort (retrospective)	5.4%≥35	ND	ND	0.27
Huderer-Duric 2000[31] Croatia	Cohort (retrospective)	73%≥35	15–22	ND	0.42
Kishida 2000[38] Japan	Cohort (prospective)	34.9±0.2 (mean ± SE)	14–20	Singleton	0.95
Lamlertkittikul 2007[41] Thailand	Cohort (prospective)	28.5±6.28 (mean ± SD) (14–46)	14–20	Singleton	0.4
O'Connell 2000[54] United Kingdom	Cohort (retrospective)	ND	ND	ND	0.10
Onda 2000[57] Japan	Cohort (prospective)	32.2	15–21.9	Singleton	0.23
Rosen 2002[61] Israel	Cohort (prospective)	>35	16–18	Singleton	1.29
Summers 2003[73] Canada	Cohort (retrospective)	16% ≥35	15–20	ND	0.17
Wald 2003 (SURUSS)[80] United Kingdom	Cohort (prospective)	ND	14–20	Singleton	0.22
Wortelboer 2008[86] Netherlands	Cohort (retrospective)	30.5 (first year) 34.5 (last year)	14–21	Singleton	0.35
Xia 2006[88] China	Cohort (prospective)	28.13 (19–49)	14–20	Singleton	0.19

Methodological quality

Two[73,80] of the 14 studies included a spectrum of patients representative of those who are likely to be seen in practice. Four studies[13,38,41,86] fully described the inclusion and exclusion criteria for entry into the study. An adequate reference standard was used in four studies.[13,23,31,61] Five studies[13,23,31,57,61] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. Participants in five studies[13,23,31,61,86] received verification of the true disease status of the fetus with the same reference standard. Five studies[10,41,80,86,88] clearly described the index test, while two studies[31,61] adequately described the reference standard procedures. Three studies[41,54,80] reported intermediate/indeterminate test results in the analysis of data whereas four studies[10,41,54,86] accounted for patient withdrawals in the analysis of data (Figure T.23).

Figure T.23: Methodological quality of studies on triple serum test for trisomy 21



Quantitative results

The median DR was 80.5% (range: 60 to 100) and the median FPR was 9.5% (range: 4 to 54). The result with the least uncertainty (Summers et al.[73]) reported a DR of 74% (95% CI: 71 to 77) and an FPR of 7% (95% CI: 7 to 7). The PPV ranged from 0.05 to 0.63% (Figure T.24). The LR+ ranged from 2.33 to 15.0; the LR- from 0 to 0.42 (Appendix T.E, Table T.E.9). The corresponding ROC curve is presented in Figure T.25. The boxes representing the studies are proportional to the sample size for individual studies.

Figure T.24: Triple serum test for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Rosen 2002	13	424	0	569	1:380	1.00 [0.75, 1.00]	0.57 [0.54, 0.60]
Lamlertkittikul 2007	4	115	0	880	1:250	1.00 [0.40, 1.00]	0.88 [0.86, 0.90]
Kishida 2000	10	368	0	677	1:299	1.00 [0.69, 1.00]	0.65 [0.62, 0.68]
Huderer-Duric 2000	11	1044	1	1777	1:300	0.92 [0.62, 1.00]	0.63 [0.61, 0.65]
Bahado-Singh 2000	39	1273	7	1072	1:250	0.85 [0.71, 0.94]	0.46 [0.44, 0.48]
Onda 2000 (T21)	63	4722	13	28127	1:295	0.83 [0.73, 0.91]	0.86 [0.85, 0.86]
Wortelboer 2008	85	3920	20	26265	ND	0.81 [0.72, 0.88]	0.87 [0.87, 0.87]
Wald 2003 (SURUSS)	66	2572	16	34708	1:250	0.80 [0.70, 0.88]	0.93 [0.93, 0.93]
Xia 2006	7	325	2	4346	1:384	0.78 [0.40, 0.97]	0.93 [0.92, 0.94]
Cocciolone 2008	50	2848	17	37833	1:250	0.75 [0.63, 0.84]	0.93 [0.93, 0.93]
Summers 2003	531	30703	186	392475	1:385	0.74 [0.71, 0.77]	0.93 [0.93, 0.93]
Gyselaers 2004	69	1993	30	34290	1:85	0.70 [0.60, 0.79]	0.95 [0.94, 0.95]
Alvarez-Nava 2008	9	173	4	2819	1:250	0.69 [0.39, 0.91]	0.94 [0.93, 0.95]
O'Connell 2000	9	577	6	14235	1:250	0.60 [0.32, 0.84]	0.96 [0.96, 0.96]

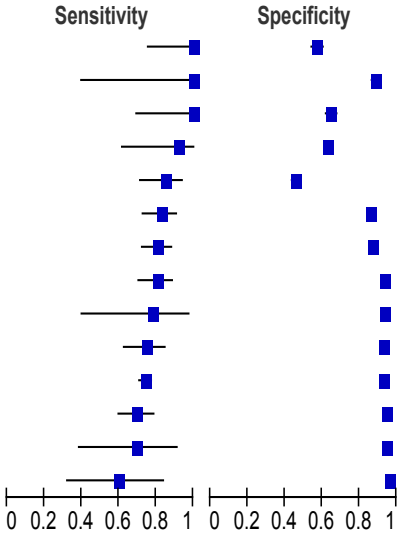
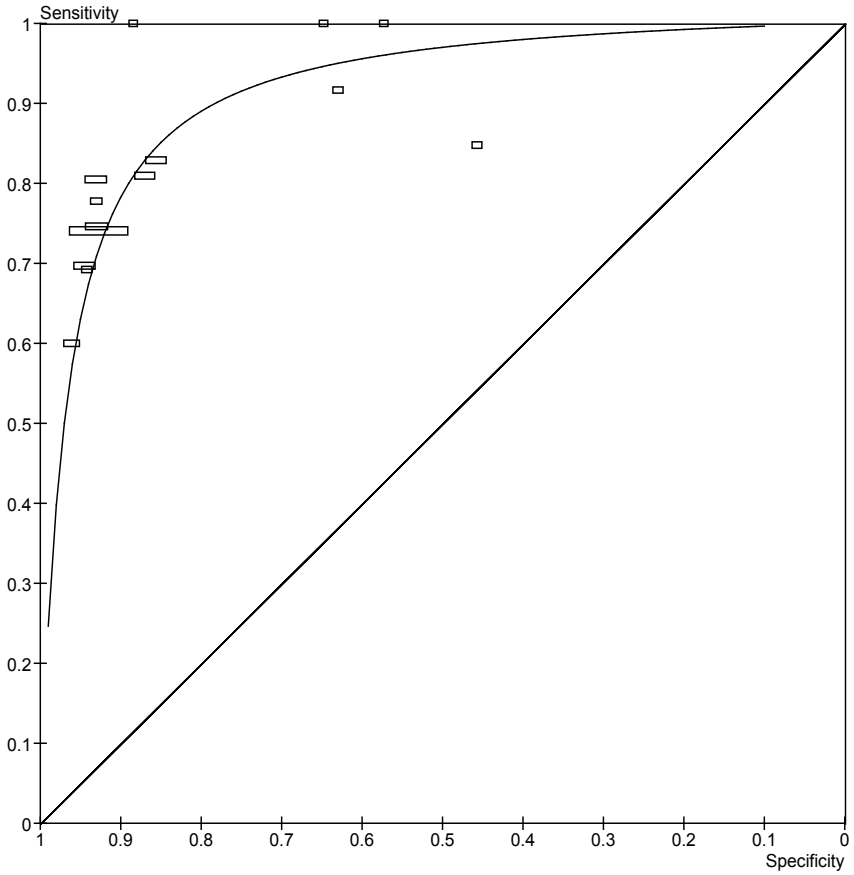


Figure T.25: ROC curve for triple serum test for trisomy 21



Trisomy 18

Study characteristics

Six studies,[21,29,38,57,73,88] published between 2000 and 2007 and including a total of 543,624 women (192 T18, 543,432 no T18), provided data on the use of the triple serum test (AFP, free-β hCG, uE3) for the detection of trisomy 18. All studies recruited participants as clinical cohorts. Most studies reported results for singleton births only with two studies not describing the pregnancy type. The within study prevalence of trisomy 18 ranged from 0.03 to 0.47% (Table T.15). Three of the six studies used a positive test threshold of 1:100. Other positive test thresholds were 1:250 (one study), 1:299 (one study) and 1:384 (one study).

Table T.15: Study characteristics for triple serum test for trisomy 18

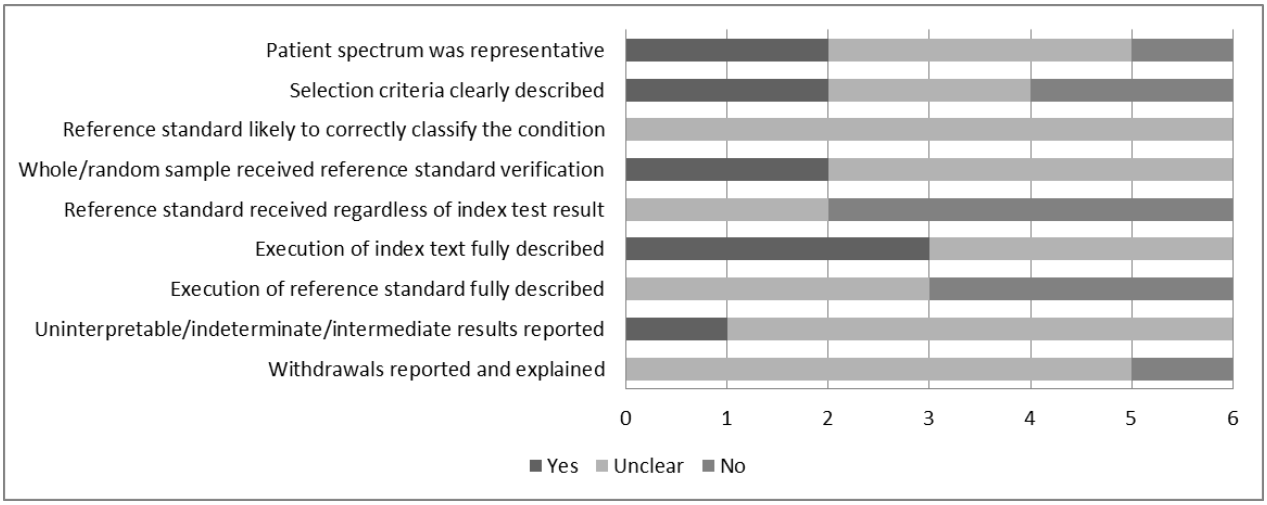
Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence
Breathnach 2007[21] USA	Cohort (prospective)	23%>35	15–18	Singleton	0.04
Hogge 2001[29] USA	Cohort (prospective)	10%≥35	ND	ND	0.03
Kishida 2000[38] Japan	Cohort (prospective)	34.9 ± 0.2 (mean±SE)	14--20	Singleton	0.47

Onda 2000[57] Japan	Cohort (prospective)	32.2	15–21.9	Singleton	0.09
Summers 2003[73] Canada	Cohort (retrospective)	16%≥35	15–20	ND	0.03
Xia 2006[88] China	Cohort (prospective)	28.3 (19–49)	14–20	Singleton	0.15

Methodological quality

Two[21,73] out of six studies that evaluated the use of triple serum test for Trisomy 18 clearly included a spectrum of patients that is representative of those who are likely to be seen in practice. Hence, it is unclear whether the reported estimates of screening accuracy are generalizable to patients in whom the test will be used in practice. Only two studies[38,92] clearly outlined the enrollment criteria. All the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Two studies[38,92] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. Three studies[21,29,88] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for risk calculation, and the positive test threshold. No studies provide an adequate description of the reference standard test. One study[21] clearly reported intermediate/indeterminate test results in the analysis of data; no studies accounted for patient withdrawals or dropouts in the analysis of data (Figure T.26).

Figure T.26: Methodological quality of studies on triple serum test for trisomy 18



Quantitative results

The median DR was 63.5% (range: 53 to 86 and the median FPR was 0.75 (95% CI: 0 to 36) (Figure T.27). The study result with the least uncertainty (Summers et al.[73]) reported a DR of 53% (95% CI: 44 to 62) and an FPR of 0.001% (95% CI: 0 to 0.001). The PPV ranged from 0.79 to 15. The LR+ ranged from 1.67 to 600 and the LR- ranged from 0.15 to 0.63 (Appendix T.E, Table T.E.10).

Figure T.27: Triple serum test for trisomy 18

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Xia 2006	6	326	1	4347	1:384	0.86 [0.42, 1.00]	0.93 [0.92, 0.94]
Onda 2000 (T18)	22	158	6	32739	1:100	0.79 [0.59, 0.92]	1.00 [0.99, 1.00]
Hogge 2001	8	242	4	44891	1:100	0.67 [0.35, 0.90]	0.99 [0.99, 1.00]
Breathnach 2007	9	51	6	35858	1:250	0.60 [0.32, 0.84]	1.00 [1.00, 1.00]
Kishida 2000	3	375	2	675	1:299	0.60 [0.15, 0.95]	0.64 [0.61, 0.67]
Summers 2003 (T18)	66	647	59	423123	1:100	0.53 [0.44, 0.62]	1.00 [1.00, 1.00]

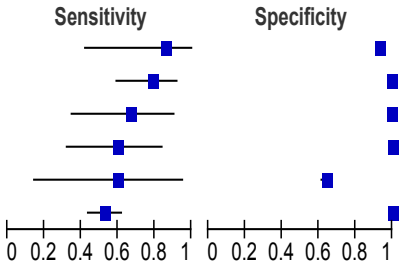
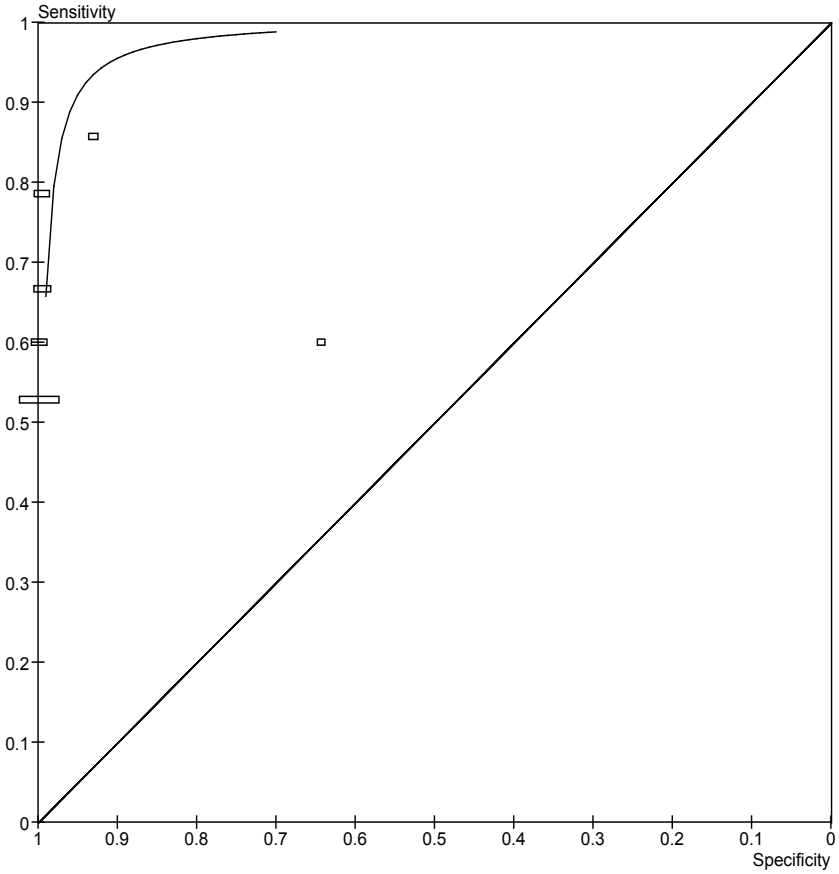


Figure T.28: ROC curve for triple serum test for trisomy



Trisomy 13

Study characteristics

One study[38] including a total of 1055 women (2 T13, 1053 no T13) provided data on the use of the triple serum test (AFP, free-β hCG, uE3) for the detection of trisomy 13. The study was published in 2000. The study population was recruited as a cohort and reported results for singleton pregnancies only. The within study prevalence of T13 was 0.19% (Table T.16). The study used a positive test threshold of 1:299.

Table T.16: Study characteristics for triple serum test for trisomy 13

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence
Kishida 2000[38] Japan	Cohort (prospective)	34.9 ± 0.2 (mean±SE)	14–20	Singleton	0.19

Methodological quality

The study did not include a spectrum of patients that is representative of those who are likely to be seen in practice; however, the study did describe the inclusion and exclusion criteria used to enroll participants into the study. The study provided insufficient information to assess its methodological quality for the remaining components including the description of the reference standard and screening test and any intermediate/indeterminate results and patient withdrawals.

Quantitative results

The DR was 50% (95% CI: 1 to 99); the FPR was 36% (95% CI: 33 to 39); PPV was 0.26%. The LR+ was 1.39 and the LR- was 0.78. The uncertainty in the DR as indicated by the wide 95% CI is a result of the small study population and low prevalence of the condition.

Open neural tube defects (spina bifida and anencephaly)

Two studies,[17,57] published in 2000 and including 83,240 pregnancies, examined the use of the triple serum test to screen for anencephaly. One study[57] examined the use of the test to screen for spina bifida. Both studies examined clinical cohorts and reported only on singleton pregnancies (Table T.17). The within study prevalence for spina bifida was 0.01% and for anencephaly was 0.07% and 0.04%, respectively. One study[96] used a positive test threshold of 1:290, the other used an AFP measurement of ≥ 2.0 MoM.

Table T.17: Study characteristics for triple serum test for open neural tube defects

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence (%)
Benn 2000[17] United States	Cohort (retrospective)	ND	ND	Singleton	0.04 (anencephaly)
Onda 2000[57] Japan	Cohort (prospective)	32.2	15–21.9	Singleton	0.01 (spina bifida) 0.07 (anencephaly)

Methodological quality

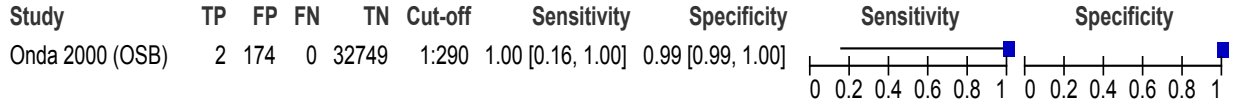
Neither study provided enough detail to adequately assess whether the spectrum of patients included in the studies is representative of those who are likely to be seen in practice, and neither study clearly described the inclusion and exclusion criteria. The reference standard classification was unclear for both studies as was the description of the execution of the index test and reference standard. Neither study reported intermediate/indeterminate test results in the analysis of data whereas or accounted for patient withdrawals in the analysis of data. One study[57] accounted for problems related to partial verification bias as all participants received confirmation of the diagnosis by the reference standard. Neither of the studies reported that verification of the true disease status of the fetus was done with the same reference standard; therefore, the results of both studies were likely affected by differential verification bias.

Quantitative results

Spina bifida

The DR was 100% (95% CI: 16 to 100) and the FPR 1% (95% CI: 0 to 1). The PPV was 1.14% and the LR+ and LR- were approximately 166.6 and 0.17.

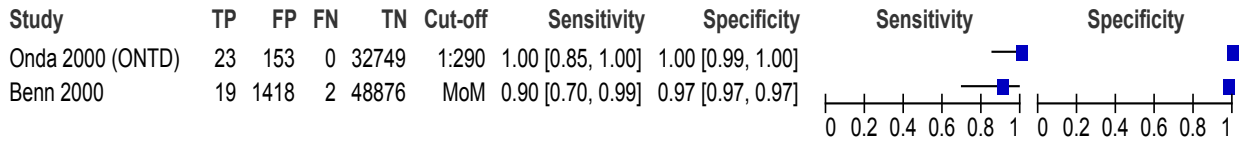
Figure T.29: Triple serum test for spina bifida



Anencephaly

The DRs and FPRs for the two studies were, respectively, 100% (95% CI: 85 to 100) and 90% (95% CI: 70 to 99), and 0% (95% CI: 0 to 1) and 3% (95% CI: 3 to 3). The PPV was 13.07 and 1.32%; the LR+ and LR- were, respectively, 195.8 and 30.0, and 0.02 and 0.10.

Figure T.30: Triple serum test for anencephaly



Quadruple serum test

Trisomy 21

Study characteristics

Seven studies,[16,33,45,46,69,79,80] published between 2003 and 2010 and including a total of 182,221 women (350 T21, 181,871 no T21), provided data on the use of the quadruple serum test (AFP, free-β hCG, uE3, inhibin-A) for the detection of trisomy 21 (Figure T.32). Six studies reported results for singleton births only and one study did not describe the pregnancy type. The within study prevalence of trisomy 21 ranged from 0.05 to 0.63%. All studies used a cohort design. Positive test thresholds varied from 1:250 (three studies), 1:270 (two studies), and 1:300 (two studies).

Table T.18: Study characteristics for quadruple test for trisomy 21

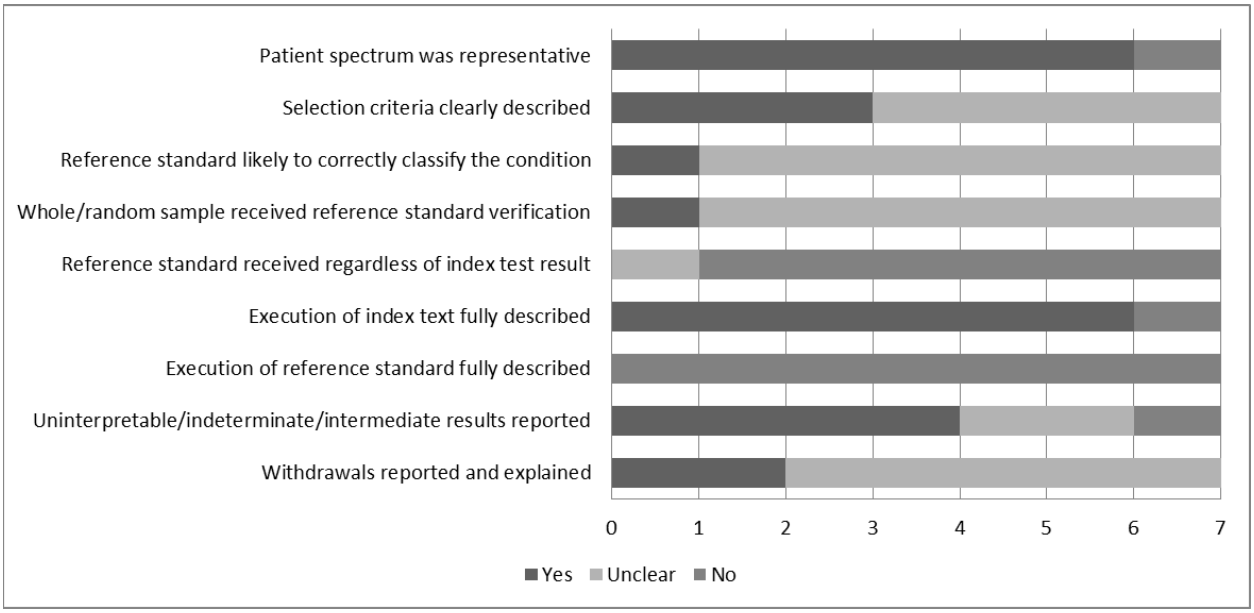
Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Benn 2003[16] USA	Cohort (retrospective)	27.8	14.0–21.9	Singleton	0.19
Jaques 2006[33] Australia	Cohort (retrospective)	30.3 (mean) (14–51)	ND	ND	0.16
MacRae 2010[45] Canada	Cohort (prospective)	30.6 (IQR: 26.6–34.4)	15–20^{+6}	Singleton	0.63
Malone 2005[46] USA	Cohort (prospective)	21.6% ≥ 35	15–18	Singleton	0.25
Shaw 2010[69] Taiwan	Cohort (prospective)	29.5 ± 3.6 (mean ± SD)	15–20	Singleton	0.05

Wald 2003 (SURUSS)[80] UK	Cohort (prospective)	ND	14–20	Singleton	0.21
Wald 2003[79] UK	Cohort (prospective)	ND	14–22	Singleton	0.19

Methodological quality

Six of the seven studies[16,33,46,69,79,80] included a spectrum of patients that is representative of those who are likely to be seen in practice. Three studies[45,46,69] provided a clear definition of both the inclusion and exclusion criteria for entry into the studies. One study[46] reported the use of an adequate reference standard to correctly classify the trisomy 21 cases. The other studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. One study[46] accounted for the effects of partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All the studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. All studies but one[33] adequately described the index test, including the characteristics of the technology, the software that was used for risk calculation and the positive test threshold. None of the studies adequately described the execution of the reference standard. Four studies[45,46,79,80] clearly reported intermediate/indeterminate test results in the analysis of data, and two[33,46] described patient withdrawals/dropouts (Figure T.31).

Figure T.31: Methodological quality of studies on quadruple serum test for trisomy 21



Quantitative results

The median DR was 85% (range: 81 to 90) and the median FPR 7% (range: 5 to 9). The study results with the least uncertainty (Malone[46]) had a DR of 85% (95% CI: 76 to 92) and FPR of 9% (95% CI: 8 to 9) (Figure T.32). PPV ranged from 0.05–0.63%. The LR+ ranged from 9.44 to 18.0;

the LR- from 0.11 to 0.19 (Appendix T.E, Table T.E.11). The corresponding ROC curve is presented in Figure T.33.

Figure T.32: Quadruple serum test for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
MacRae 2010	9	82	1	1501	1:200	0.90 [0.55, 1.00]	0.95 [0.94, 0.96]
Benn 2003	39	2133	6	21571	1:270	0.87 [0.73, 0.95]	0.91 [0.91, 0.91]
Jaques 2006	23	1122	4	15458	1:250	0.85 [0.66, 0.96]	0.93 [0.93, 0.94]
Malone 2005	74	2988	13	32161	1:300	0.85 [0.76, 0.92]	0.91 [0.91, 0.92]
Wald 2003 (SURUSS)	69	2125	13	35155	1:250	0.84 [0.74, 0.91]	0.94 [0.94, 0.95]
Shaw 2010	9	968	2	20502	1:270	0.82 [0.48, 0.98]	0.95 [0.95, 0.96]
Wald 2003	71	3200	17	42905	1:300	0.81 [0.71, 0.88]	0.93 [0.93, 0.93]

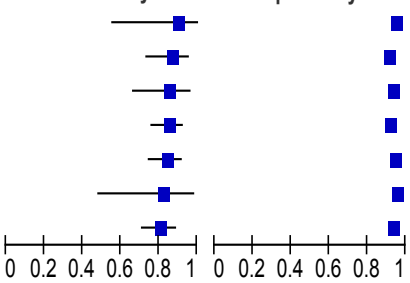
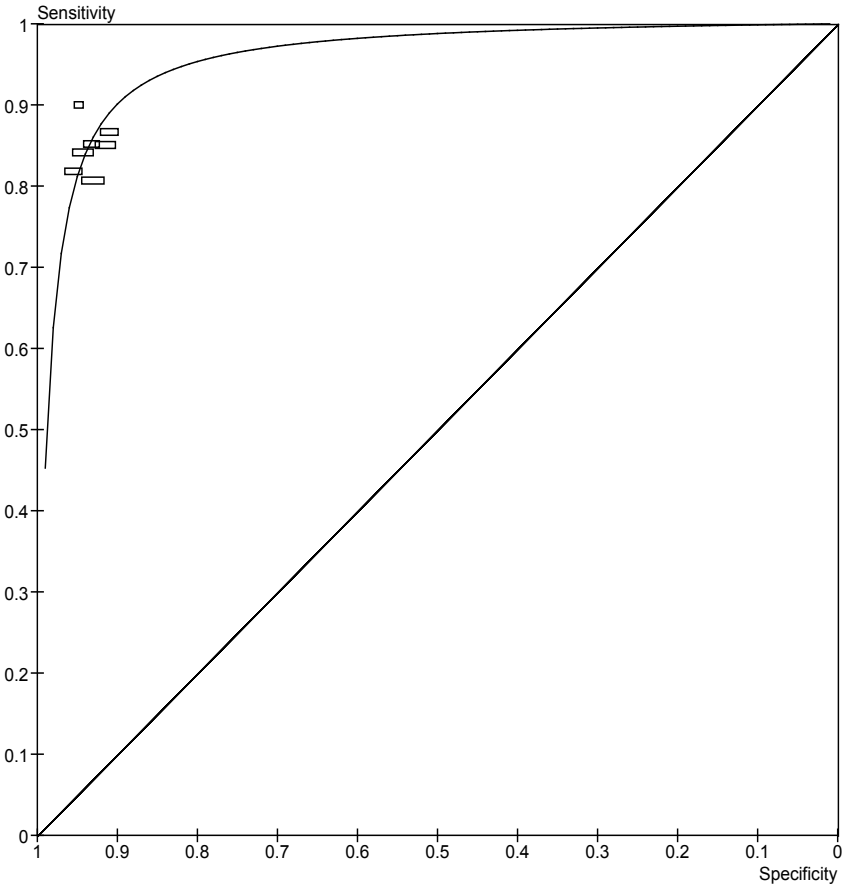


Figure T.33: ROC curve for quadruple serum test for trisomy 21



Trisomy 18

Study characteristics

Two studies,[21,33] published, respectively, in 2006 and 2007 and including a total of 51,740 women (22 T18, 51,718 no T18), provided data on the use of the quadruple serum test (AFP, free-β hCG, uE3, inhibin-A) for screening for trisomy 18 (Table T.19). Both studies recruited study participants as

clinical cohorts. One study reported results for singleton births only and the other did not report pregnancy type. The within study prevalence of trisomy 21 was 0.04 and 0.05%. Both studies used a positive test threshold of 1:250.

Table T.19: Study characteristics for quadruple serum test for trisomy 18

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Breathnach 2007[21] USA	Cohort (prospective)	23%>35	15–18	Singleton	0.04
Jaques 2006[33] Australia	Cohort (retrospective)	30.3 (mean) (14–51)	ND	ND	0.05

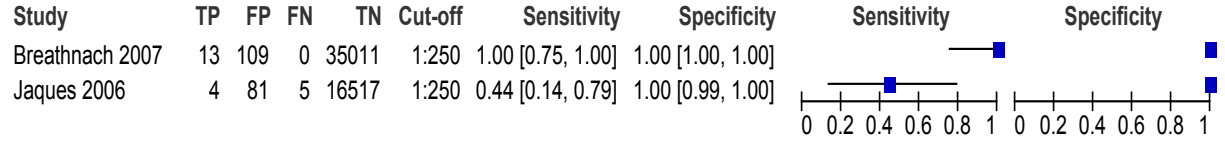
Methodological quality

The two studies[21,33] included a spectrum of patients that is representative of those who are likely to be seen in practice; however, only one of the studies[21] provided an adequate description of the inclusion and exclusion criteria. Neither study used an adequate reference standard to assess all pregnancies. One study[21] clearly accounted for the effects of partial verification bias as all participants received confirmation of the diagnosis by the reference standard. Both studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. One study[21] fully reported the characteristics of the technology, the software that was used for risk calculation and the positive test threshold. None of the studies provided a complete description of the reference standard procedures. One study[21] clearly reported intermediate/indeterminate test results in the analysis of data whereas the other[33] accounted for patient withdrawals in the analysis of data.

Quantitative results

The DRs were 100% (95% CI: 75 to 100) and 44% (95% CI: 14 to 79) and the FPRs were 0.3 (95% CI: 0 to 0) and 0.5% (95% CI: 0 to 0). The DR reported by Jaques et al.[33] was 56% lower than that reported by Breathnach et al.;[21] however, there was great uncertainty in the two results. The PPV was 15% and 4.71%, respectively (Figure T.34). The LR+ values for the studies were, respectively, 333.3 and 88.0 and the LR- values 0 and 0.56.

Figure T.34: Quadruple serum test for T18



Trisomy 13

No studies provided outcome data on the use of the quadruple serum test for trisomy 13.

Open neural tube defects (spina bifida and anencephaly)

Study characteristics

One study[33] published in 2006 and including 17,281 pregnancies examined the use of the quadruple serum test to screen for open neural tube defects. The study included a clinical cohort and did not

describe the pregnancy type included. The within study prevalence of spina bifida was 0.05% and of anencephaly was 0.03%. The study used a positive test threshold of 1:250 (see Table T.19 above).

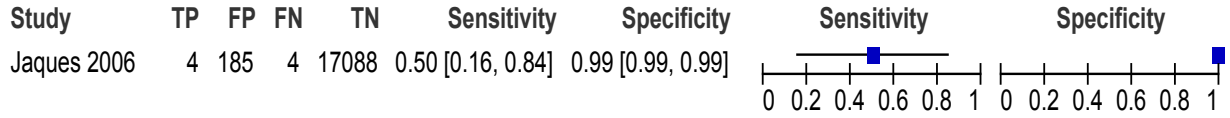
Methodological quality

The study clearly included a spectrum of patients that is representative of those who are likely to be seen in practice; however, the enrollment criteria, appropriateness of reference standards, and attempt to minimize partial verification bias were unclear. The study did not use the same reference standard to assess all index test results; therefore, the effect of differential verification bias needs to be taking into account in the analysis of screening accuracy. Further, the study did not provide a complete description of the execution of the index test, including the characteristics of the technology, and failed to provide a complete description of the reference standard procedures. The study did not report intermediate/indeterminate test results in the analysis of data, but it did account for patient withdrawals in the analysis of data.

Quantitative results

The DR was 50% and there was great uncertainty with respect to this result (95% CI: 16 to 84).The FPR was 1% (95% CI: 1 to 1), and the PPV 2.12% (Figure T.35). The LR+ and LR- values were 50.0 and 0.51.

Figure T.35: Quadruple serum test for spina bifida

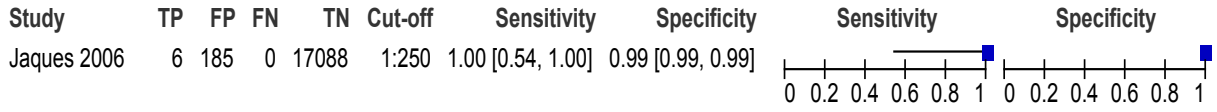


Anencephaly

Quantitative results

The DR was 50% and there was great uncertainty regarding the result (95% CI: 54 to 100); the FPR was 1% (95% CI: 1 to 1). The PPV was 3.14% (Figure T.36). The LR+ and LR- values were 50.0 and 0.51

Figure T.36: Quadruple serum test for anencephaly



Full integrated screening

Trisomy 21

Study characteristics

Four studies,[15,45,80,84] published between 2003 and 2010 and including a total of 38,002 women (89 T21, 37,913 no T21), provided data on the use of full integrated screening (PAPP-A and NT, quadruple serum test) for the detection of trisomy 21 (Figure T.38). One study[15] was reported as an assessment of sequential screening; however, the results reported by the authors were for only those women who received the combined results of first and second trimester tests and therefore equivalent to full integrated screening. All studies recruited participants as cohorts. Three studies

reported results for singleton births only; one study[84] did not describe the type of pregnancies screened. The within study prevalence of trisomy 21 ranged from 0.18 to 0.51%. Two studies used positive test thresholds of 1:250 with the remaining two studies using thresholds of 1:200 and 1:270.

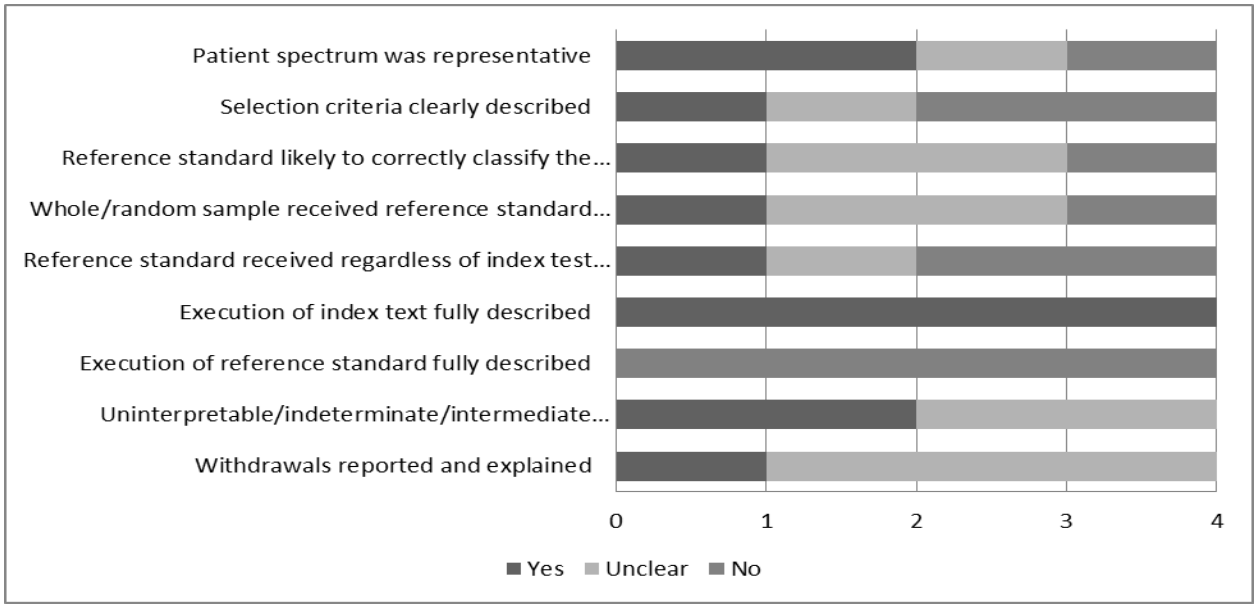
Table T.20: Study characteristics for full integrated screening for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Benn 2007[15] USA	Cohort (retrospective)	36.2	ND	Singleton	0.31
MacRae 2010[45] Canada	Cohort (prospective)	30.6 (IQR: 26.6–34.4)	15–20^{+6}	Singleton	0.18
Wald 2003 (SURUSS)[80] UK	Cohort (prospective)	ND	14–20	Singleton	0.21
Weisz 2007[84] UK	Cohort (retrospective)	31.7 (mean) 15–47	11–13$^{+6/7}$ (NT), second component measured at/before 15	ND	0.51

Methodological quality

Two[15,80] of the four studies included a spectrum of patients that is representative of those who are likely to be seen in practice. One study[45] clearly described the inclusion and exclusion criteria for the study. One study[15] used an adequate reference standard to correctly classify the trisomy 21 cases. The other three studies[45,80,84] used a combination of reference standards that included karyotyping for screen-positive cases. One study[15] clearly accounted for the effects of partial verification bias as all participants received confirmation of the diagnosis by a reference standard. The same study provided a complete description of the execution of the index test, the characteristics of the technology, the software that was used for risk calculation and positive test threshold. None of the studies adequately described the execution of the reference standard. Two studies[45,80] clearly reported intermediate/indeterminate test results in the analysis of data and one[15] study clearly accounted for patient withdrawals in the analysis of data (Figure T.37).

Figure T.37: Methodological quality of studies on full integrated screening for trisomy 21



Quantitative results

The median DR was 85% (range: 80 to 91) and the median FPR was 7% (range: 3 to 6) (Figure T.38). The PPV ranged from 4.32 to 10.87%. The study results with the least uncertainty (Wald[80]) had a DR of 91% (95% CI: 81 to 97) and an FPR of 3% (95% CI: 3 to 3). The LR+ ranged from 14.33 to 30.0 and the LR- from 0.09 to 0.21 (Appendix T.E, Table T.E.12). The corresponding ROC curve is presented in Figure T.39. The boxes representing the studies are proportional to the sample size for the individual studies.

Figure T.38: Full integrated screening for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
Wald 2003 (SURUSS)	59	849	6	29461	1:250	0.91 [0.81, 0.97]	0.97 [0.97, 0.97]
Benn 2007	6	133	1	2316	1:270	0.86 [0.42, 1.00]	0.95 [0.94, 0.95]
Weisz 2007	10	82	2	2238	1:250	0.83 [0.52, 0.98]	0.96 [0.96, 0.97]
MacRae 2010	4	71	1	2763	1:260	0.80 [0.28, 0.99]	0.97 [0.97, 0.98]

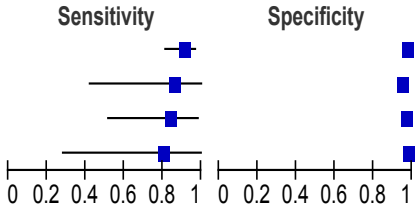
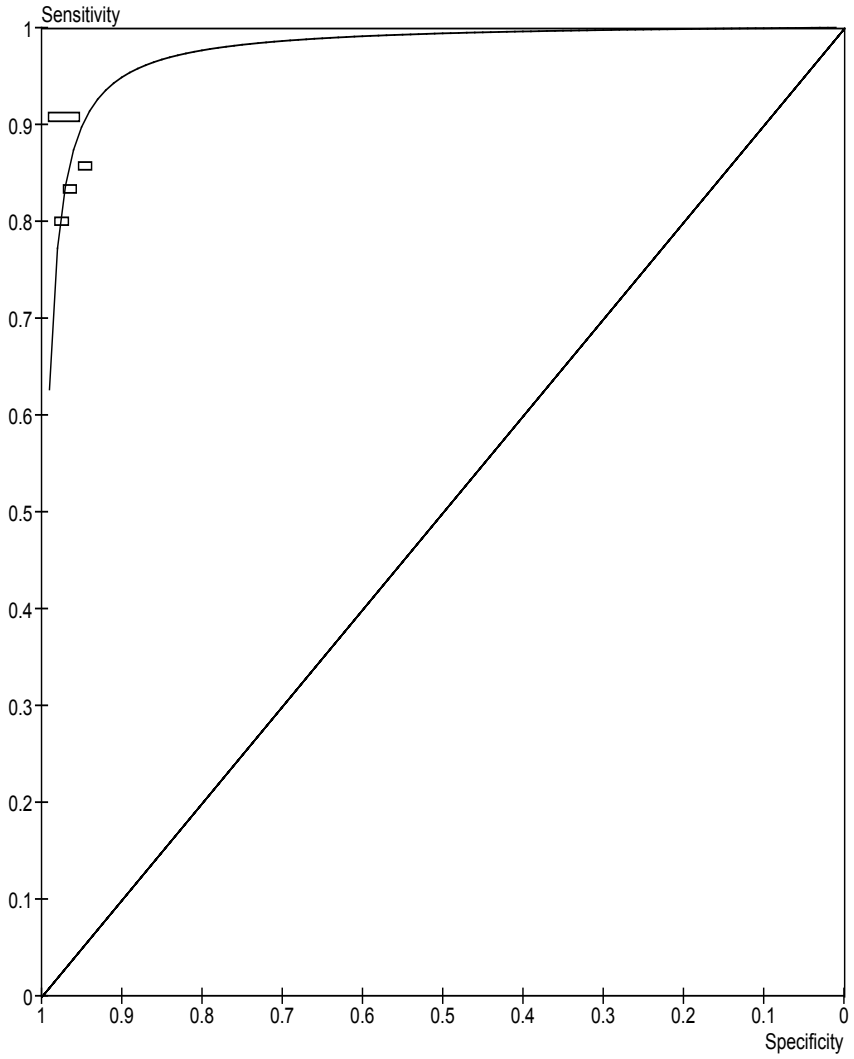


Figure T.39: ROC curve for full integrated test for trisomy 21



Trisomy 18

Study characteristics

One study[15] published in 2007 and including a total of 2256 pregnancies (3 T18/2253 no T18) provided data on the use of full integrated serum screening for the risk of trisomy 18. The study recruited participants as a clinical cohort and reported results for singleton births only. The within study prevalence was 0.13%, and used a positive test threshold of 1:100 (Table T.21).

Table T.21: Study characteristics for full integrated test for trisomy 18

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence
Benn 2007[15] USA	Cohort (retrospective)	36.2 (mean)	ND	Singleton	0.13

Methodological quality

The study included a spectrum of patients that is representative of those who are likely to be seen in practice; however, the study did not provide definitions for the exclusion and exclusion criteria that were applied to enroll participants into the study. The study used a reference standard that would correctly classify trisomy 13 cases and applied the reference standard to minimize partial confirmation bias. The index test results were verified by the same reference standard, hence it is unlikely that the results were affected by differential verification bias. The study used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. The study provided a complete description of both the execution of the index test (including the characteristics of the technology, the software that was used for prenatal trisomy 13 risk calculation and the cut-off level of risk for invasive testing), as well as a full description of the execution of the reference standard. The study did not account for intermediate/indeterminate results, but did provide an adequate description of patient withdrawals in the analysis of data.

Quantitative results

The DR and FPR were, respectively, 100% (95% CI: 29 to 100) and 6% (95% CI: 5 to 7). The positive predictive value was 2.16% and the LR+ and LR- were 16.7 and approximately 0.13.

Trisomy 13

No studies provided outcome data on the use of full integrated screening for T13.

Integrated screening – Inhibin A

Trisomy 21

Study characteristics

Three studies,[45,55,78] published between 2008 and 2010 and including a total of 49,965 women (141 T21, 49,824 no T21), provided data on the use of the integrated test without inhibin-A for the risk of trisomy 21 (Table T.22). The participants were all recruited as clinical cohorts, and the studies reported results for singleton births only. The within study prevalence of trisomy 21 ranged from 0.23 to 0.33%. All studies recruited participants in clinical cohorts. Each study used a different positive test threshold: 1:150, 1:200, and 1:260.

Table T.22: Study characteristics for integrated screening-inhibin A for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
MacRae 2010[45] Canada	Cohort (prospective)	30.6 (IQR: 26.6–34.4)	8–13^{+6} (FT), 15–20^{+6} (ST)	Singleton	0.23
Okun 2008[55] Canada	Cohort (prospective)	32 (mean)	12.5 (FT), at/before 18 (ST)	Singleton	0.27
Wald 2009[78] UK	Cohort (retrospective)	33 (15–51)	12^{+4}–16^{+1}	Singleton	0.33

Methodological quality

Two[55,78] of the three studies clearly included a spectrum of patients that is representative of those who are likely to be seen in practice. Only one study[45] provided a clear definition of both the inclusion and exclusion criteria for entry into the study. The three studies used a combination of

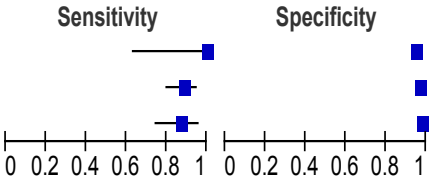
reference standards that included karyotyping for screen-positive cases and a less thorough standard such as physician examination upon birth or termination (without subsequent karyotyping) or follow-up with patients or health providers for the negative cases. One study[78] clearly accounted for the effects of partial verification bias as all participants received confirmation of the diagnosis by the reference standard. All studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Two studies[45,55] provided a complete description of the execution of the index test, including the characteristics of the technology, the software that was used for risk calculation and the positive test threshold. Two studies[55,78] adequately described the execution of the reference standard. Indeterminate and intermediate test results were accounted for in the data analysis of two studies,[45,55] and two studies[55,78] adequately described withdrawals/dropouts.

Quantitative results

The median DR was 84.5% (range: 87 to 100) and the median FPR was 3.5% (range: 2 to 5). The study results with the least uncertainty (Okun[55]) reported a DR of 88% (95% CI: 80 to 94) and an FPR of 3% (95% CI: 3 to 4). The PPV ranged from 4.35 to 12.06% (Figure T.40). The LR+ were, respectively, 20.00, 29.33, and 43.50. The LR- were 0, 0.12, and 0.13.

Figure T.40: Integrated screening - Inhibin A for trisomy 21

Study	TP	FP	FN	TN	Cut-off	Sensitivity	Specificity
MacRae 2010	8	176	0	3258	1:260	1.00 [0.63, 1.00]	0.95 [0.94, 0.96]
Okun 2008	76	1068	10	31073	1:200	0.88 [0.80, 0.94]	0.97 [0.96, 0.97]
Wald 2009	41	299	6	13950	1:150	0.87 [0.74, 0.95]	0.98 [0.98, 0.98]



Trisomy 18

No studies provided outcome data on screening for T18 using the integrated test without inhibin-A.

Trisomy 13

No studies provided outcome data on screening for T13 using the integrated test without inhibin-A.

Serum integrated screening

Trisomy 21

Study characteristics

Two studies,[39,80] published in 2003 and 2005 and including a total of 49,965 women (141 T21, 49,824 no T21), provided data on the use of integrated serum screening for the detection of trisomy 21 (Table T.23). Both studies recruited participants in clinical cohorts and reported results for singleton births only. The within study prevalence of trisomy 21 ranged was 0.18 and 0.21%. The studies used positive test thresholds of, respectively, 1:100 and 1:250.

Table T.23: Study characteristic for serum integrated screening for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Knight 2005[39] USA	Cohort (prospective)	27.8 ± 5.5 (mean±SD)	8–13 (FT), ND (ST)	ND	0.18
Wald 2003 (SURUSS)[80] UK	Cohort (prospective)	ND	10–13 (FT), 14–20 (ST)	Singleton	0.21

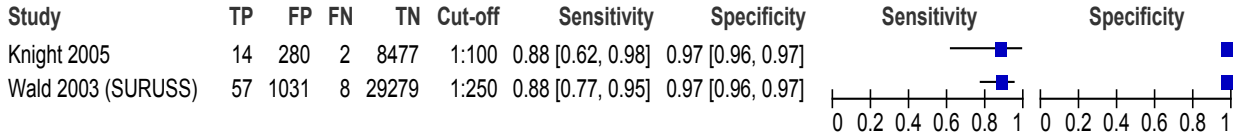
Methodological quality

One[80] of the two studies included a spectrum of patients that is representative of those who will likely to be seen in practice. Neither study clearly reported the inclusion and exclusion criteria. One study[39] used an adequate reference standard and adequately accounted for the effects of partial verification bias as all participants received confirmation of the diagnosis by the reference standard. Both studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Both studies provided an adequate description of the index test in terms of the characteristics of the technology, the software that was used for risk calculation and the positive test threshold; however, they did not provide an adequate description of the reference standard procedures. Both studies accounted for the presence of indeterminate or intermediate test results in the analysis of data and one[39] adequately described withdrawals/dropouts.

Quantitative results

The DRs were, respectively, 88% (95% CI: 62 to 98) and 88% (95% CI: 77 to 95) the FPR for both studies was 3% (95% CI: 3 to 4) (Figure T.41). The PPV was 4.76 and 5.24%, respectively. For both studies the LR+ was 29.33 and the LR- was 0.12.

Figure T.41: Serum integrated test for trisomy 21



Trisomy 18

No studies provided outcome data on the use of serum integrated screening for trisomy 18.

Trisomy 13

No studies provided outcome data on the use of serum integrated screening for trisomy 13.

Sequential screening

Trisomy 21

Study characteristics

Two studies,[46,59] published in 2005 and 2004 and including a total of 41,751 women provided data on the use of sequential screening for the detection of trisomy 21 (148 T21, 41,603 no T21) (Table T.24). Both studies recruited participants in clinical cohorts and the studies reported results for

singleton births only. The within study prevalence of trisomy 21 were 0.26 and 0.74%. One study used a positive test threshold of 1:300, the other a threshold of 1:270.

Table T.24: Study characteristics for sequential screening for trisomy 21

Author year Country	Recruitment (Timing)	Median maternal age (yr) (range)	Median gestational age (wk) (range)	Pregnancy type	Study prevalence %
Malone 2005[46] USA	Cohort (prospective)	21.6%≥35	10^{+3}–13^{+6} (FT)	Singleton	0.26
Platt 2004[59] USA and Canada	Cohort (prospective)	34.5±4.6 (mean±SD)	12.2±0.8 (mean±SD) (FT)	Singleton	0.74

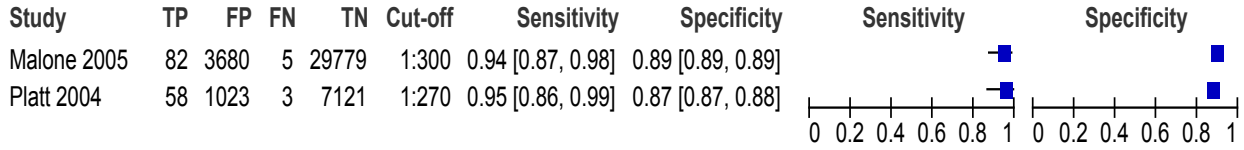
Methodological quality

The two studies[46,59] included a spectrum of patients that is representative of those who are likely to be seen in practice. Both studies provided a clear definition of the criteria used for inclusion and exclusion of participants from the study. One study[46] used an adequate reference standard to correctly classify the trisomy 21 cases. The two studies clearly accounted for the effects of partial verification bias as all participants received confirmation of the diagnosis by the reference standard. Both studies used a combination of reference standards that included karyotyping for screen-positive cases and physician examination upon birth or termination (without subsequent karyotyping) for negative cases, or follow-up with patients or health providers. Both studies failed to provide an adequate description of the index and reference standard tests. The two studies accounted for the presence of indeterminate or intermediate test results and patient withdrawals/dropouts in the analysis of data.

Quantitative results

The DR were, respectively, 94% (95% CI: 87 to 98) and 95% (95% CI: 86 to 99); the FPRs, respectively, 11% (95% CI: 11 to 11) and 12% (95% CI: 12 to 13) (Figure T.42). The PPV ranged from 2.18 to 5.37%. The LR+ were 8.55 and 7.31; the LR- were 0.07 and 0.06.

Figure T.42: Sequential screening test for trisomy 21



Trisomy 18

No studies provided outcome data on the use of sequential screening for trisomy 18.

Trisomy 13

No studies provided outcome data on the use of sequential screening for trisomy 13.

Contingent screening test

The literature search and selection did not identify any empirical screening accuracy studies examining the use of contingent screening for trisomy 13, 18, or 21.

Repeated measures screening tests

The literature search and selection did not identify any empirical screening accuracy studies examining the use of repeated measures screening for trisomy 13, 18, or 21.

Second trimester ultrasound screening for open neural tube defects

The initial search for this review identified two systematic reviews[97,98] reporting on the use of second trimester ultrasound for the detection of spina bifida, anencephaly, and encephalocele among other chromosomal and structural anomalies. Both reviews provided individual study data on the detection rate and false positive rates. The review by Ritchie et al.[98] provided an overview of the earlier review by Bricker et al.[97] and included an additional electronic and grey literature search for studies on second trimester ultrasound for ONTDs that provided data sufficient to calculate DRs and FPRs for spina bifida, anencephaly, or encephalocele. The electronic search was current to September 2003. Hence, the review by Ritchie et al. was considered the most up-to-date and rigorous review on the performance of second trimester ultrasound for the detection of specific ONTDs.

Spina bifida

Study characteristics

Ritchie et al.[98] reported the results of six studies that provided sufficient outcome data to calculate the performance characteristics of second trimester ultrasound for the detection of spina bifida. Two of the studies (Crane 1994 and Levi 1995) were reported in the review by Bricker et al.,[97] and the remaining four studies were identified through the search conducted by Ritchie et al.[98] The studies were published between 1994 and 2001 and varied in design and setting and in the training of the sonographer conducting the ultrasound. The prevalence of spina bifida within the study population varied from 0.05 to 0.26%.

Table T.25: Study characteristics for ultrasound for spina bifida (from Ritchie et al.[98])

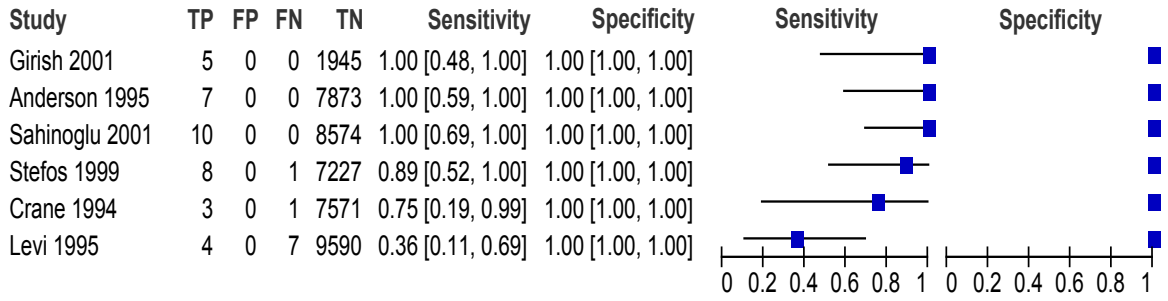
Author year Country	Recruitment (Timing)	Median gestational age (wk) (range)	Sonographer	Pregnancy type	Study prevalence %
Anderson 1995	(prospective)	ND	ND	ND	0.09
Crane 1994 USA	RCT (prospective)	15–22	Technicians, physicians, sonologists, radiologists	Unselected	0.05
Girish 2001 India	ND (prospective)	ND	ND	ND	0.26
Levi 1995 Belgium	ND (prospective)	16–20	Obstetricians, technicians, sonographers	Unselected	0.11
Sahinoglu 2001	ND (prospective)	ND	ND	ND	0.12
Stefos 1999	ND (prospective)	ND	ND	ND	0.12

Quantitative results

The median DR was 92% (range: 36 to 100) and the FPR was 0% in all studies. There was great uncertainty around all DR results due to the small study sample size and the low prevalence of the condition (the narrowest range of uncertainty was a 95% CI of 69 to 100). There was little

uncertainty with respect to the FPR. The positive preditive values ranged from 90 to 97%. The estimated LR+ ranged from 3033 to 9500; the estimated LR- ranged from 0.05 to 0.65 (Appendix T.E, Table T.E.13).

Figure T.43: Ultrasound for spina bifida



Anencephaly

Study characteristics

Ritchie et al.[98] report the results of six studies that provided sufficient outcome data to calculate the performance characteristics of second trimester ultrasound for the detection of anencephaly. Two of the studies (Crane 1994 and Levi 1995) were reported in the review by Bricker et al.,[97] and the remaining four studies were identified through the search conducted by Ritchie et al.[98] The studies were published between 1994 and 2001 and varied in design and setting and in the training of the sonographer conducting the ultrasound. The prevalence of anencephaly within the study population varied from 0.4 to 0.26%.

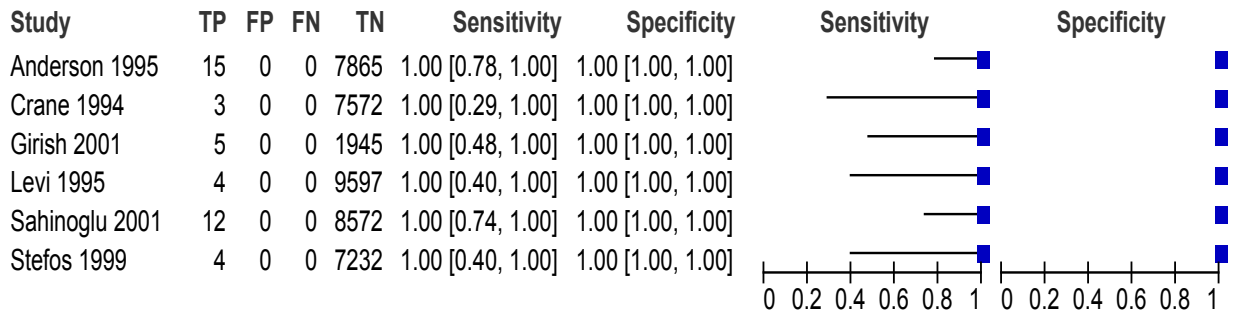
Table T.26: Study characteristics for ultrasound for anencephaly

Author year Country	Recruitment (Timing)	Median gestational age (wk) (range)	Sonographer	Pregnancy type	Study prevalence %
Anderson 1995	(prospective)	ND	ND	ND	0.19
Crane 1994 USA	RCT (prospective)	15–22	Technicians, physicians, sonologists, radiologists	Unselected	0.04
Girish 2001 India	(prospective)	ND	ND	ND	0.26
Levi 1995 Belgium	ND (prospective)	16–20	Obstetricians, technicians, sonographers	Unselected	0.04
Sahinoglu 2001	(prospective)	ND	ND	ND	0.06
Stefos 1999	(prospective)	ND	ND	ND	0.14

Quantitative results

The DR and FPR for a all studies was 100% and 0%, respectively. Nevertheless, there was great uncertainty regarding the DR with the narrowest range of uncertainty being a 95% CI of 78 to 100. The positive preditive value was 100% in each study. The estimated LR+ ranged from 3066 to 9700; the estimated LR- ranged from 0.03 to 0.12 (Appendix T.E, Table T.E.14).

Figure T.44: Ultrasound for anencephaly



Encephalocele

No empirical studies were identified that provided outcome data on the use of second trimester ultrasound for the detection of encephalocele.

Summary of data on screen performance for all conditions and tests

Tables T.27 to T.31 summarize the main results presented on this section regarding the performance of the first and second trimester and two-step screening tests.

Table T.27: Summary of screening test performance for estimating risk of trisomy 21

Test	Total no. studies (total +T21/total –T21)	Median DR % (range)	Median FPR % (range	Within study prevalence %	PPV %
First Trimester					
Nuchal translucency	23 (756/170,347)	75 (40–100)	5 (1–23)	0.08–2.41	1.59–25.45
Double	9 (220/66,129)	76 (62–88)	9 (5–19)	0.17–0.56	1.02–6.01
Combined	30 (1706/395,315)	88 (50–100)	5 (1–9)	0.15–3.56	1.96–82.4
Second Trimester					
Dual	8 (423/222,592)	65 (50–76)	6 (3–11)	0.08–0.81	0.47–7.67
Triple	14 (1268/631,160	80.5 (60–100)	9.5 (4–54)	0.10–1.92	1.04–4.95
Quadruple	7 (350/181,871)	85 (81–90)	7 (5–9)	0.05–0.63	0.92–9.89
Two-step Screens					
Full integrated	4 (89/39,713)	85 (80–91)	7 (3–6)	0.18–0.51	5.3–10.87
Integrated – inhibin A	3 (141/49,824)	84.5 (87–100)	3.5 (2–5)	0.23–0.33	4.35–12.06
Serum integrated	2 (81/39,067)	88	3	0.18–0.21	4.76–5.24
Sequential	2 (148/41,603)	94–95	11–13	0.26–0.74	2.18–5.37
Contingent	No studies	---	---	---	---
Repeated measures	No studies	---	---	---	---

Table T.28: Summary of screening test performance for estimating risk of trisomy 18

Test	Total no. studies (total +T18/total – T18)	Median DR % (range)	Median FPR % (range	Within study prevalence %	PPV %
First Trimester					
Nuchal translucency	7 (145/59,269)	90 (67–100)	4 (2–14)	0.03–0.51	0.63–4.62
Double	No studies	---	---	---	---
Combined	9 (119/79,181)	90 (33–100)	6 (0–8)	0.09–0.31	0.58–15.15
Second Trimester					
Dual	1 (9/25,521)	89	3	0.04	0.90
Triple	6 (192/543,432)	63.5 (53–86)	0.75 (0–36)	0.08–0.81	0.79–15.0
Quadruple	2 (22/51,718)	44–100	0.3–0.5	0.04–0.05	4.71–15.0
Two-step Screens					
Full Integrated	1 (3/2,253)	100	6	0.13	2.16
Integrated – Inhibin A	No studies	---	---	---	---
Serum Integrated	No studies	---	---	---	---
Sequential	No studies	---	---	---	---
Contingent	No studies	---	---	---	---
Repeated measures	No studies	---	---	---	---

Table T.29: Summary of screening test performance for estimating risk of trisomy 13

Test	Total no. studies (total +T13/total – T13)	Median DR % (range)	Median FPR % (range	Within study prevalence %	PPV %
First Trimester					
Nuchal translucency	5 (39/52,762)	97 (33–100)	3 (2–15)	0.02–0.13	0.16–1.69
Double	No studies	---	---	---	---
Combined	4(41/39,910)	78 (57–100)	8 (4–8)	0.09–0.23	0.94–2.03
Second Trimester					
Dual	No studies	---	---	---	---
Triple	1 (2/1,053)	50	36	0.26	0.19
Quadruple	No studies	---	---	---	---
Two-step Screens					
Full integrated	No studies	---	---	---	---
Integrated – inhibin A	No studies				
Serum integrated	No studies	---	---	---	---
Sequential	No studies	---	---	---	---
Contingent	No studies	---	---	---	---
Repeated Measures	No studies				

Table T.30: Summary of screening test performance for estimating risk of ONTDs

Test	Total no. studies (total +ONTD/total –ONTD)	DR %	FPR %	Within study prevalence %	PPV %
Triple					
Spina bifida	1 (2/32,923)	100	1	0.01	1.14
Anencephaly	2 (44/83,196)	90–100	0–3	0.04–0.07	1.32–13.07
Quadruple					
Spina bifida	1 (8/17,273)	50	1	0.05	2.12
Anencephaly	1 (6/17,273)	100	1	0.03	3.14

Table T.31: Summary of second trimester ultrasound screening for ONTDs (from Ritchie et al.[98])

Condition	Total no. studies (no. + condition/no. - condition)	Median DR % (range)	Median FPR % (range	Within study prevalence %	PPV %
Spina bifida	6 (37/42,780)	92 (35–100)	0 (0–0)	0.05–0.26	100
Anencephaly	6 (43/42,783)	100 (100–100)	0 (0–0)	0.04–0.26	100
Encephalocele	No studies	---	---	---	---

Effect Modifiers and Sensitivity Analyses

The effectiveness of an intervention may vary by particular characteristics of the study population, the technology being assessed, the health care providers, and the study setting (referred to as "effect modifiers").[99] Methodological choices may also influence the results and key methodological decisions should be investigated to determine the influence, if any, of these decisions on the findings of the review.[99] Due to the time limits imposed on this assessment, the investigation of potential effective modifiers and the robustness of results to methodological decisions was restricted to the two prenatal screening tests currently in use in Alberta, namely, the first trimester combined screen and the second trimester quadruple screen. The comparison of the relative influence of these factors and decisions was limited to an informal assessment (i.e. no formal statistical comparison between groups of studies was conducted). The potential effect modifiers examined were the gestational age at time of testing, and the positive test threshold; the methodological decisions examined concerned the size of the study population and the methodological quality of the studies.

Gestational age at testing

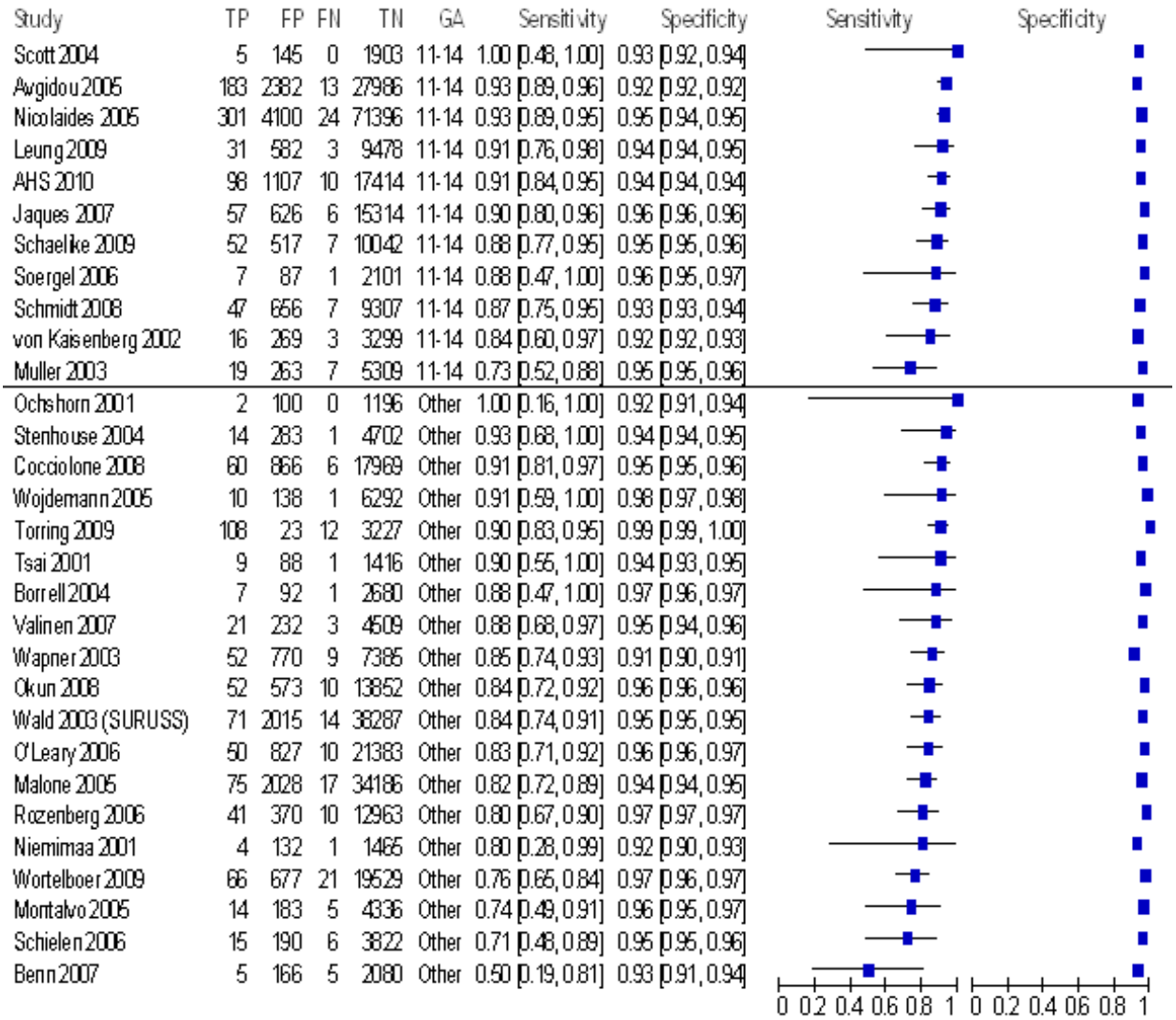
PAPP-A is most accurately assessed at 9 to 10 weeks' gestation, whereas satisfactory NT measurements are most consistently obtained between 11 to 13 weeks.[8] To enable collection of both measurements at the same visit, the SOGC guidelines recommend that the NT measurement and PAPP-A and hCG samples be taken between 11 to 13^{+6} weeks gestation.[8] Other researchers[80] recommend 10 weeks as providing the optimal compromise and consider 10–13 weeks an acceptable range. Neither the SOGC guidelines[8] nor the Alberta Maternal Serum Prenatal program indicate an optimal gestational age range for the measurement of the four biochemical measures (AFP, hCG, uE3, and inhibin-A) that comprise the quadruple serum test (Figure T.46 and Table T.32). In their large and influential studies, Wald et al.[80] used a gestational age of 14 to 20 weeks for second trimester serum tests, including the quadruple test, while Malone et al.[46] used a gestational age range of 15 to 18 weeks. To investigate the effect gestational age may have on test performance in screening programs, we grouped study data according to whether a study reported collecting

measurements from 11 to 14 weeks or used a wider range for the combined test and from 14 to 20 weeks or a wider range for the quadruple test.

Combined test

Eleven studies[7,9,32,42,50,51,64,66,67,70,77] indicated clearly (via study inclusion criteria or description of participant characteristics) that the included pregnancies were between 11 and 14 weeks' gestation at the time of combined testing. The remaining 19 studies (categorized as "other") either tested at gestational ages less than 11 weeks or slightly more than 14 weeks or did not report the gestational age at testing (Figure T.45 and Table T.32). There was substantial overlap between the results of both groups; however, the median DR for studies measuring NT and biochemical markers between 11 and 14 weeks was substantially better than that of studies that collected measurements starting earlier (as early as 7 weeks): 90.5% (73–100) vs. 84% (50–100), but only a small difference was observed between the median FPRs: 6% (4–8) vs. 5% (1–9).

Figure T.45: Subgroup analysis of combined test using gestational age



Quadruple Serum Test

Four studies[45,46,69,80] took biochemical measurements within 14 to 20 weeks. There was no obvious difference between the performance demonstrated by the studies that collected sera from 14 to 20 weeks and the studies that used a moderately wider range (14 to 22 weeks). There were no substantial differences between the median DR and FPR: 84.5% (82–90) vs. 84% (81–87) and 5.5% (5–9) vs. 7% (7–9).

Figure T.46: Subgroup analysis of quadruple test using gestational age

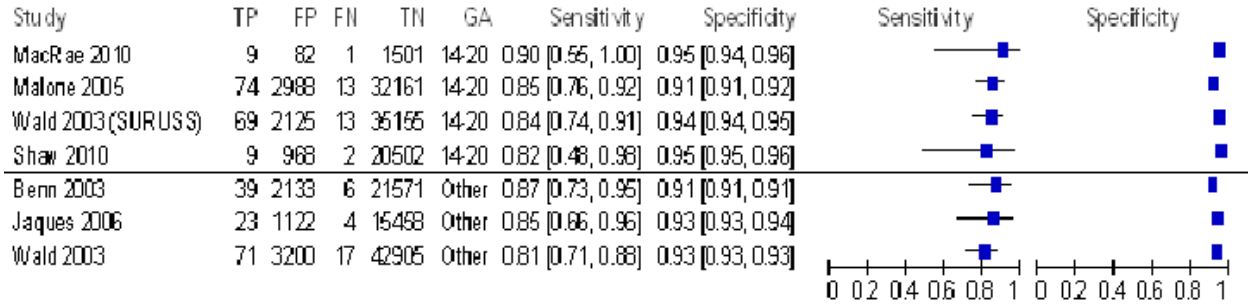


Table T.32: Subgroup analysis using gestational age

Test	Total no. studies (total T21/total no T21)	Median DR % (range)	Median FPR % (range)
Combined			
11-14 wk	11 (904/184,283)	90.5 (73–100)	6 (4–8)
Other	19 (819/211,032)	84 (50–100)	5 (1–9)
Quadruple			
14-20 wk	4 (190/95,482)	84.5 (82–90)	5.5 (5–9)
Other	3 (160/86,389)	84 (81–87)	7 (7–9)

Positive test threshold

The choice of positive test threshold varied across studies and raised the question of whether and to what degree test performance varied by choice of threshold. For this reason, we conducted an informal subgroup analysis of studies examining the combined and quadruple test for T21 based on the positive test threshold used.

Combined test

When the studies examining the combined test for T21 were grouped by positive test threshold, of the 29 studies, 14 used a threshold of 1:250 and 11 used a threshold of 1:300 (Figure T.47). There was a 2.5% difference in the median DR favoring the studies using a threshold of 1:300: 86.5% (range: 71 to 93) vs 89% (range: 82 to 100). There appeared to be little difference between the median FPR: 5% (range: 2 to 9) vs 5.5.% (range: 1 to 8). Nevertheless, as this is only an informal comparison, it is at best suggestive of a difference in performance and a formal comparison is required for stronger conclusions to be drawn. There were too few studies in the remaining groups and too much uncertainty in their results to determine whether the performance varied substantially when other thresholds were used.

Figure T.47: Subgroup analysis of combined test using positive test threshold

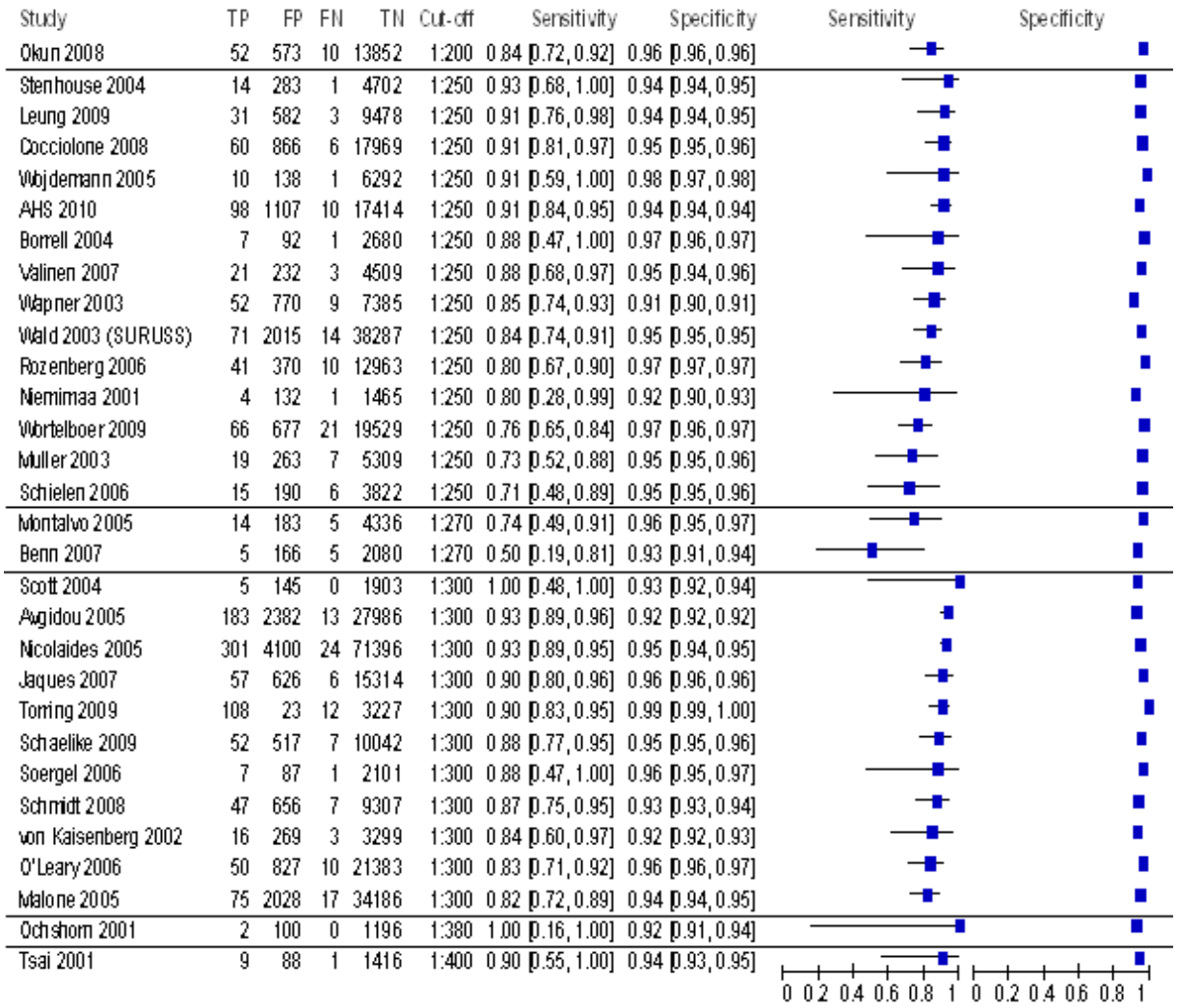


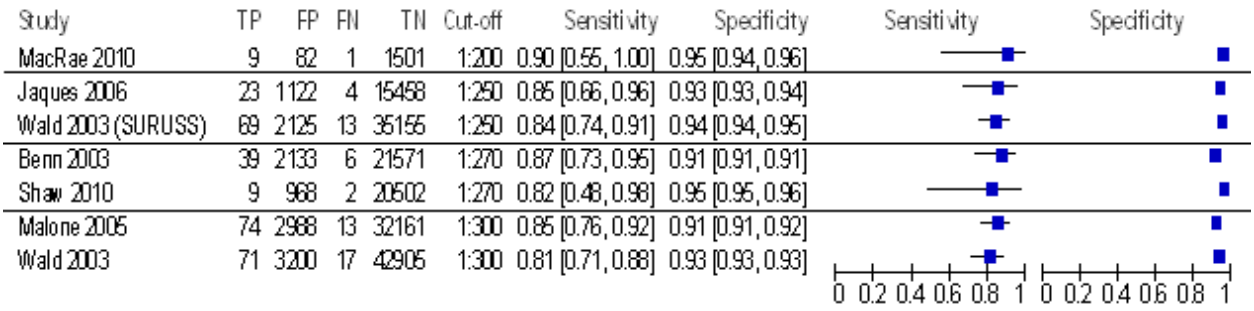
Table T.33: Subgroup analysis based on positive test threshold

Test	Total no. studies (total T21/total no T21)	Median DR % (range)	Median FPR % (range)
Combined			
1:250	14 (602/159,521)	86.5 (71–93)	5 (2–9)
1:300	11 (1001/211,804)	89 (82–100)	5.5 (1–8)

Quadruple serum test

When the studies examining the quadruple test for T21 were grouped by positive test threshold, there were no obvious differences between results of any of the test-cut-off categories. The small numbers of studies per group (maximum group size was two studies) and the uncertainty around the DR made it unlikely that clear differences would be made apparent using informal methods. None of the studies used a positive test threshold as low as that used by the Alberta Maternal Serum Prenatal Serum screening program, which uses a risk cut-off of 1:385 for trisomy 21.

Figure T.48: Subgroup analysis of quadruple test using positive test threshold



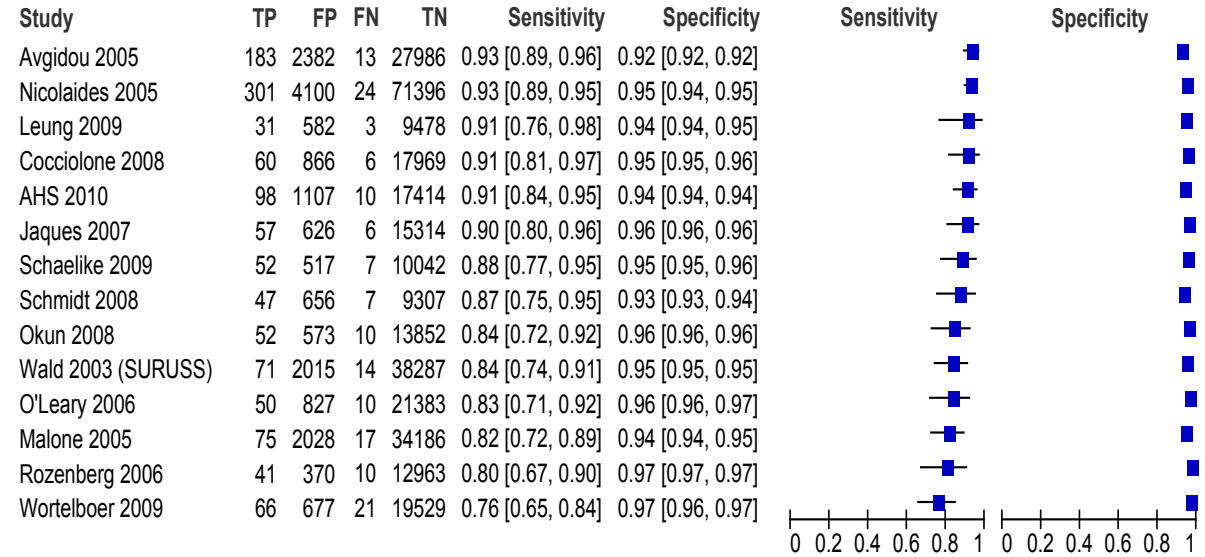
Study size

Due to the low prevalence of the conditions being examined, the included studies were restricted to those with at least 1000 participants. To investigate whether larger study populations would have resulted in more consistent and more precise estimates of test performance, we examined the effect of restricting the analysis to those studies with at least 10,000 participants.

Combined test

Fourteen[7,9,23,32,42,46,51,55,56,62,64,66,80,86] of the 30 studies examining the combined test included ≥ 10,000 pregnancies. The range of DR and FPR values for all studies was somewhat wider than those for studies with ≥ 10,000 pregnancies (88 [50–100] vs. 87% [76–93] and 5% [1–9] vs. 5% [3–8] , respectively); however, the median values for these measures showed little difference between all studies and those with ≥ 10,000 pregnancies (Figure T.49 and Table T.34).

Figure T.49: Studies on combined test with ≥10,000 pregnancies



Quadruple test

Six[16,33,46,69,79,80] of the seven studies examining the quadruple serum test included in the original analysis included ≥ 10,000 pregnancies. As a result, the sensitivity analysis was unable to indicate if an obvious difference in overall findings would have resulted by restricting the included studies to those with ≥ 10,000 pregnancies (Figure T.50 and Table T.34).

Figure T.50. Studies on quadruple test with ≥ 10,000 pregnancies

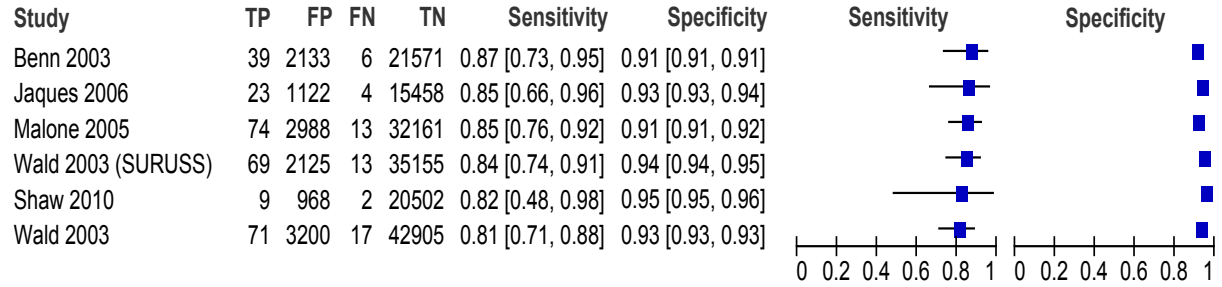


Table T.34: Sensitivity analysis based on study size

Test	Total no. studies (total T21/total no T21)	Median DR % (range)	Median FPR % (range)
Combined			
All studies	30 (1706/395,315)	88 (50–100)	5 (1–9)
≥ 10,000 pregnancies	13 (1283/325,873)	87 (76–93)	5 (3–8)
Quadruple			
All studies	7 (350/181,871)	85 (81–90)	7 (5–9)
≥ 10,000 pregnancies	6 (340/180,288)	84.5 (81–87)	7 (5–9)

Study quality

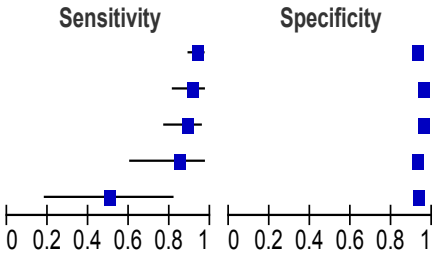
There is good empirical evidence that three potential limitations are associated with substantial over estimation of diagnostic test performance.[100] The differential verification of index test results (affecting almost 90% of the studies) is associated with a 2-fold overestimation of effect, not adequately describing the test being evaluated is associated with a 1.7-fold overestimation of effect, and not adequately describing the study population is associated with a 1.4-fold overestimation of effect. To investigate the potential influence of study quality on estimates of test performance for each of the two tests (first trimester combined and second trimester quadruple serum screening), we removed studies that were considered "unclear" or at high risk of bias for differential verification. In the analysis of the quadruple test, all studies were considered susceptible to differential verification bias, so a sensitivity analysis was based on the risk of bias due to an inadequate description of the index test.

Combined test

Five studies[7,15,23,64,77] assessing the combined test were not considered at low risk of differential verification bias. Four of the studies[7,15,64,77] were also considered to have adequately described the index text and one[64] also provided an adequate description of the study participants (Figure T.51 and Table T.35). The median DR for all studies of the combined test was 0.5% higher than for studies considered at low risk of bias (88% [81–90] vs. 87.5% [50–93]); the median FPR for all studies was 2% lower than for studies considered at low risk of bias (5% [1–9] vs. 7% [3–8]).

Figure T.51: Studies on combined test at low risk of bias

Study	TP	FP	FN	TN	Sensitivity	Specificity
Avgidou 2005	183	2382	13	27986	0.93 [0.89, 0.96]	0.92 [0.92, 0.92]
Cocciolone 2008	60	866	6	17969	0.91 [0.81, 0.97]	0.95 [0.95, 0.96]
Schaelike 2009	52	517	7	10042	0.88 [0.77, 0.95]	0.95 [0.95, 0.96]
von Kaisenberg 2002	16	269	3	3299	0.84 [0.60, 0.97]	0.92 [0.92, 0.93]
Benn 2007	5	166	5	2080	0.50 [0.19, 0.81]	0.93 [0.91, 0.94]



Quadruple test

No studies examining the use of the quadruple test were considered to have adequately addressed bias due to the use of a differential reference standard; however, three studies[45,46,69] were considered to have adequately described the study population and the index test (Figure T.52 and Table T.35). There was no difference between the median and range in DR for all studies compared with those considered at low risk of bias (85% [81–90] vs. 85% [82–90]; the median FPR for all studies was 2% higher than for those studies at low risk of bias (7% [5–9] vs. 5% [5–9]).

Figure T.52: Studies on quadruple serum test at low risk of bias

Study	TP	FP	FN	TN	Sensitivity	Specificity
MacRae 2010	9	82	1	1501	0.90 [0.55, 1.00]	0.95 [0.94, 0.96]
Malone 2005	74	2988	13	32161	0.85 [0.76, 0.92]	0.91 [0.91, 0.92]
Shaw 2010	9	968	2	20502	0.82 [0.48, 0.98]	0.95 [0.95, 0.96]

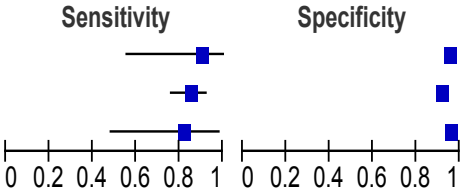


Table T.35: Sensitivity analysis based on study quality

Test	Total no. studies (total T21/total no T21)	Median DR % (range)	Median FPR % (range)
Combined			
All studies	30 (1706/395,315)	88 (50–100)	5 (1–9)
Low risk of bias	5 (350/65,576)	87.5 (50–93)	7 (5–8)
Quadruple			
All studies	7 (350/181,871)	85 (81–90)	7 (5–9)
Low risk of bias	3 (110/58,202)	85 (82–90)	5 (5–9)

Other potential modifiers that may have influenced the estimates of test performance include the accuracy of the dating of gestational age, the timing of the screen (because the sensitivity of the markers to fetal condition varies with gestational age), the training and experience of sonographer or others conducting ultrasound assessments, and, in biochemical screening, the assay methods employed. However, as noted above, these have not been investigated due to time constraints and limited data. Hence, it is unclear to in what way and to what degree these factors may influence test performance.

Availability of Evidence

A key aspect of the question of effects and effectiveness outlined in the Charter concerns the level of evidence available to address the Charter questions and the identification of gaps in the evidence

and an indication of whether these gaps are likely to addressed in the future. The gold standard for assessing the relative performance of two or more the screening or diagnostic technologies is an intervention study (randomized clinical trial or observational management study) with patient-important outcomes.[101] In the absence of such evidence, researchers must rely on test accuracy studies and use the surrogate outcome of accuracy to make inferences about the potential impact of the test on patient management. All the studies included in this review were test accuracy studies, two of which assembled the study population using cases and controls. All other studies assembled the study populations using clinical cohorts (a higher level of evidence than case-control studies) either prospectively or retrospectively. The greatest amount of evidence was available to assess the first trimester screens (NT, double serum, and combined) and the second trimester serum screens (dual, triple, and quadruple). Relatively few empirical studies have assessed the performance of any of the two-step screens. No empirical studies were identified that assessed the performance of the contingent or repeated measures screens for screening fetal aneuploidy. To our knowledge, the available information regarding these tests is based on epidemiological models.[102] Finally, few studies examining second trimester serum screens reported condition specific data for screening for ONTDs. The extent to which these research gaps will be addressed by future research is unknown.

Discussion

The literature search and selection process for empirical accuracy studies examining any one of the 14 prenatal screening tests published between 2000 and 2010 identified 72 primary studies from electronic databases, including one report[9] from the grey literature that provided data on the performance of the combined test in southern Alberta. The studies were conducted in a variety of countries; however, most studies took place in industrialized Western countries, particularly the United Kingdom and United States, but also Australia, Canada, France, and Germany. The studies conducted screening in a variety of settings including university/academic hospitals, community hospitals, and maternity clinics. Most studies examined the performance of the tests in providing risk assessments for singleton pregnancies for a wide age range of women using common positive test thresholds.

In general, the accuracy studies suffer from several major methodological limitations with all studies subject to more than one source of potential bias. The greatest single potential source of bias[100] is the use of a case-control design (associated with a 3-fold overestimation of effect); however, only two of the included studies[13,30] employed this design and neither had results that differed greatly from the cohort studies with which they were compared. As Lijmer et al.[100] have noted, there is good empirical evidence that three potential limitations (differential verification, inadequate description of index test, and inadequate description of study population) are associated with substantial over estimation of diagnostic test performance. Differential verification bias affected almost 90% of the studies and is associated with a 2-fold overestimation of effect; not adequately describing the test being evaluated is associated with a 1.7-fold overestimation, and not adequately describing the study population with a 1.4-fold overestimation. The results of our informal sensitivity analysis of the observed performance of the combined test and quadruple test did not indicate a substantial difference between the DR of all studies and those studies considered at lowest risk of bias; however, given that this was only an informal comparison, the potential for bias due to these factors cannot be discounted. In the case of prenatal screening for trisomy 21 (and likely also for trisomy 13 and 18), the use of different reference standards also leads to overestimation because of a general fetal loss bias.[80] Because trisomy 21 pregnancies are more likely to miscarry than are unaffected pregnancies, the number of trisomy 21 pregnancies detected does not account for spontaneous fetal loss, whereas the number of trisomy 21 pregnancies missed (and ascertained at birth) may not

include all those cases that could have been detected.[80] Study timing, that is, whether a study was conducted prospectively or retrospectively, does not appear to be associated with potential bias.

This review adds to the current evidence base on prenatal screening by providing a summary and assessment of the most current empirical evidence (published 2000–2010) regarding the tests being considered. No previous reviews have summarized the performance of all of these tests in the detail provided here and provided a measure of the variation and relative uncertainty of the results across studies.

First trimester screening

Nuchal translucency for T21 was assessed in 22 studies, the double test (PAPP-A and hCG) in 8 studies, and the combined test in 29 studies. Of the three first trimester screens, the combined test was considered to have the highest DR and lowest FPR. In addition, the subgroup analyses of studies of the combined test based on gestational age indicated that taking measures between the recommended period of 11 and 14 weeks for the combined test may produce a better DR than will taking those measures over a wider range.

Second trimester screening

The dual serum test for T21 was assessed in eight studies, the triple test in 14 studies, and the quadruple test in seven studies. Of the three second trimester serum screens, the quadruple test was considered to have the highest DR and lowest FPR. In contrast to the first trimester combined test, there was no indication of a difference in performance between the two gestational age subgroups for the quadruple test. The subgroup analyses for the combined test and quadruple test based on positive test threshold indicated that there was little if any difference between the performance of the combined test or the quadruple test using cut-offs of 1:250 and 1:300. There were too few studies to assess the relative performance of other thresholds.

With respect to serum screening for ONTDs, the summary and assessment here was limited by the availability of reporting. A 2009 review and meta-analysis[103] of 22 studies (684,112 pregnancies) reporting on the use of maternal AFP screening for NTDs (assessing performance for screening for all neural defects rather than for specific conditions), found a combined DR of 75% (95% CI: 71 to 79) and an FPR of 2% (no 95% CI reported).

The results of a good quality systematic review[98] of second trimester ultrasound screening for spina bifida and anencephaly indicate that this method of screening provides a very accurate assessment of the risk of ONTDs and outperforms maternal AFP screening.

Two step screens

The full integrated screen was assessed in four studies, the integrated – inhibin A in three studies, and the serum integrated and sequential screens were each assessed in two studies. No empirical studies were identified that assessed the accuracy of either the contingent screen or repeated measures screening.

The overall conclusions of this review agree with those of an earlier comprehensive review[104] of strategies for prenatal Down syndrome screening, which concluded that the quadruple test was the best performing second trimester screen, that the combined test was the best first trimester screen, and outperformed the quadruple test, and that the integrated and sequential screens may have improved performance compared to both first and second trimester screens.

Consistent with the SOGC guidelines,[105] this review has evaluated the combined safety and efficacy of the screening tests by indicating the performance of the tests in terms of detection rates and false

positive rates (1-specificity). The adequacy of any screening method must balance minimizing the number of invasive procedures and thus the number of wanted pregnancies lost to diagnostic procedures, against a high rate of detection.[105] In addition, this assessment has provided the strength of the tests by calculating the positive and negative likelihood ratios for each test. The strength of a test is considered excellent if the LR+ exceeds 10 and the LR- is less than 0.1.[106] Though larger studies provided more precise estimates, there was no clear indication that the results of larger studies differed consistently from smaller ones, which suggests true variation in performance rather than the tendency for the results of smaller studies to differ from the results of larger studies for methodological and other reasons.[107] Variations in performance may be a reflection of different maternal age distributions, methods of calculating the risk estimates, and risk thresholds.[32] Other explanations for variation include lack of uniformity in technique (especially for NT), failure to consider baseline risk of aneuploidy, inaccurate gestational dating, and the use of risk estimation techniques not derived from the target population (e.g. when FMF software is outside the United Kingdom).[108]

Though results have not been pooled, the graphical display of the results allows for an overall assessment of the strength of the evidence risk of bias due to methodological flaws, consistency across results, precision of results, and directness of outcome measure on the outcome of interest.[101,109] The overall methodological weaknesses have already been described above. A second weakness of accuracy studies is their indirectness in measuring the primary outcome of interest in implementing a screening program, namely, the improvement of health outcomes. Though test accuracy has been assessed and thus provides an indication of the effectiveness and safety of the test in generating a risk assessment, none of the studies assessed here compare directly the use of different screening and diagnostic options in terms of improved fetal or women's health outcomes. Finally, the low prevalence of these conditions meant that study estimates of detection rates were generally imprecise. This imprecision in results may hide potentially important differences in the DR of the tests. The exception to this was the comparatively precise and consistent results for the combined test.

There exist other variations in screening that have not been assessed here. For example, researchers have reported the use of risk-oriented two-stage first trimester and ultrasound screening[51] in which those considered at low-risk based on the combined screen do not have further assessment, those at high-risk are offered CVS diagnosis, and those at intermediate risk are offered further ultrasound examination for other risk markers such as an absent nasal bone.

The SOGC has recommended that acceptable first trimester screens have a minimum 75% DR and 3% FPR for trisomy 21.[8] Based on this minimum standard, the SOGC considered the first trimester combined, full integrated, integreated – inhibin A, serum integrated, and sequential screens to be acceptable options. The results of the ROC summaries presented here support the findings of the SOGC, with the exception of the integrated – inhibin A screen for which there were an insufficient number of study results with which to calculate an ROC curve. (The observed results do not suggest that it meets this threshold) (Table T.36). The guidelines also recommend that an acceptable second trimester screen have a minimum 75% DR and 5% FPR for trisomy 21. The results of this summary and assessment agrees with the SOGC in finding that the quadruple screen meets this threshold.

Table T.36: Screening tests for trisomy 21 meeting SOGC minimum performance values[110]

Threshold of 75% DR and 3% FPR
First trimester combined (NT and PAPP-A, hCG serum test)
Full integrated (NT, PAPP-A + quadruple screen)
Serum integrated (PAPP-A, hCG serum test + quadruple screen)
Threshold of 75% DR and 5% FPR
Second trimester quadruple (AFP, hCG, uE3, inhibin-A serum test)

No studies were found examining the impact of screening results on physician decision-making or maternal or fetal outcomes.

Context of provision

For those screening tests that use NT, Wald et al.[80] have shown that both sonographer training and the make and model of ultrasound equipment influence the probability of obtaining a usable NT measurement. The SOGC guidelines[105] recommend that prenatal screening programs be implemented with appropriately trained and accredited sonographers (for NT) and ongoing quality assurance. In addition, programs should have the resources adequate to support audited screening and diagnostics lab services, ultrasound, genetic counselling services, patient and health care provider education, and resources for administration, annual clinical audit, and data management. Performance varies with the positive test threshold value, but selecting the trade-offs inherent in a cut-off value is not solely a technical matter and such trade-offs should align with risks women are willing to accept. O'Connell et al.[104] report that the perceived accuracy of the screening test and social, ethnic, and cultural factors may influence uptake and recommend that it would be wise to conduct a local study of the acceptability of both screening and invasive testing before implementing a screening program.

Applicability

Four of the studies included in this review examined the use of screening tests within a Canadian context: two[9,55] assessed the combined screen, one[73] the triple serum screen, one[45] the quadruple screen and full integrated screen, and two[45,55] the integrated screen - inhibin A. The results of these studies are likely the most applicable to the Alberta context and provide important insight into the potential performance of these tests within Alberta.

Limitations

The present review has several potential limitations. As the performance of screening programs are context sensitive, the information provided by studies performed in contexts that closely match that of Alberta are most likely to provide the best estimate of the performance of a screening program. Hence, the most serious limitation may be the applicability of the results from studies from such widely varying settings and contexts. With the exception of four studies[9,45,55,73] that provided information specific to prenatal screening programs in Canada, the studies varied widely in terms of the countries in which they were conducted and the settings with most programs being conducted in

university/academic hospitals. However, standard training and certification in both ultrasound and plasma and serum collection and analysis, and quality control measures in many of the studies may have helped to minimize the heterogeneity due to these factors.

In addition to the 72 studies included in this review, four studies were considered relevant buy did not have data extracted and 20 studies remained to be retrieved and evaluated at the time of analysis. Based on the proportion of studies retrieved and evaluated and considered relevant, it is estimated that four of these 20 may provide data relevant to the review. Based on the titles and abstracts for these studies, these studies are likely to evaluate first or second trimester screens for T21, tests for which there is already a larger number of studies. Hence, it is unlikely that their inclusion would change the conclusions of this report.

A thorough assessment of the potential risk of bias would include an examination of financial and non-financial conflicts of interest.[111] This information was not extracted and summarized for this review. Moreover, though there is ample evidence of the influence of financial conflicts of interest in intervention studies, less evidence exists for this for diagnostic accuracy studies.

The performance measures for individual studies have been calculated and displayed, but no attempts were made to statistically combine these results to provide a "pooled" measure for each screen. Though this makes it challenging to arrive at an overall conclusion regarding the comparative performance of individual screens, this approach was reasonable given the heterogeneity in study populations, positive test thresholds, and the reference standards used.

As noted above, the accuracy and reliability of ultrasound depends mainly on the experience and training of the person performing the scan and also, to a lesser extent, on the equipment available. Though information regarding these dimensions was extracted, no technical comparisons of ultrasound devices or ultrasound technician training was conducted.

Finally, the primary patient important outcome for the diagnostic tests is the ability of the test to provide meaningful information that women can use to make decisions regarding their pregnancies. Though the relative accuracy of the first and second trimester screens is well-established, no studies were found that examined the impact of screening results on physician decision-making or maternal or fetal outcomes. Importantly, the review has not examined the utility of the test results to support women's decision making regarding pregnancy. Other jurisdictions in Canada[112,113] and internationally[114] have considered an assessment of this utility, as well as of the consistency of prenatal screening with societal values, to be crucial before implementing prenatal screening programs.

Conclusions

For the risk assessment for trisomy 21 (and other chromosomal aneuploidies), empirical evidence most strongly supports the use of the combined test for first trimester screening. For second trimester screening, the quadruple serum test provides the best detection rate and lowest false positive rate. The use of any screen requires the existence of well-trained sonographers (for NT), high-quality equipment and diagnostic lab services, and a program of quality control. More large empirical studies may strengthen the little existing evidence that suggests that two-step screening may exceed the combined test in terms of increasing detection and reducing the number of false positives. These results are consistent with and provide further support for the current SOGC practice guidelines on the selection of appropriate screens for fetal aneuploidy. Second trimester ultrasound is superior to second trimester serum screening for screening for ONTDs. Studies assessing screening accuracy have not evaluated whether the information provided by prenatal

screening improves pregnancy outcomes or provides information that is meaningful to women when making decisions regarding their pregnancy.

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Appendices

Appendix T.A: Methodology

Literature search

A comprehensive literature search was conducted to identify the most recent primary studies, HTAs, and clinical practice guidelines that examined the effectiveness of various first and second trimester screening tests (FASTS). A detailed description of the literature search strategy, including sources (databases, websites, grey literature), dates searched, and search terms used, is provided in Appendix T.A.1.

Search strategy

A literature search was conducted by the IHE Research Librarian for articles published between 2000 and December 2, 2010. All major medical databases were searched including MEDLINE, EMBASE, the Cochrane Library and ISI Web of Science. An update of the search was conducted on March 21, 2011 in order to retrieve anything new that had been published since December. The search was further limited to English language publications and diagnostic accuracy studies and was developed and carried out prior to the study selection process.

Search for grey literature

Grey literature searches were conducted between April 8, 2010 and September 22, 2010 with an update on March 21, 2011. A thorough review of HTA agency websites was conducted, as were searches for clinical practice guidelines.

Reference lists from the included studies were also checked for other relevant items.

Table T.A.1: Search strategy

Database	Edition or date searched	Search Terms ††
The Cochrane Library	2000 - Nov 29 2010	#1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester):ti,ab,kw #2 MeSH descriptor Mass Screening, this term only #3 MeSH descriptor Genetic Testing explode all trees #4 MeSH descriptor Prenatal Diagnosis, this term only #5 (screen* or diagnos* or test or tests or testing):ti #6 ("maternal age"):ti,ab,kw #7 MeSH descriptor Amniocentesis, this term only #8 MeSH descriptor Chorionic Villi Sampling, this term only #9 MeSH descriptor Ultrasonography, Prenatal, this term only #10 (ultrasound* or ultrason* or sonogra*):ti,ab,kw #11 (amniocentes* or chorionic vill* or cvs):ti,ab,kw #12 MeSH descriptor Nuchal Translucency Measurement, this term only #13 ("nuchal translucency"):ti,ab,kw #14 ("maternal serum" or "serum marker"):ti,ab,kw #15 MeSH descriptor Biological Markers, this term only #16 ((biochemical or serum or soft) NEAR/1 marker*):ti,ab,kw #17 MeSH descriptor Chorionic Gonadotropin, this term only #18 MeSH descriptor Chorionic Gonadotropin, beta Subunit, Human, this term only #19 ((chorionic NEAR/2 gonadotrop*) or hcg):ti,ab,kw #20 (PAPP A):ti,ab,kw #21 MeSH descriptor Pregnancy-Associated Plasma Protein-A, this term only #22 MeSH descriptor alpha-Fetoproteins, this term only #23 (afp or alpha fetoprotein*):ti,ab,kw

		#24 MeSH descriptor Estriol, this term only #25 (uE3 or estriol):ti,ab,kw #26 (inhibin*):ti,ab,kw #27 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) #28 MeSH descriptor Aneuploidy, this term only #29 (aneuploid*):ti,ab,kw #30 MeSH descriptor Neural Tube Defects explode all trees #31 (neural tube defect* or ancephal* or encephalocele* or "spina bifida"):ti,ab,kw #32 ((down* or patau or edwards) NEXT syndrome):ti,ab,kw #33 MeSH descriptor Down Syndrome, this term only #34 (Trisom*):ti,ab,kw #35 MeSH descriptor Trisomy, this term only #36 MeSH descriptor Congenital Abnormalities, this term only #37 MeSH descriptor Chromosome Disorders, this term only #38 ((congenital or chromosom* or anatomic*) NEXT anomal*):ti,ab,kw #39 ((chromosom* or anatomic*) NEXT abnormalit*):ti,ab,kw #40 (#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39) #41#1 AND #27 AND #40)
MEDLINE (includes in-process and non-medline citations) OVID Licensed Resource	2000 – Nov 29, 2010	1. (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester).sh,ti. 2. mass screening/ or genetic testing/ 3. prenatal diagnosis/ 4. (screen* or diagnos* or test or tests or testing).ti./668412 5. maternal age.tw./9647 6. amniocentesis/ or chorionic villi sampling/ or ultrasonography, prenatal/ 7. (ultrasound* or ultrason* or sonogra*).tw. 8. (amniocentes* or chorionic vill* or cvs).tw. 9. Nuchal Translucency Measurement/564 10. nuchal translucency.tw./1340 11. (maternal serum or serum marker*).tw./9611 12. biological marker/110747 13. ((biochemical or serum or soft) adj marker*).tw. 14. Chorionic Gonadotropin/ or Chorionic Gonadotropin, beta Subunit, Human 15. ((chorionic adj2 gonadotrop*) or hcg).tw./26052 16. PAPP A.tw./858 17. Pregnancy-Associated Plasma Protein- A/ 18. alpha-Fetoproteins/12898 19. (afp or alpha fetoprotein*).tw./14499 20. exp Estriol/5590 21. (uE3 or estriol).tw./3562 22. inhibin*.mp./6467 23. or/2-22/1096003 24. Aneuploidy/9448 25. aneuploid*.tw./14050 26. exp Neural Tube Defects/21593 27. (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw./10265 28. ((down* or patau or edwards) adj syndrome).tw./15257 29. Down syndrome/18777 30. Trisom*.tw./14368 31. Trisomy/9953 32. congenital abnormalities/27920 33. Chromosome Disorders/16876 34. ((congenital or chromosom* or anatomic*) adj anomal*).tw./14225 35. ((chromosom* or anatomic*) adj abnormalit*).tw./13646 36. or/24-35/129803

		37. 1 and 23 and 36/15538 38. exp "Sensitivity and Specificity"/329657 39. (sensitivity or specificity).tw./591662 40. Reference Values/133631 41. false negative reactions/ or false positive reactions/30851 42. ((detection adj2 rate*) or false positive*or predictive value* or reference value* or performance or MoM or "multiples of the median" or screen positive* or accura* or reliab*).tw./987992 43. 38 or 39 or 40 or 41 or 42/1735573 44. 37 and 43/4102 45. limit 44 to (english language and yr="2000 - 2011") **1820 results**
EMBASE Licensed Resource (Ovid Platform)	2000- 29 Nov 2010	1. (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester).sh,ti. 2. mass screening/ or genetic testing/54343 3. prenatal diagnosis/39820 4. (screen* or diagnos* or test or tests or testing).ti./724193 5. maternal age.tw./10304 6. amniocentesis/ or chorionic villi sampling/ or ultrasonography, prenatal/19092 7. (ultrasound* or ultrason* or sonogra*).tw./261803 8. (amniocentes* or chorionic vill* or cvs).tw./14513 9. Nuchal Translucency Measurement/809 10. nuchal translucency.tw./1527 11. (maternal serum or serum marker*).tw./10431 12. biological markers//69742 13. ((biochemical or serum or soft) adj marker*).tw./15116 14. Chorionic Gonadotropin/ or Chorionic Gonadotropin, beta Subunit, Human/36547 15. ((chorionic adj2 gonadotrop*) or hcg).tw./26672 16. PAPP A.tw./973 17. Pregnancy-Associated Plasma Protein-A/18. alpha-Fetoproteins/17150 19. (afp or alpha fetoprotein*).tw./15689 20. exp Estriol/6697 21. (uE3 or estriol).tw./3314 22. inhibin*.mp./6545 23. or/2-22/1150968 24. Aneuploidy/12164 25. aneuploid*.tw./14618 26. exp Neural Tube Defects/21320 27. (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw./11026 28. ((down* or patau or edwards) adj syndrome).tw./16474 29. Down syndrome/21195 30. Trisom*.tw./14900 31. Trisomy/6812 32. Congenital abnormalities/2990 33. Chromosome Disorders/8493 34. ((congenital or chromosom* or anatomic*) adj anomal*).tw./15756 35. ((chromosom* or anatomic*) adj abnormalit*).tw./14772 36. or/24-35/106727 37. 1 and 23 and 36/11982 38. "sensitivity and specificity"/130206 39. (sensitivity or specificity).tw./616214 40. reference value/43848 41. ((detection adj2 rate*) or false positive* or false negative* or predictive value* or reference value* or performance or MoM or "multiples of the median" or screen positive* or accura* or reliab*).mp./1420432 42. false positive result/ or false negative result/ or laboratory diagnosis/ or diagnostic accuracy/183968 43. diagnostic error/34156 44. 38 or 39 or 40 or 41 or 42 or 43/1970134 45. 37 and 44/3539

		46. limit 45 to (english language and yr="2000 - 2011")/1773 **1775 results**
Web of Science (Licensed Resource)	2000-Nov 30 2010	#1 TS=(pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester) #2 TS=(screen* or diagnos* or test or tests or testing) #3 TS=("maternal age" or ultrasound* or ultrason* or sonogra*or amniocentes* or chorionic vill* or cvs or "nuchal translucency" or "maternal serum" or serum marker* or biological marker*or biochemical marker*or soft marker* or chorionic gonadotrop*or hcg or " PAPP A" or "Pregnancy Associated Plasma Protein A" or afp or alpha fetoprotein or uE3 or estriol or inhibin*) #4 #2 or #3 #5 TS= (aneuploid* or neural tube defect* or ancephal* or encephalocele* or spina bifida or down* syndrome or patau syndrome or edwards syndrome or trisom*) #6 TS=(congenital abnormalit* or chromosom* abnormalit* or anatomic* abnormalit* or congenital anomal* or chromosom* anomal* or anatomic* anomal* or chromosome disorder*) #7 #5 or #6 #8 #1 and #4 and #7 #9 #8 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2000-2010 #10 TS=(sensitiv* or specific* or (detection SAME rate*) or (false SAME positive*) or (false SAME negative*) or (predictive SAME value*) or performance or MoM or "multiples of the median" or (screen SAME positive*) or accura* or reliab*) #11 #8 and #10 **2779 results**
Biosis previews Licensed Resource)	2000- Dec 1, 2010	#1 TS=(pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester) #2 TS=(screen* or diagnos* or test or tests or testing) #3 TS=("maternal age" or ultrasound* or ultrason* or sonogra*or amniocentes* or chorionic vill* or cvs or "nuchal translucency" or "maternal serum" or serum marker* or biological marker*or biochemical marker*or soft marker* or chorionic gonadotrop*or hcg or " PAPP A" or "Pregnancy Associated Plasma Protein A" or afp or alpha fetoprotein or uE3 or estriol or inhibin*) #4 #2 or #3 #5 TS= (aneuploid* or neural tube defect* or ancephal* or encephalocele* or spina bifida or down* syndrome or patau syndrome or edwards syndrome or trisom*) #6 TS=(congenital abnormalit* or chromosom* abnormalit* or anatomic* abnormalit* or congenital anomal* or chromosom* anomal* or anatomic* anomal* or chromosome disorder*) #7 #5 or #6 #8 #1 and #4 and #7 #9 #8 Timespan=2000-2010 #10 TS=(sensitiv* or specific* or (detection SAME rate*) or (false SAME positive*) or (false SAME negative*) or (predictive SAME value*) or performance or MoM or "multiples of the median" or (screen SAME positive*) or accura* or reliab*) #11 #8 and #10 **1277 results**
Clinical Practice Guidelines		
AMA Clinical Practice Guidelines http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines. html	April 8, 2010	Browsed lists of guidelines **2 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	April 8, 2010	Browsed lists of guidelines **5 results**

National Guideline Clearinghouse http://www.ngc.gov	April 7, 2010	Prenatal or antenatal or trimester or fetal or maternal or pregnancy AND Diagnosis or Screening **11 results**
NICE Guidance http://guidance.nice.org.uk/	April 7, 2010	Browsed lists of guidelines **No results**
Health Regulatory sites		
Alberta Health and Wellness http://www.health.gov.ab.ca	Sept 22, 2010	Browsed list of publications **7 results**
Health Canada (http://www.hc-sc.gc.ca) Medical Devices active license listing (MDALL) http://webprod.hc-sc.gc.ca/mdll-limh/index-eng.jsp	Sept 22, 2010	down's-syndrome OR down-syndrome OR aneuploidy OR aneuploidies OR spina-bifida OR neural-tube-defects site:http://www.hc-sc.gc.ca **0 Results**
CDC – Centers for Disease Control and Prevention http://www.cdc.gov/obesity/index.html	Sept 22, 2010	Browsed topics list **11 results**
Aetna Clinical Policy Bulletins http://www.aetna.com/about/cov_det_policies.htm	Sept 22, 2010	Browsed topics list **4 results**
MHRA http://www.mhra.gov.uk/index.htm		**NA**
Library Catalogues		
NEOS (Cenral Alberta Library Consortium) http://www.library.ualberta.ca/catalogue	Sept 22, 2010	"neural tube defect*" OR Any field "down* syndrome" OR Any field "aneuploid* or trisom*" OR Any field "prenatal screening" OR Any field "prenatal diagnosis" OR Any field "(antenatal screening) or (antenatal diagnosis)" **291 results**
AMICUS http://www.nlc-bnc.ca/amicus (Command search interface)		**NA**
LocatorPLUS (National Library Medicine US) http://locatorplus. gov/		**NA**
Theses Canada Portal http://www.nlc-bnc.ca/thesescanada		**NA**
Proquest Dissertations and Theses Full Text Licensed Resource	Sept 22, 2010	neural tube defect* or down* syndrome or aneuploid* or spina bifida) OR (trisom* or "prenatal screening" or "prenatal diagnosis" or "antenatal screening" or "antenatal diagnosis" or trimester screen or trimester screening or trimester testing or "prenatal testing") OR (amniocentes* or chorionic vill* sampling or "maternal

(Proquest Interface)		serum" or "nuchal translucency") AND PDN(>10/4/2000) or congenital abnormalit* or chromosomal abnormalit* or congenital anomal* or chromosomal anomal* or chromosome disorder*) AND PDN(>10/4/2000) **1000 results**
Internet Search Engine		
Google http://www.google.ca	October 20, 2010	1. down's-syndrome OR down-syndrome 2. aneuploidy OR aneuploidies OR spina-bifida OR 3. neural-tube-defects or trisomy 4. congenital-abnormality OR congenital-abnormalities OR chromosomal-abnormality OR chromosomal-abnormalities OR congenital-anomaly OR congenital-anomalies OR chromosomal-anomaly OR chromosomal-anomalies OR chromosome-disorder OR chromosome-disorders 5. prenatal-screening OR prenatal-diagnosis OR antenatal-screening OR antenatal-diagnosis OR trimester-screen OR trimester-screening OR trimester-testing OR prenatal-testing 6. amniocenteses OR amniocentesis OR chorionic-villi-sampling OR chorionic-villus-sampling OR maternal-serum OR nuchal-translucency *6 separate searches **42 results**
Grey Literature Sources		
Intute http://www.intute.ac.uk/healthandlifesciences/nursing/	Sept 20, 2010	Browsed lists of publications under MESH headings : prenatal diagnosis, down syndrome, Amniocentesis, Chronic villi sampling, chromosome abberations **8 relevant results**
Centre for Health Economics and Policy Analysis http://www.chepa.org	Oct. 1, 2010	Prenatal or antenatal or trimester or amniocentesis or chorionic or maternal or downs syndrome or spina bifida or neural tube or congenital or chromosomal or chromosome or aneuploidy or nuchal **2 results**
NLH (National Library for Health) http://www.library.nhs.uk/Default. aspx	Sept 22, 2010	pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester OR (((down* or patau or edwards) NEAR syndrome) or (spina bifida) or Trisom*) or (aneuploid* or ((congenital or chromosom* or anatomic*) NEAR anomal*) or ((chromosom* or anatomic*) NEAR abnormalit*)) or (neural tube defect*) OR Amniocentesis or chorionic vill* sampling or maternal serum or nuchal translucency In title **12 results**
AETMIS: http://www.aetmis.gouv.qc.ca/site/ home.phtml	October 1, 2010	Browsed list of publications **2 results**
CADTH: http://www.cadth.ca	October 1, 2010	Prenatal or antenatal or trimester or amniocentesis or chorionic or maternal or downs syndrome or spina bifida or neural tube or congenital or chromosomal or chromosome or aneuploidy or nuchal **2 results**
Health Technology Assessment Unit at McGill: http://www.mcgill.ca/tau	October 1, 2010	Browsed list of publications **No results**

Institute for Clinical and Evaluative Sciences (ICES) http://www.ices.on.ca	October 1, 2010	Browsed list of publications **2 results**
EuroScan: http://www.euroscan.bham.ac.uk	October 1, 2010	Browsed list of publications **3 results**
ASERNIP-S: http://www.surgeons.org/asernip-s	October 1, 2010	Browsed list of publications **0 results**
Society of Obstetricians and Gynaecologists of Canada	October 1, 2010	Browsed list of publications **2 results**

Literature Selection

Systematic Review

Two reviewers independently screened the results of the electronic search.

Studies were excluded if, on the basis of a review of the title, abstract, and keywords they were judged clearly

- a primary screening study (e.g., it is a review, editorial, comment paper, or letter)
- on Down syndrome, trisomy 13, 18 or NTD (i.e., indicates it is on another condition entirely)
- on at least one of the screening test(s) of interest or their combination: NT, PAAP-A, HCG, free-beta HCG, AFP, uE3, inhibin A (e.g., it is on other serum tests, screening, or diagnostic procedures [amnio or CVS])

In all other cases, the citation was judged potentially relevant and INCLUDED. If it was unclear whether the study was relevant or not, it was INCLUDED.

Inclusion and Exclusion

Two reviewers independently applied the detailed selection criteria to the full text report of the study. Studies were rated as include, exclude or unsure. Disagreements were resolved through discussion and consensus or third-party adjudication if necessary.

Studies were included if they met the following criteria:

- Screening study (RCT, NRCT, cohort study, case-control study)
- Pregnant women (no restriction on age, ethnicity, or use of assisted reproductive technologies (ARTs)
- Screening test is used to estimate fetal risk for Trisomy 13 (Patau syndrome), 18 (Edward syndrome), 21 (Down syndrome), or an open neural tube defect
- Study examines at least one of the screening test(s) of interest or their combination: NT, PAAP-A, HCG, free-beta HCG, AFP, uE3, inhibin A
- Reference standard is a diagnosis based on results from any one or more of the following: chromosomal analysis as a result of CVS or amniocentesis, fetal autopsy, or newborn testing.

- Reports test accuracy data to complete 2 x 2 table or calculated measures (see guide) **or** numerical data on risks or harmful effects of tests

Studies were excluded if they were

- Review, simulation or modeling study, editorial, comment paper, or letter
- Studies not reporting numeric data for the outcomes specified in the review

Studies were not excluded based on timing of study, i.e. prospective or retrospective. Wald et al.[80] has made the distinction between interventional screening accuracy studies and observational screening accuracy studies. Interventional studies are those in which the screening marker being studied is itself used in screening. No distinction was made in this review between these two study designs.

Review of reviews

Studies are included if they meet all of the following criteria:

Study design: systematic reviews (SRs) and or Health Technology Assessments (HTAs) with no restrictions in terms of the study design of primary research included in the systematic reviews. If evidence from SRs and/or HTAs is insufficient to address the research questions, individual RCTs and/or diagnostic studies will be included.

Note: An article is deemed to be a systematic review if it meets all of the following criteria as defined by Cook et al. 1997:

- focused clinical question
- explicit search strategy
- use of explicit, reproducible, and uniformly applied criteria for article selection
- critical appraisal of the included studies
- qualitative or quantitative data synthesis

Population: pregnant women of any age with a live fetus including multiple gestation, pregnancy resulting from a donor oocyte, and pregestational diabetes mellitus or other major comorbidities for which there are adjustments made for interpreting prenatal screening results.

Intervention: first and second trimester screening for aneuploidies (Trisomy 21, Trisomy 18, and Trisomy 13) and open NTDs.

Comparator: acceptable reference tests ("gold standard", criterion standard) are the invasive tests using amniocentesis and/or CVS, and/or the clinical follow-up for aneuploidies and NTDs at the end of pregnancy. Ideally all participants should receive the same reference test.

Outcome of interest:

- **Screening tests**
    - **Performance** (screening test which finds the most number of abnormalities for the least number of "at risk" cases when used in various combinations and integrations). Information should be available to allow the construction of the diagnostic 2 x 2 table with its four cells: true positives, false negatives, false positives and true negatives. Reported sensitivity (detection rate), specificity, positive predictive value, negative

predictive value, false positive rate, risk cut-offs, likelihood ratios, odds of having the disease after applying the test, measurement of biochemical markers converted into multiples of the median (MoM) for gestational age, number needed to diagnose.

- **Safety** - potential risks or harmful effects related with the screening tests only.
- **Other screening test outcomes** - advantages and disadvantages or risks of the screening tests. Information on the factors that might affect the performance of the screening test such as patient characteristics, training and experience of the service provider, and equipment. Information collected incidentally on the performance of the included screening tests to screen for other conditions or chromosomal abnormalities.

- **Other background information:** approval status of the screening tests assays by Health Canada, current context of service provision in Alberta, recommendations from clinical practice guidelines in Alberta, Canada, and North America.

Publication: Full text articles published in English from 2000 onwards.

Exclusion criteria

Studies are excluded if they meet any of the following criteria:

Study design: conference abstract, letter, news, editorial comments.

Intervention: pre-conceptual and antenatal diagnostic, ultrasound for other screening indications (Doppler, echocardiography, assessment of morphology and vascularization of the fetus and placenta, fetal biometry including estimation of fetal weight, growth retardation or macrosomia), screening for other congenital malformations and conditions other than those listed in the inclusion criteria, screening with markers to predict pre-eclampsia. Excluded are primary studies which evaluate the safety of doing invasive diagnostic tests as an outcome of the screening test.

Comparator: exclude studies that conduct head-to-head comparisons among the different screening options without a common reference test/criterion standard.

Data Extraction and Analysis

Systematic Review

Data on the study characteristics (study timing, recruitment, year of publication, country, number of centres, setting, etc.) population characteristics, test characteristics, and data on test performance were extracted. Data were extracted by a single review and verified by a second. All data was extracted into a spreadsheet program (Microsoft Excel 2010).

Review of reviews

Required information will be extracted by one reviewer according to a predetermined data extraction form. Information will be collected on the following:

- Study design and methods: country, year, type of publication, aim, duration of the study, number of participating centres, source of funding.
- Population: demographic characteristics of pregnant women, inclusion and exclusion criteria, gestational age at screening.

- Intervention: screening strategy, time of data collection, testing procedures, time interval between tests, accuracy, reproducibility, risk cut-offs, comparison of two or more tests, adverse effects.
- Comparator: reference test characteristics.
- Outcome of interest: accuracy and efficiency in clinical practice, risks or harmful effects related with the screening tests.

In addition, the following data will be extracted from systematic reviews/HTAs: methodological characteristics (search strategy, language and publication restrictions, study selection process, methods for quality assessment of primary studies and type of analysis); results (number of primary studies included, effect size, direction of the results, adverse effects/events); and conclusions and recommendations for practice.

Analysis

Calculation of test performance

Detection and false positive rates and their corresponding 95% confidence intervals were based on the TP, TN, FP, FN data reported in individual studies and were calculated using the diagnostic review module of Review Manager (Review Manager (RevMan) [Computer program]. In some cases, 2 x 2 data was generated using the reported size of the screened population and the DR and FPR. Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.). Positive predictive values and likelihood ratios were calculated in Microsoft Office 2010 Excel® using standard formulas.[111] In cases in which sensitivity or specificity was 100%, 0.5 was added to the data in each cell of the 2 x 2 table to allow for an estimation of the likelihood ratios. Informal subgroup and sensitivity analyses[99] were also conducted to assess the potential influence of study population characteristics (e.g. gestational age at testing, positive test cut-off) and methodology (e.g. including only studies at low risk of bias). Graphical summaries of test performance (i.e. forest plots and ROC curves) were produced, but no statistical pooling of results was performed due to the presumed heterogeneity between studies.

Quality Assessment

Systematic review

The methodological quality assessment of the diagnostic accuracy studies was assessed using the QUADAS checklist.[8] Based on our review of the QUADAS items and FASTS tests being evaluated, we removed QUADAS items 4, 7, and 10-12. As a result, the studies were assessed using nine items that evaluated the susceptibility of bias along the following dimensions of diagnostic study design and conduct: patient selection and spectrum, adequate of reference standard, differential and partial verification, execution of the index and reference standard tests, and reporting of indeterminate results, and withdrawals and dropouts. Two reviewers independently rated each study on each of the nine items. The items were rated as Yes, no, or unclear based on a priori decision criteria. Study quality was reported by study component and graphical summaries were produced. No summary rating was produced.

Review of reviews

The systematic reviews will be appraised with the systematic review quality assessment checklist developed in-house by the IHE research team. This checklist contains six quality subsections (grey

sections) that, according to the literature, reflect aspects considered essential for a good quality systematic review (see Appendix T.B: Table T.B.2).

External Review

The draft report was reviewed by the members of the provincial expert advisory committee assembled for this project.

Appendix T.B: Excluded Studies (N=288)

A total of 281 reports were excluded. Main reasons for exclusion were 1) not being primary research on screening accuracy (91 reports); 2) not containing a population of pregnant women (six reports); 3) not examining at least one of the six conditions of interest (T21, 18, 13, spina bifida, anencephaly, or encephalocele) (21 reports); 4) not examining at least one of the screening methods or tests (37 reports); 5) not using one of the established reference standards of diagnosis (10 reports); 6) not providing outcome data sufficient to calculate test accuracy (101 reports); and 7) having fewer than 1000 study subjects (22 reports). At the time the review was completed, 20 reports had not been retrieved and evaluated and were considered pending.

Not primary research on screening accuracy (N=91)

1. Abu-Rustum RS, Daou L, bu-Rustum SE. Role of first-trimester sonography in the diagnosis of aneuploidy and structural fetal anomalies. *Journal of Ultrasound in Medicine* 2010;29(10):1445-52.
2. Abushoufa RA, Talbot JA, Brownbill K, Rafferty B, Kane JW, Robertson WR. The development of a sialic acid specific lectin-immunoassay for the measurement of human chorionic gonadotrophin glycoforms in serum and its application in normal and Down's syndrome pregnancies. *Clinical Endocrinology* 2000;52(4):499-508.
3. Alberman E, Huttly W, Hennessy E, McIntosh A. The use of record linkage for auditing the uptake and outcome of prenatal serum screening and prenatal diagnostic tests for Down syndrome. *Prenatal Diagnosis* 2003;23(10):801-6.
4. Bahado-Singh RO, Choi SJ, Cheng CC. First- and midtrimester Down syndrome screening and detection. *Clinics in Perinatology* 2004;31(4):677-+.
5. Benacerraf BR. Should sonographic screening for fetal Down syndrome be applied to low risk women? *Ultrasound in Obstetrics and Gynecology* 2000;15(6):451-5.
6. Benn PA, Kaminsky LM, Ying J, Borgida AF, Egan JF. Combined second-trimester biochemical and ultrasound screening for Down syndrome. *Obstetrics & Gynecology* 2002;100(6):1168-76.
7. Benn P, Ying J, Beazoglou T, Egan J. New estimates for the efficacy of second-trimester serum screening for Down syndrome and trisomy 18; adjustment for cross-identification and double-positive results. *American Journal of Obstetrics and Gynecology* 2001;184(1).
8. Biggio JR, Wenstrom KD. Biochemical screening for fetal aneuploidy. *Infertility and Reproductive Medicine Clinics of North America* 2001;12(4):713-41.
9. Budorick NE. Prenatal diagnosis for detection of aneuploidy: The options. *Radiologic Clinics of North America* 2003;41(4):695-708.
10. Bush MC, Malone FD. Down syndrome screening in twins. *Clinics in Perinatology* 2005;32(2):373.
11. Canick JA, Lambert-Messerlian GM, Palomaki GE, Neveux LM, Malone FD, Ball RH, et al. Comparison of serum markers in first-trimester down syndrome screening. *Obstetrics & Gynecology* 2006;108(5):1192-9.
12. Cate S. Maternal serum triple analyte screening in pregnancy. *American Family Physician* 740;62(4):738.

13. Cheong M-L. Can first-trimester maternal serum level of pregnancy-associated plasma protein-A predict subsequent fetal growth restriction? *Taiwanese Journal of Obstetrics and Gynecology* 2005;44(2):148-52.

14. Christiansen M, Larsen SO, Norgaard-Pedersen B. Antenatal screening policies for Down's syndrome. Serum screening for Down's syndrome is better than age screening. *BMJ* 2002;325(7371):1034.

15. Cicero S, Bindra R, Rembouskos G, Spencer K, Nicolaides KH. Integrated ultrasound and biochemical screening for trisomy 21 using fetal nuchal translucency, absent fetal nasal bone, free beta-hCG and PAPP-A at 11 to 14 weeks. *Prenatal Diagnosis* 2003;23(4):306-10.

16. Cicero S, Spencer K, Avgidou K, Faiola S, Nicolaides KH. Maternal serum biochemistry at 11-13(+6) weeks in relation to the presence or absence of the fetal nasal bone on ultrasonography in chromosomally abnormal fetuses: an updated analysis of integrated ultrasound and biochemical screening. *Prenatal Diagnosis* 2005;25(11):977-83.

17. Comstock CH. Is there a nuchal translucency millimeter measurement above which there is no added benefit from first trimester serum screening? *American Journal of Obstetrics and Gynecology* 2006;195(3):843-7.

18. Cuckle HS. Correlation between maternal serum PAPP-A and inhibin [4]. *Prenatal Diagnosis* 2002;22(2):161-2.

19. Cusick W. First trimester diagnosis of fetal abnormalities. *Infertility and Reproductive Medicine Clinics of North America* 2003;14(2):353-66.

20. Egan JF, Benn P, Borgida AF, Rodis JF, Campbell WA, Vintzileos AM. Efficacy of screening for fetal Down syndrome in the United States from 1974 to 1997. *Obstetrics & Gynecology* 2000;96(6):979-85.

21. Evans M, Van Decruyes H, Nicolaides K. Nuchal translucency (NT) measurements for 1st trimester screening: The "price" of inaccuracy. *American Journal of Obstetrics and Gynecology* 2004;191(6, Suppl. S).

22. Fortuny A. First trimester aneuploidy screening combining biochemical and ultrasound markers. *Ultrasound Review of Obstetrics and Gynecology* 2005;5(1):9-17.

23. Gasiorek-Wiens A. A mixture model of nuchal translucency thickness in screening for chromosomal defects: Validation of a single operator dataset. *Prenatal Diagnosis* 2010;30(11):1100-6.

24. Graves JC, Miller KE, Sellers AD. Maternal serum triple analyte screening in pregnancy. *American Family Physician* 2002;65(5):915-20.

25. Gyselaers WJ, Vereecken AJ, Van Herck EJ, Straetmans DP, de Jonge ET, Ombelet WU, et al. Audit on nuchal translucency thickness measurements in Flanders, Belgium: a plea for methodological standardization. *Ultrasound in Obstetrics & Gynecology* 2004;24(5):511-5.

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Fewer than 1000 study participants (N=22)

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Appendix T.C: Individual Study Characteristics of Included Studies

Study	Participant Characteristics	Screen Characteristics
AHS, 2010[9] **Country (# centers):** Canada (1) **Setting:** Maternal fetal medicine clinic **Study recruitment (timing):** cohort (prospective) **Data collected:** March 2006–March 2009	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 18,727/18,727 **Median maternal age (range):** 32 yr (mean) (15–52) **Median gestational age (range):** 11–13+6 wk **Pregnancy type:** singleton	**Test**: Combined **Software:** Astraia software **NT training (if applicable):** FMF certification **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** 1:300 Reference: + / −; Screen +: 98 / 1107; Screen −: 10 / 17,414 **DR (95% CI):** 91% (84–95) **FPR (95% CI):** 6% (6–6)		

Study	Participant Characteristics	Screen Characteristics
Alvarez-Nava et al., 2008[10] **Country (# centers):** Venezuela (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** January 1998–December 2007	**Inclusion criteria:** ND **Exclusion criteria:** multiple pregnancy, structural fetal malformations, chromosomal abnormalities detected at previous karyotyping, pregnancy loss at any time, still birth, or death in the neonatal period. **Screening $N_{analyzed}/N_{screened}$:** 2992/3005 **Median maternal age (range):** ND **Median gestational age (range):** 15–20 wk **Pregnancy type:** singleton	**Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:270 Reference: + / −; Screen +: 9 / 173; Screen −: 4 / 2819 **DR (95% CI):** 69% (39–91) **FPR (95% CI):** 6% (5–7)		

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Audibert et al., 2001[11]
Country (# centers): France (1)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: May 1994–December 1997</td><td>Inclusion criteria: Patients presenting to institution for NT
Exclusion criteria: Twin or multiple pregnancy, CRL <38 mm or >89 mm, maternal age > 38 yr, NT not measured or not recorded
Screening $N_{analyzed}/N_{screened}$: 4130 (NT)/4130 (NT), 3790 (Dual)/3790 (Dual)
Median maternal age (range): 30.1 yr (mean) (16-37)
Median gestational age (range): 12–13 wk (NT), 14–17+6 wk (Dual)
Pregnancy type: singleton</td><td>Test: NT
Software: Prenata Software (Ortho Clinical Diagnostics)
NT training (if applicable): Physicians or midwives specially trained in first-trimester ultrasound
Test: Dual
Software: ND
NT training (if applicable): NA
Other conditions detected: T18, T13, T9, and sex chromosome disjunctions</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>NT: T21
Positive test threshold: 1:250
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>8</td><td>178</td></tr>
<tr><td></td><td>-</td><td>4</td><td>3940</td></tr>
</table>
DR (95% CI): 67% (35–90)
FPR (95% CI): 4% (4–5)</td><td>Dual: T21
Positive test threshold: 1:250
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>6</td><td>124</td></tr>
<tr><td></td><td>-</td><td>4</td><td>3656</td></tr>
</table>
DR (95% CI): 60% (26–88)
FPR (95% CI): 3% (3–4)</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Avgidou et al., 2005[7]
Country (# centers): UK (1)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: July 1999–December 2003
Associated publication: Bindra et al., 2002[18]</td><td>Inclusion criteria: All women attending Fetal Medicine Centre, London and eligible for screening at 11 to 13+6 wk
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 30564/31904
Median maternal age (range): 34 yr (15–49)
Median gestational age (range): 11–13+6 wk
Pregnancy type: ND</td><td>Test: Combined
Software: ND
NT training (if applicable): Sonographers who had obtained FMF certification
Other conditions detected: Turner syndrome</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Combined: T21
Positive test threshold: 1:300
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>183</td><td>2382</td></tr>
<tr><td></td><td>-</td><td>13</td><td>27986</td></tr>
</table>
DR (95% CI): 93% (89–96)
FPR (95% CI): 8% (8–8)</td><td>Combined: T18
Positive test threshold: 1:300
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>48</td><td>2517</td></tr>
<tr><td></td><td>-</td><td>4</td><td>27995</td></tr>
</table>
DR (95% CI): 92% (81–98)
FPR (95% CI): 8% (8–9)</td><td>Combined: T13
Positive test threshold: 1:300
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>24</td><td>2541</td></tr>
<tr><td></td><td>-</td><td>3</td><td>27996</td></tr>
</table>
DR (95% CI): 89% (71–98)
FPR (95% CI): 8% (8–9)</td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Babbur et al., 2005[12] **Country (# centers):** UK (>2) **Setting:** general/community hospital **Study recruitment (timing):** cohort (Prospective) **Data collected:** August 2001–March 2004	**Inclusion criteria:** Women with singleton pregnancies attending for NT measurement; previous pregnancy history of fetal abnormality **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 3188/3188 **Median maternal age (range):** 37 yr (19–46) **Median gestational age (range):** 11–14 wk **Pregnancy type:** singleton	**Test:** NT **Software:** Astraia GmBH (Munich, Germany) **NT training (if applicable):** ND **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** ≥3.0 mm **DR (95% CI):** 64% (43–82) **FPR (95% CI):** 2% (1–2)		

		Reference	
		+	-
Screen	+	16	57
	-	9	3106

Study	Participant Characteristics	Screen Characteristics
Bahado-Singh et al., 2000[13] **Country (# centers):** USA (ND) **Setting:** ND **Study recruitment (timing):** case-control (retrospective) **Data collected:** January 1992– November 1997	**Inclusion criteria:** Fetuses with Down syndrome, fetuses with normal karyotype **Exclusion criteria:** Condition other than Down syndrome **Screening $N_{analyzed}/N_{screened}$:** 2391/2391 **Median maternal age (range):** 35.0 yr (normal) (14.0–46.0 (normal), 38.0 yr (T21) (17.0–44.4) **Median gestational age (range):** 17.1 wk (14.0–24.0) (normal), 16.6 wk (15.0–21.6) (T21) **Pregnancy type:** singleton	**Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 85% (71–94) **FPR (95% CI):** 54% (52–56)		

		Reference	
		+	-
Screen	+	39	1273
	-	7	1072

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Beaman et al., 2001[14]
Country (# centers): UK (4)
Setting: maternity clinic
Study recruitment (timing): cohort (Prospective)
Data collected: 1992–1998</td><td>Inclusion criteria: Women attending for prenatal care
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 66,631/66,631
Median maternal age (range): 28.2 yr ±5.14 (mean±SD), 11%≥35 yr
Median gestational age (range): 15–20 wk
Pregnancy type: ND</td><td>Test: Dual
Software:
NT training (if applicable): NA
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Dual: T21
Positive test threshold: 1:250
<table>
<tr><td colspan="2"></td><td>Reference</td><td></td></tr>
<tr><td colspan="2"></td><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>72</td><td>3858</td></tr>
<tr><td>-</td><td>36</td><td>62,665</td></tr>
</table>
DR (95% CI): 67% (57–75)
FPR (95% CI): 6% (6–6)</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Benn et al., 2007[15]
Country (# centers): USA (>1)
Setting: university/academic hospital
Study recruitment (timing): cohort (Retrospective)
Data collected: September 2004–October 2006</td><td>Inclusion criteria: Singleton pregnancy received first- and second-trimester Down syndrome and T18 screening
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 2456/2456
Median maternal age (range): 36.2 yr
Median gestational age (range): ND
Pregnancy type: singleton</td><td>Test: Combined
Software: ND
NT training (if applicable): Accredited (ND) sonographers and maternal/fetal medicine physicians
Test: Full IPS
Software: ND
NT training (if applicable): Accredited (ND) sonographers and maternal/fetal medicine physicians
Other conditions detected: ND</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Combined: T21
Positive test threshold: 1:270
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>5</td><td>166</td></tr>
<tr><td></td><td>-</td><td>5</td><td>2080</td></tr>
</table>
DR (95% CI): 50% (19–81)
FPR (95% CI): 7% (6–9)</td><td>Combined: T18
Positive test threshold: 1:100
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>1</td><td>170</td></tr>
<tr><td></td><td>-</td><td>2</td><td>2083</td></tr>
</table>
DR (95% CI): 33% (1–91)
FPR (95% CI): 8% (6–9)</td><td></td></tr>
<tr><td>Full IPS: T21
Positive test threshold: 1:270
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>6</td><td>133</td></tr>
<tr><td></td><td>-</td><td>1</td><td>2316</td></tr>
</table>
DR (95% CI): 86% (42–100)
FPR (95% CI): 5% (5–6)</td><td>Full IPS: T18
Positive test threshold: 1:100
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>3</td><td>136</td></tr>
<tr><td></td><td>-</td><td>0</td><td>2117</td></tr>
</table>
DR (95% CI): 100% (29–100)
FPR (95% CI): 6% (5–7)</td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Benn et al., 2003[16] **Country (# centers):** USA (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (Retrospective) **Data collected:** November 1999–June 2002	**Inclusion criteria:** Any singleton pregnancy with gestational ages 14.0–21.9 wk at time of screening **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 23,749/23,749 **Median maternal age (range):** 27.8 yr , 17.1% ≥35 yr **Median gestational age (range):** 14.0–21.9 wk **Pregnancy type:** singleton	**Test:** Quadruple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Quadruple: T21 **Positive test threshold:** 1:270 **DR (95% CI):** 87% (73–95) **FPR (95% CI):** 9% (9–9)		

		Reference	
		+	-
Screen	+	39	2133
	-	6	21,571

Study	Participant Characteristics	Screen Characteristics
Benn et al., 2000[17] **Country (# centers):** USA (ND) **Setting:** ND **Study recruitment (timing):** cohort (retrospective) **Data collected:** April 1993–December 1998	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 50,315/50,315 **Median maternal age (range):** ND **Median gestational age (range):** ND **Pregnancy type:** singleton and doubleton	**Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: anencephaly **Positive test threshold:** AFP≥2.0 MoM **DR (95% CI):** 90% (70–99) **FPR (95% CI):** 3% (3–3)		

		Reference	
		+	-
Screen	□	19	1418
	-	2	48,876

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Borrell et al., 2004[19]
Country (# centers): Spain (ND)
Setting:
Study recruitment (timing): cohort (prospective)
Data collected: October 1999–December 2001</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 2780/2976
Median maternal age (range): 31 yr (mean) (14–45)
Median gestational age (range): 7–12 wk
Pregnancy type: singleton</td><td>Test: Combined
Software: Delfia (Wallac, PerkinElmer®)
NT training (if applicable): ND
Other conditions detected: ND</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Combined: T21
Positive test threshold: 1:250
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>7</td><td>92</td></tr>
<tr><td></td><td>-</td><td>1</td><td>2680</td></tr>
</table>
DR (95% CI): 88% (47–100)
FPR (95% CI): 3% (3–4)</td><td>Combined: T18
Positive test threshold: 1:250
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>3</td><td>92</td></tr>
<tr><td></td><td>-</td><td>1</td><td>2684</td></tr>
</table>
DR (95% CI): 75% (19–99)
FPR (95% CI): 3% (3–4)</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Breathnach et al., 2007[21]
Country (# centers): USA (15)
Setting: university/academic hospital
Study recruitment (timing): cohort (Prospective)
Data collected: October 1999–December 2002</td><td>Inclusion criteria: Maternal age of 16 yr or older, pregnancy with a singleton live fetus, fetal CR of 36–79mm
Exclusion criteria: Diagnosis of multiple gestation or anencephaly.
Screening $N_{analyzed}/N_{screened}$: 36,171/36,171 (FT), 35,236/35,236 (ST)
Median maternal age (range): 8254>35 yr
Median gestational age (range): 10^{+3}–15 wk (FT), 15–18 wk (STS)
Pregnancy type: singleton</td><td>Test: Triple
Software: ND
NT training (if applicable): NA
Test: Quadruple
Software: ND
NT training (if applicable): NA
Other conditions detected: T13, Turner syndrome, and triploidy</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Triple: T18
Positive test threshold: 1:100
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>9</td><td>51</td></tr>
<tr><td></td><td>-</td><td>6</td><td>35,858</td></tr>
</table>
DR (95% CI): 60% (32–84)
FPR (95% CI): 0% (0–0)</td><td>Quadruple: T18
Positive test threshold: 1:100
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>13</td><td>109</td></tr>
<tr><td></td><td>-</td><td>0</td><td>35,011</td></tr>
</table>
DR (95% CI): 100% (75–100)
FPR (95% CI): 0% (0–0)</td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Chasen et al., 2003[22] **Country (# centers):** USA (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** April 2000–April 2002	**Inclusion criteria:** All cases of singleton or multifetal pregnancy undergoing NT measurement **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 2248/2339 (fetuses) **Median maternal age (range):** 33 yr (IQR: 31–36) **Median gestational age (range):** 11–14 wk **Pregnancy type:** unselected	**Test:** NT **Software:** FMF software **NT training (if applicable):** ND **Other conditions detected:** Klinefelter syndrome, trisomy 12
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 10 / 185 Screen -: 2 / 2051 **DR (95% CI):** 83% (52–98) **FPR (95% CI):** 8% (7–9)	NT: T18 **Positive test threshold:** 1:300 Reference: + / - Screen +: 9 / 186 Screen -: 1 / 2052 **DR (95% CI):** 90% (55–100) **FPR (95% CI):** 8% (7–10)	

Study	Participant Characteristics	Screen Characteristics
Cocciolone et al., 2008[23] **Country (# centers):** Australia (ND) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** 1995–2005	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 18,901/18,901 (FT), 40,748/40,748 (ST) **Median maternal age (range):** 31.3 yr (FT), 29.5 yr (ST) **Median gestational age (range):** 12^{+2} (FT), 16^{+1} (ST) **Pregnancy type:** ND	**Test:** Combined **Software:** ND **NT training (if applicable):** ND **Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 60 / 866 Screen -: 6 / 17,969 **DR (95% CI):** 91% (81–97) **FPR (95% CI):** 5% (4–5)	Triple: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 50 / 2848 Screen -: 17 / 37,833 **DR (95% CI):** 75% (63–84) **FPR (95% CI):** 7% (7–7)	

Study	Participant Characteristics	Screen Characteristics
Garchet-Beaudron et al., 2008[24] **Country (# centers):** France (45) **Setting:** ND **Study recruitment (timing):** cohort (prospective) **Data collected:** 1998–2006	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** Singleton: 64,815/64,815 Twin: 11,040/11,040 **Median maternal age (range):** Singleton: 35 yr (17–43) (T21), 29 yr (13–49) (no T21) Twin: 35 .5 yr (18–44) (T21), 30 yr (15–46) (no T21) **Median gestational age (range):** ND **Pregnancy type:** singleton and doubleton	**Test:** Dual **Software:** MultiCalc (PerkinElmer, Turku, Finland) **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Dual: T21 (singleton) **Positive test threshold:** 1:250 **DR (95% CI):** 74% (64–83) **FPR (95% CI):** 10% (10–11)	Dual: T21 (twin) **Positive test threshold:** 1:250 **DR (95% CI):** 63% (42–81) **FPR (95% CI):** 11% (10–11)	

		Reference	
		+	-
Screen	+	64	6682
	-	22	58047

		Reference	
		+	-
Screen	+	17	1199
	-	10	9814

Study	Participant Characteristics	Screen Characteristics
Gasiorek-Wiens et al., 2001[25] **Country (# centers):** Germany, Switzerland, Austria (≥3) **Setting:** ND **Study recruitment (timing):** cohort (prospective) **Data collected:** June 1995–August 2001 **Associated publication:** von Kaisenberg et al., 2002[77]	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 21,959/23,805 **Median maternal age (range):** 33 yr (15–49), 36%≥35 yr **Median gestational age (range):** 12 wk (12–14) **Pregnancy type:** singleton	**Test:** NT **Software:** FMF software **NT training (if applicable):** Sonographers with FMF certification **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 88% (82–92) **FPR (95% CI):** 14% (14–14)	NT: T18 **Positive test threshold:** 1:300 **DR (95% CI):** 94% (88–97) **FPR (95% CI):** 14% (14–15)	NT: T13 **Positive test threshold:** 1:300 **DR (95% CI):** 97% (82–100) **FPR (95% CI):** 15% (14–15)

		Reference	
		+	-
Screen	+	184	3039
	-	26	18,710

		Reference	
		+	-
Screen	+	105	3118
	-	7	18,729

		Reference	
		+	-
Screen	+	28	3195
	-	1	18,735

Study	Participant Characteristics	Screen Characteristics
Gyselaers et al., 2004[26] **Country (# centers):** Belgium (>1) **Setting:** Samples collected from all geographic regions (setting ND) **Study recruitment (timing):** cohort (retrospective) **Data collected:** 1992–2002 **Associated publication:** Gyselaers et al., 2004[27]	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 36,382/40,490 **Median maternal age (range):** 1974≥35 yr **Median gestational age (range):** ND **Pregnancy type:** ND	**Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 70% (60–79) **FPR (95% CI):** 5% (5–6)		

		Reference	
		+	-
Screen	+	69	1993
	-	30	34,290

Study	Participant Characteristics	Screen Characteristics
Gyselaers et al., 2004[27] **Country (# centers):** Belgium (ND) **Setting:** ND **Study recruitment (timing):** cohort (retrospective) **Data collected:** 1999–2003 **Main publication:** Gyselaers et al., 2004[26]	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 7079/7079 **Median maternal age (range):** 8.6%≥35 yr **Median gestational age (range):** ND **Pregnancy type:** ND	**Test:** Double **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Double test: T21 **Positive test threshold:** 1:85 **DR (95% CI):** 62% (32–86) **FPR (95% CI):** 5% (4–6)		

		Reference	
		+	-
Screen	+	8	352
	-	5	6714

Study	Participant Characteristics	Screen Characteristics
Has et al., 2006[28] **Country (# centers):** Turkey (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** December 1998–ND	**Inclusion criteria:** All pregnant women between 11–14 wk gestation presenting to hospital. **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 4365/4365 **Median maternal age (range):** 28.2 yr±5.3 (mean±SD) (15–47) **Median gestational age (range):** 11–14 wk **Pregnancy type:** ND	**Test:** NT **Software:** FMF software **NT training (if applicable):** ND **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 Reference: + / − Screen +: 14 / 200 Screen −: 5 / 4146 **DR (95% CI):** 74% (49–91) **FPR (95% CI):** 5% (4–5)	NT: T18 **Positive test threshold:** 1:300 Reference: + / − Screen +: 4 / 210 Screen −: 1 / 4150 **DR (95% CI):** 80% (28–99) **FPR (95% CI):** 5% (4–5)	

Study	Participant Characteristics	Screen Characteristics
Hogge et al., 2001[29] **Country (# centers):** USA (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** May 1993–June 1998	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 45,145/45,145 **Median maternal age (range):** 10%≥35 yr **Median gestational age (range):** ND **Pregnancy type:** ND	**Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** adverse pregnancy outcomes, other trisomies
Screen Performance		
Triple: T18 **Positive test threshold:** 1:100 or AFP≤0.75 MoM, uE3≤0.60 Mom, and hCG≤0.55 MoM Reference: + / − Screen +: 8 / 242 Screen −: 4 / 44,891 **DR (95% CI):** 67% (35–90) **FPR (95% CI):** 1% (0–1)		

Study	Participant Characteristics	Screen Characteristics
Hsieh et al., 2007[30] **Country (# centers):** Taiwan (ND) **Setting:** university/academic hospital **Study recruitment (timing):** case-control (retrospective) **Data collected:** ND	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 96 (cases)/11,720 (controls) **Median maternal age (range):** 33.1 yr±5.8 (cases, mean±SD), 29.4 yr ±3.5 (controls, mean±SD) **Median gestational age (range):** 17.9 wk ±5.2) (cases, mean±SD), 16.8 wk±1.6 (controls, mean±SD) **Pregnancy type:** ND	**Test:** Dual **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Dual: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 63% (52–72) **FPR (95% CI):** 6% (6–7)		

		Reference	
		+	-
Screen	+	60	727
	-	36	10,993

Study	Participant Characteristics	Screen Characteristics
Huderer-Duric et al., 2000[31] **Country (# centers):** Croatia (ND) **Setting:** ND **Study recruitment (timing):** cohort (retrospective) **Data collected:** 1996–1998	**Inclusion criteria:** Women enrolled in antenatal care program **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 2833/2833 **Median maternal age (range):** 73%≥35 yr **Median gestational age (range):** 15–22 wk **Pregnancy type:** ND	**Test:** Triple **Software:** Prenata (Ortho-Clinical Diagnostics, USA) **NT training (if applicable):** NA **Other conditions detected:** trisomy 13, 18, 22
Screen Performance		
Triple: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 92% (62–100) **FPR (95% CI):** 37% (35–39)		

		Reference	
		+	-
Screen	+	11	1044
	-	1	1777

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Jaques et al., 2007[32]
Country (# centers): Australia (14)
Setting: private obsetric ultrasound practice
Study recruitment (timing): cohort (retrospective)
Data collected: February 2000–June 2002</td><td>Inclusion criteria: All women screened by Genetic Health Screening Laboratory during study period
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 16,002/16,153
Median maternal age (range): 33 yr (16–51)
Median gestational age (range): <13^{+6} wk
Pregnancy type: unselected</td><td>Test: Combined
Software: ND
NT training (if applicable): FMF certification
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Combined: T21
Positive test threshold: 1:300
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>57</td><td>626</td></tr><tr><td></td><td>-</td><td>6</td><td>15,314</td></tr></table>DR (95% CI): 90% (80–96)
FPR (95% CI): 4% (4–4)</td><td>Combined: T18
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>10</td><td>56</td></tr><tr><td></td><td>-</td><td>5</td><td>15,932</td></tr></table>DR (95% CI): 67% (38–88)
FPR (95% CI): 0% (0–0)</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Jaques et al., 2006[33]
Country (# centers): Australia (ND)
Setting: ND
Study recruitment (timing): cohort (retrospective)
Data collected: July 1998–June 2000</td><td>Inclusion criteria: All women screened by Genetic Health Screening Laboratory during study period
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 18,989/19,143
Median maternal age (range): 30.3 yr (mean) (14–51), 20%≥35
Median gestational age (range): ND
Pregnancy type: ND</td><td>Test: Quadruple
Software: ND
NT training (if applicable): NA
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Quadruple: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>23</td><td>1122</td></tr><tr><td></td><td></td><td>4</td><td>15,458</td></tr></table>DR (95% CI): 85% (66–96)
FPR (95% CI): 7% (6–7)</td><td>Quadruple: T18
Positive test threshold: 1:200
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>4</td><td>81</td></tr><tr><td></td><td>-</td><td>5</td><td>16,517</td></tr></table>DR (95% CI): 44% (14–79)
FPR (95% CI): 0% (0–1)</td><td>Quadruple: spina bifida
Positive test threshold: ≥2.5 MoM
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>4</td><td>185</td></tr><tr><td></td><td>-</td><td>4</td><td>17,088</td></tr></table>DR (95% CI): 50% (16–84)
FPR (95% CI): 1% (1–1)</td></tr>
<tr><td>Quadruple: anencephaly
Positive test threshold: ≥2.5 MoM
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>6</td><td>185</td></tr><tr><td></td><td>-</td><td>0</td><td>17,088</td></tr></table>DR (95% CI): 100% (54–100)
FPR (95% CI): 1% (1–1)</td><td></td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Jou et al., 2002[34] **Country (# centers):** Taiwan (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** June 1994–ND	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 25,530/25,530 **Median maternal age (range):** 29.56 yr (16–45), 29.46 yr±3.17 (mean±SD), 6%≥35 yr **Median gestational age (range):** 17.1 wk (15–22) **Pregnancy type:** ND	**Test:** Dual **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Dual: T18 **Positive test threshold:** MoM: AFP≤0.75, hCG≤0.55 **DR (95% CI):** 89% (52–100) **FPR (95% CI):** 3% (3–4)		

		Reference	
		+	-
Screen	+	8	879
	-	1	24642

Study	Participant Characteristics	Screen Characteristics
Jou et al., 2000[35] **Country (# centers):** Taiwan (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** June 1994–July 1998	**Inclusion criteria:** ND **Exclusion criteria:** Multiple pregancies, intrauterine fetal death, fetal congenital anomaly, incomplete data, foreigner **Screening $N_{analyzed}/N_{screened}$:** 17,742/17,742 **Median maternal age (range):** 29 yr (15–45), 29.45 yr (mean) **Median gestational age (range):** 17 wk (14–22) **Pregnancy type:** ND	**Test:** Dual **Software:** RAM (Robert Maciel Associates Inc, MA, USA) **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Dual: T21 **Positive test threshold:** 1:270 **DR (95% CI):** 63% (35–85) **FPR (95% CI):** 6% (6–7)		

		Reference	
		+	-
Screen	+	10	1143
	-	6	16,583

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Kishida et al., 2000[38]
Country (# centers): Japan (ND)
Setting: ND
Study recruitment (timing): cohort (prospective)
Data collected: May 1995–February 1998</td><td>Inclusion criteria: ND
Exclusion criteria: Polycyesis, diabetes, pregnancy with any other major complication
Screening $N_{analyzed}/N_{screened}$: 1055/1055
Median maternal age (range): 34.9 yr±0.2 (mean±SE), 63%≥35 yr
Median gestational age (range): 14–20 wk
Pregnancy type: singleton</td><td>Test: Triple
Software: ND
NT training (if applicable): NA
Other conditions detected: ND</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Triple: T21
Positive test threshold: 1:299 or AFP ≥2.5
<table>
<tr><td></td><td></td><td>Referenc</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>10</td><td>368</td></tr>
<tr><td></td><td>-</td><td>0</td><td>677</td></tr>
</table>
DR (95% CI): 100% (69–100)
FPR (95% CI): 35% (32–38)</td><td>Triple: T18
Positive test threshold: 1:299 or AFP ≥2.5
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>3</td><td>375</td></tr>
<tr><td></td><td>-</td><td>2</td><td>675</td></tr>
</table>
DR (95% CI): 60% (15–95)
FPR (95% CI): 36% (33–39)</td><td>Triple: T13
Positive test threshold: 1:299 or AFP ≥2.5
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td></td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>1</td><td>377</td></tr>
<tr><td></td><td>-</td><td>1</td><td>676</td></tr>
</table>
DR (95% CI): 50% (1–99)
FPR (95% CI): 36% (33–39)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Knight et al., 2005[39]
Country (# centers): USA (229)
Setting: Prenatal care practitioners' clinics (ND)
Study recruitment (timing): cohort (prospective)
Data collected: August 2001–August 2003</td><td>Inclusion criteria: Women in Maine receiving prenatal care between 8 and 13 wk gestation
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 11,159/11,159 (FT), 9723/9723 (ST), 8773/8773 (FT & ST)
Median maternal age (range): 27.8±5.5 yr (mean±SD)
Median gestational age (range): 8–13 wk
Pregnancy type: ND</td><td>Test: Serum IPS
Software: ND
NT training (if applicable): NA
Other conditions detected: ND</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Serum IPS: T21
Positive test threshold: 1:100
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>14</td><td>280</td></tr>
<tr><td></td><td>-</td><td>2</td><td>8477</td></tr>
</table>
DR (95% CI): 88% (62–98)
FPR (95% CI): 3% (3–4)</td><td></td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Lam et al., 2002[40] **Country (# centers):** Hong Kong (5) **Setting:** Prenatal and ultrasound clinics of participating hospitals **Study recruitment (timing):** cohort (prospective) **Data collected:** January 1997– August 2000	**Inclusion criteria:** Pregnant women who presented at or before 14 wk gestation and agreed to be screened for fetal Down syndrome **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 15,253/16,237 **Median maternal age (range):** 30.5 yr (mean), 19%≥35 yr **Median gestational age (range):** 12.4 wk (FT), 16 wk (ST) **Pregnancy type:** ND	**Test:** NT **Software:** ND **NT training (if applicable):** Experienced obsetricians with training (ND) in NT measurement **Test:** Dual **Software:** Robert Macial, USA **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** 1:320 Reference: + / - Screen +: 24 / 761 Screen -: 11 / 14457 **DR (95% CI):** 69% (51–83) **FPR (95% CI):** 5% (5–5)	Dual: T21 **Positive test threshold:** 1:320 Reference: + / - Screen +: 26 / 810 Screen -: 9 / 15392 **DR (95% CI):** 74% (57–88) **FPR (95% CI):** 5% (5–5)	

Study	Participant Characteristics	Screen Characteristics
Lamlertkittikul et al., 2007[41] **Country (# centers):** Thailand (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** February 2003–March 2004	**Inclusion criteria:** ND **Exclusion criteria:** Diabetes milletus, dead fetus in utero, and multiple pregnancies **Screening $N_{analyzed}/N_{screened}$:** 999/999 **Median maternal age (range):** 28.5 yr ±6.28 (mean±SD), 20%≥35 yr (14–46) **Median gestational age (range):** 14–20 wk **Pregnancy type:** singleton	**Test:** Triple **Software:** Prisca 3.5 DPC **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 4 / 115 Screen -: 0 / 880 **DR (95% CI):** 100% (40–100) **FPR (95% CI):** 12% (10–14)		

Study	Participant Characteristics	Screen Characteristics
Leung et al., 2009[42] **Country (# centers):** Hong Kong (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** June 2003–March 2007 **Associated publication:** Leung et al., 2007[43]	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 10,308/10,363 **Median maternal age (range):** 32 yr (IQR: 30, 35) **Median gestational age (range):** 11^{+0}–13^{+6} wk **Pregnancy type:** singleton and doubleton	**Test:** Combined **Software:** FMF software **NT training (if applicable):** FMF certified doctors **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 91% (76–98) **FPR (95% CI):** 6% (5–6)	Combined: T18 **Positive test threshold:** 1:300 **DR (95% CI):** 93% (68–100) **FPR (95% CI):** 6% (5–6)	

		Reference	
		+	-
Screen	+	31	582
	-	3	9478

		Reference	
		+	-
Screen	+	14	599
	-	1	9480

Study	Participant Characteristics	Screen Characteristics
MacRae et al., 2008[44] **Country (# centers):** UK (1) **Setting:** General/community hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** July 1998–January 2004	**Inclusion criteria:** Consecutive women between 11 and 13^{+6} wk gestation **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 18,965/18,965 fetuses **Median maternal age (range):** 12.4 wk (IQR: 12.3, 12.9), 27.4%≥35 yr **Median gestational age (range):** 10–13^{+6} wk **Pregnancy type:** ND	**Test:** NT **Software:** ViewPoint (Harris Birthright Research Centre, London) **NT training (if applicable):** ND **Other conditions detected:** T13, Turner syndrome
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 70% (53–84) **FPR (95% CI):** 3% (3–3)	NT: T18 **Positive test threshold:** 1:300 **DR (95% CI):** 80% (28–99) **FPR (95% CI):** 3% (3–4)	NT: T13 **Positive test threshold:** 1:300 **DR (95% CI):** 33% (1–91) **FPR (95% CI):** 3% (3–4)

		Reference	
		+	-
Screen	+	26	606
	-	11	18,322

		Reference	
		+	-
Screen	+	4	628
	-	1	18,332

		Reference	
		+	-
Screen	+	1	631
	-	2	18,331

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>MacRae et al., 2010[45]
Country (# centers): Canada (>2)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: January 2003–June 2006</td><td>Inclusion criteria: Patients from Manitoba and Ontario recruited through established province-wide referral program for women of advanced maternal age.
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: IPS: 3408/3897, IPS-inhibin A: 2816/3094, Quad: 1593/1595
Median maternal age (range): 30.6 yr (IQR: 26.6–34.4), 19.2≥35 yr
Median gestational age (range): 8–13^{+6} (FT), 15–20^{+6} (ST)
Pregnancy type: singleton</td><td>Test: Full IPS
Software: Benetech prenatal risk assessment software (Benetech Inc., Toronto, Canada)
NT training (if applicable): FMF certified sonographers
Test: IPS - ihibin A
Software: Benetech prenatal risk assessment software (Benetech Inc., Toronto, Canada)
NT training (if applicable): FMF certified sonographers
Test: Quadruple
Software: Benetech prenatal risk assessment software (Benetech Inc., Toronto, Canada)
NT training (if applicable): NA
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Full IPS: T21
Positive test threshold: 1:260
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>4</td><td>71</td></tr><tr><td></td><td>-</td><td>1</td><td>2763</td></tr></table>DR (95% CI): 80% (28–99)
FPR (95% CI): 3% (2–3)</td><td>IPS - ihibin A: T21
Positive test threshold: 1:260
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>8</td><td>176</td></tr><tr><td></td><td>-</td><td>0</td><td>3258</td></tr></table>DR (95% CI): 100% (63–100)
FPR (95% CI): 5% (4–6)</td><td>Quadruple: T21
Positive test threshold: 1:260
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>9</td><td>82</td></tr><tr><td></td><td>-</td><td>1</td><td>1501</td></tr></table>DR (95% CI): 90% (55–100)
FPR (95% CI): 5% (4–6)</td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Malone et al., 2005[46] **Country (# centers):** USA (15) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** October 1999–December 2002	**Inclusion criteria:** Maternal age of 16 yr or older, pregnancy with a singleton live fetus, fetal CR of 36–79mm **Exclusion criteria:** Prior measurement of NT or anencephaly **Screening $N_{analyzed}/N_{screened}$:** 33,546/36,120 **Median maternal age (range):** 21.6%≥35 yr **Median gestational age (range):** 10^{+3}–13^{+6} **Pregnancy type:** singleton	**Test:** Combined **Software:** ND **NT training (if applicable):** specially trained ultrasonographers performed according to standardized protocol. **Test:** Quadruple **Software:** ND **NT training (if applicable):** NA **Test:** Sequential **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** Cyctic hygroma (excluded)
Screen Performance		
Combined: T21 **Positive test threshold:** 1:300 Reference: + / − Screen +: 75 / 2028 Screen −: 17 / 34,186 **DR (95% CI):** 82% (72–89) **FPR (95% CI):** 6% (5–6)	Quadruple: T21 **Positive test threshold:** 1:300 Reference: + / − Screen +: 74 / 2988 Screen −: 13 / 32,161 **DR (95% CI):** 85% (76–92) **FPR (95% CI):** 9% (8–9)	Sequential: T21 **Positive test threshold:** 1:150 (FT), 1:300 (ST) Reference: + / − Screen +: 82 / 3680 Screen −: 5 / 29,779 **DR (95% CI):** 94% (87–98) **FPR (95% CI):** 11% (11–11)

Study	Participant Characteristics	Screen Characteristics
Michailidis et al., 2001[47] **Country (# centers):** UK (1) **Setting:** general/community hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** 1995–2000	**Inclusion criteria:** Live intrauterine pregnancy, presenting at 10–14 wk gestation or having had an NT measurement **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 7447/8536 (NT), 4864/8536 (Dual) **Median maternal age (range):** 30.1 yr (NT) (mean) (13–50), 21.1%≥35 yr **Median gestational age (range):** 12^{+5} wk (mean) **Pregnancy type:** unselected	**Test:** NT **Software:** **NT training (if applicable):** ND **Test:** Dual **Software:** Screenlab (QC Technology, New Hampshire, USA) **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** NT > 99 percentile for gestational age Reference: + / − Screen +: 20 / 371 Screen −: 3 / 7053 **DR (95% CI):** 87% (66–97) **FPR (95% CI):** 5% (5–6)	Dual: T21 **Positive test threshold:** 1:250 Reference: + / − Screen +: 2 / 423 Screen −: 2 / 4437 **DR (95% CI):** 50% (7–93) **FPR (95% CI):** 9% (8–10)	

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Monni et al., 2005[48]
Country (# centers): Italy (1)
Setting: university/academic hospital
Study recruitment (timing): cohort (retrospective)
Data collected: 1996–December 2004
Associated publications:
Zoppi et al., 2005[89]
Zoppi et al., 2001[90]</td><td>Inclusion criteria: Singleton pregnancies with no chromosomal abnormalities as assessed prenatally or postnatally or presumed by clinical examination after delivery and Down syndrome fetuses diagnosed prenatally or postnatally or other chromosomal abnormatlities
Exclusion criteria: Multiple pregnancies and unknown outcomes
Screening $N_{analyzed}/N_{screened}$: 16,654/32,000
Median maternal age (range): 32 yr (14–49)
Median gestational age (range): 11–14
Pregnancy type: singleton</td><td>Test: NT
Software: FMF software
NT training (if applicable): FMF certification
Other conditions detected: ND</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td colspan="3">NT: T21
Positive test threshold: NT > 95 percentile of FMF software reference values
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>72</td><td>744</td></tr>
<tr><td></td><td>-</td><td>24</td><td>15,769</td></tr>
</table>
DR (95% CI): 75% (65–83)
FPR (95% CI): 5% (4–5)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Montalvo et al., 2005[49]
Country (# centers): Spain (1)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: July 1999–October 2004</td><td>Inclusion criteria: Fetuses between 10–14 wk (confirmed by sonography), single gestation
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 4538 /4538
Median maternal age (range): 31.08 yr ±5.13 (mean±SD) (14–49), 25.9%≥35 yr
Median gestational age (range): 11^{+5} wk ±6.6 (mean±SD)
Pregnancy type: singleton</td><td>Test: Combined
Software: ND
NT training (if applicable): Level IV (ND) sonographers
Other conditions detected: ND</td></tr>
<tr><th colspan="3">Screen Performance</th></tr>
<tr><td>Combined: T21
Positive test threshold: 1:270
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>14</td><td>183</td></tr>
<tr><td></td><td>-</td><td>5</td><td>4336</td></tr>
</table>
DR (95% CI): 74% (49–91)
FPR (95% CI): 4% (3–5)</td><td>Combined: T18
Positive test threshold: 1:270
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>5</td><td>192</td></tr>
<tr><td></td><td>-</td><td>0</td><td>4341</td></tr>
</table>
DR (95% CI): 100% (48–100)
FPR (95% CI): 4% (4–5)</td><td>Combined: T13
Positive test threshold: 1:270
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td>Screen</td><td>+</td><td>4</td><td>193</td></tr>
<tr><td></td><td>-</td><td>3</td><td>4338</td></tr>
</table>
DR (95% CI): 57% (18–90)
FPR (95% CI): 4% (4–5)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Muller et al., 2003[50]
Country (# centers): France (9)
Setting: maternity clinic
Study recruitment (timing): cohort (ambispective)
Data collected: January 1998–June 2001</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 5606/5694 (NT), 5633/5694 (double), 5598/5694 (combined)
Median maternal age (range): ND
Median gestational age (range): 11–13 wk
Pregnancy type: singleton</td><td>Test: NT
Software: ND
NT training (if applicable): Sonographer trained by FMF-certified sonographer, other special training, and self-taught
Test: Double test
Software: ND
NT training (if applicable): NA
Test: Combined
Software: ND
NT training (if applicable): Sonographer trained by FMF-certified sonographer, other special training, and self-taught
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>NT: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>16</td><td>281</td></tr><tr><td>-</td><td>10</td><td>5298</td></tr></table>DR (95% CI): 62% (41–80)
FPR (95% CI): 5% (4–5)</td><td>Double test: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>18</td><td>451</td></tr><tr><td>-</td><td>8</td><td>5156</td></tr></table>DR (95% CI): 69% (48–86)
FPR (95% CI): 8% (7–9)</td><td>Combined: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>19</td><td>263</td></tr><tr><td>-</td><td>7</td><td>5309</td></tr></table>DR (95% CI): 73% (52–88)
FPR (95% CI): 5% (4–5)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Nicolaides et al., 2005[51]
Country (# centers): UK (7)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: June 1998–December 2003
Associated publications:
Kagan et al., 2010[37]
Kagan et al., 2008[36]</td><td>Inclusion criteria: All women booked for maternity care at participating hospitals
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 75,821/78,428
Median maternal age (range): 31 yr (13–49)
Median gestational age (range): 12 wk (11^{+0}–13^{+6})
Pregnancy type: singleton</td><td>Test: Combined
Software: ND
NT training (if applicable): Sonographers with FMF certification
Other conditions detected: Trisomy 13, 18, and other (ND)</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Combined: T21
Positive test threshold: 1:300
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>301</td><td>4100</td></tr><tr><td>-</td><td>24</td><td>71,396</td></tr></table>DR (95% CI): 93% (89–95)
FPR (95% CI): 5% (5–6)</td><td></td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Niemimaa et al., 2001[52] **Country (# centers):** Finland (ND) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** January–December 1999	**Inclusion criteria:** Volunteer pregnant women during the 10th–13th wk of pregnancy in 1999 **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 1602/2515 (NT and combined), 2515/2515 (double) **Median maternal age (range):** 17.5%≥35 yr **Median gestational age (range):** 10–13 wk **Pregnancy type:** ND	**Test:** NT **Software:** Wallac 1T-risk (research version, 2000) **NT training (if applicable):** Personnel trained in tertiary university centres **Test:** Double **Software:** Wallac 1T-risk (research version, 2000) **NT training (if applicable):** NA **Test:** Combined **Software:** Wallac 1T-risk (research version, 2000) **NT training (if applicable):** Personnel trained in tertiary university centres **Other conditions detected:** T18
Screen Performance		
NT: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 3 / 186 Screen -: 2 / 1411 **DR (95% CI):** 60% (15–95) **FPR (95% CI):** 12% (10–13)	Double: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 6 / 243 Screen -: 2 / 2264 **DR (95% CI):** 75% (35–97) **FPR (95% CI):** 10% (9–11)	Combined: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 4 / 132 Screen -: 1 / 1465 **DR (95% CI):** 80% (28–99) **FPR (95% CI):** 8% (7–10)

Study	Participant Characteristics	Screen Characteristics
Ochshorn et al., 2001[53] **Country (# centers):** Israel (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** January 1998–December 1999	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 1298/1408 **Median maternal age (range):** ND **Median gestational age (range):** 10–13 wk **Pregnancy type:** singleton	**Test:** Combined **Software:** Alpha software (Version 5.2, Logical Medical Systems, London, UK) **NT training (if applicable):** Trained sonographers (ND) **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** 1:380 Reference: + / - Screen +: 2 / 100 Screen -: 0 / 1196 **DR (95% CI):** 100% (48–100) **FPR (95% CI):** 7% (6–8)	Combined: T18 **Positive test threshold:** 1:380 Reference: + / - Screen +: 2 / 100 Screen -: 2 / 1194 **DR (95% CI):** 50% (7–93) **FPR (95% CI):** 8% (6–9)	Combined: T13 **Positive test threshold:** 1:380 Reference: + / - Screen +: 2 / 100 Screen -: 1 / 1195 **DR (95% CI):** 67% (9–99) **FPR (95% CI):** 8% (6–9)

Study	Participant Characteristics	Screen Characteristics
O'Connell et al., 2000[54] **Country (# centers):** UK (1) **Setting:** Maternity hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** May 1992–April 1997	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 14,827/14,827 **Median maternal age (range):** ND **Median gestational age (range):** ND **Pregnancy type:** ND	**Test:** Triple **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 60% (32–84) **FPR (95% CI):** 4% (4–4)		

		Reference	
		+	-
Screen	+	9	577
	-	6	14,235

Study	Participant Characteristics	Screen Characteristics
Okun et al., 2008[55] **Country (# centers):** Canada (2) **Setting:** general/community hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** November 2002–December 2005	**Inclusion criteria:** Women with singleton live fetus at time of testing **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 14,487/46,714 (combined), 32,227/46,714 (IPS) **Median maternal age (range):** 34 yr (combined), 32 yr (IPS) (mean) **Median gestational age (range):** 12.5 wk (FT), at/before 18 wk (ST) **Pregnancy type:** singleton	**Test:** Combined **Software:** Prenatal Assessment Software (Benetech Inc., Toronto, Canada) **NT training (if applicable):** predominantly FMF certification **Test:** IPS - ihibin A **Software:** Alpha software (Logical Medical System, UK) **NT training (if applicable):** predominantly FMF certification **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** ≥1:200 or NT ≥3.5mm **DR (95% CI):** 84% (72–92) **FPR (95% CI):** 4% (4–4)	IPS - ihibin A: T21 **Positive test threshold:** ≥1:200 or NT ≥3.5mm **DR (95% CI):** 88% (80–94) **FPR (95% CI):** 3% (3–4)	

		Reference	
		+	-
Screen	+	52	573
	-	10	13,852

		Reference	
		+	-
Screen	+	76	1068
	-	10	31,073

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>O'Leary et al., 2006[56]
Country (# centers): Australia (ND)
Setting: university/academic hospital
Study recruitment (timing): cohort (retrospective)
Data collected: August 2001–October 2003
Associated publication: Brameld et al., 2008[20]</td><td>Inclusion criteria: ND
Exclusion criteria: Multiple pregnancy
Screening $N_{analyzed}/N_{screened}$: 22,280/22,280
Median maternal age (range): 31 yr (14–47)
Median gestational age (range): 12^{+3} wk (8.9–14.4 wk) for blood collection and 12^{+4} wk (10–14.4) for NT
Pregnancy type: singleton</td><td>Test: NT
Software: ND
NT training (if applicable): Sonographers received training and FMF certification
Test: Double
Software: PIA-Fetal Database (Viewpoint, Munich, Germany)
NT training (if applicable):
Test: Combined
Software: PIA-Fetal Database (Viewpoint, Munich, Germany)
NT training (if applicable): Sonographers received training and FMF certification
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>NT: T21
Positive test threshold: 1:300
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference</td></tr>
<tr><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>44</td><td>1902</td></tr>
<tr><td>-</td><td>16</td><td>20,318</td></tr>
</table>
DR (95% CI): 73% (60–84)
FPR (95% CI): 9% (8–9)</td><td>Double test: T21
Positive test threshold:
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference</td></tr>
<tr><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>51</td><td>2560</td></tr>
<tr><td>-</td><td>2611</td><td>19,660</td></tr>
</table>
DR (95% CI): 85% (73–93)
FPR (95% CI): 12% (11–12)</td><td>Combined: T21
Positive test threshold: 1:300
<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Reference</td></tr>
<tr><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>50</td><td>827</td></tr>
<tr><td>-</td><td>10</td><td>21,383</td></tr>
</table>
DR (95% CI): 83% (71–92)
FPR (95% CI): 4% (3–4)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Onda et al., 2000[57]
Country (# centers): Japan (ND)
Setting: ND
Study recruitment (timing): cohort (prospective)
Data collected: April 1994–March 1999</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 32,925/32,925
Median maternal age (range): 32.2 yr, 31.4%≥35 yr
Median gestational age (range): 16 wk (15–21)
Pregnancy type: singleton</td><td>Test: Triple
Software: ND
NT training (if applicable): ND
Other conditions detected: meningocele, omphalocele, gstroschisis, T13</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Triple: T21
Positive test threshold: 1:295
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>63</td><td>4722</td></tr><tr><td></td><td>-</td><td>13</td><td>28127</td></tr></table>DR (95% CI): 83% (73–91)
FPR (95% CI): 14% (14–15)</td><td>Triple: T18
Positive test threshold:1:100
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>22</td><td>158</td></tr><tr><td></td><td>-</td><td>6</td><td>32739</td></tr></table>DR (95% CI): 79% (59–92)
FPR (95% CI): 0% (0–1)</td><td>Triple: anencephaly
Positive test threshold: 1:290
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>23</td><td>153</td></tr><tr><td></td><td>-</td><td>0</td><td>32749</td></tr></table>DR (95% CI): 100% (85–100)
FPR (95% CI): 0% (0–1)</td></tr>
<tr><td>Triple: anencephaly
Positive test threshold: 1:290
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>23</td><td>153</td></tr><tr><td></td><td>-</td><td>0</td><td>32749</td></tr></table>DR (95% CI): 100% (16–100)
FPR (95% CI): 1% (0–1)</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Panburana et al., 2001[58]
Country (# centers): Thailand (ND)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: January 1996–June 1999</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 2353/2353
Median maternal age (range): 28.71 yr± 0.13 (mean±SD)
Median gestational age (range): 11.94 wk ±1.07 (mean±SD)
Pregnancy type: ND</td><td>Test: NT
Software: ND
NT training (if applicable): ND
Other conditions detected: T13</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>NT: T21
Positive test threshold: ≥2.5 mm
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>2</td><td>63</td></tr><tr><td></td><td>-</td><td>0</td><td>2288</td></tr></table>DR (95% CI): 100% (16–100)
FPR (95% CI): 3% (2–3)</td><td>NT: T18
Positive test threshold: : ≥2.5 mm
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>2</td><td>63</td></tr><tr><td></td><td>-</td><td>0</td><td>2288</td></tr></table>DR (95% CI): 100% (16–100)
FPR (95% CI): 3% (2–3)</td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Platt et al., 2004[59] **Country (# centers):** USA and Canada (12) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** ND **Main publication:** Wapner et al., 2003[81]	**Inclusion criteria:** Any age with singleton pregnancy between 74 and 97 days gestation (according to CR length) **Exclusion criteria:** Multiple gestation, recent vaginal bleeding equivalent to a menstrual period, pregestational DM, pregnancy from donor oocyte. Patients with indications for prenatal diagnosis other than risk of trisomy also excluded. **Screening $N_{analyzed}/N_{screened}$:** 8205/8205 **Median maternal age (range):** 34.5 yr ±4.6 (median±SD) **Median gestational age (range):** 12.2 wk ±0.81 (mean±SD) (FT) **Pregnancy type:** singleton	**Test:** Sequential **Software:** NTD Laboratories **NT training (if applicable):** Sonographers with FMF certification **Other conditions detected:** ND
Screen Performance		
Sequential: T21 **Positive test threshold:** 1:270 **DR (95% CI):** 95% (86–99) **FPR (95% CI):** 13% (12–13)		

		Reference	
		+	-
Screen	+	58	1023
	-	3	7121

Study	Participant Characteristics	Screen Characteristics
Roberts et al., 2000[60] **Country (# centers):** UK (2) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** February 1992–January 1997	**Inclusion criteria:** Women booked for second trimester ultrasound before 20 wk gestation **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 26,080/26,080 **Median maternal age (range):** 27 yr (mean) (14–55) **Median gestational age (range):** 15–20 wk **Pregnancy type:** ND	**Test:** Dual **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Dual: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 76% (60–88) **FPR (95% CI):** 5% (5–5)		

		Reference	
		+	-
Screen	+	31	1323
	-	10	24716

Study	Participant Characteristics	Screen Characteristics
Rosen et al., 2002[61] **Country (# centers):** Israel (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** January 1995–March 1997	**Inclusion criteria:** All women with singleton pregnancy scheduled to undergo amniocentesis for advanced maternal age (≥35 yr) **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 1006/1006 **Median maternal age (range):** ≥35 yr **Median gestational age (range):** 16–18 wk **Pregnancy type:** singleton	**Test:** Triple **Software:** Israeli National Prenatal Screening Program software **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:380 **DR (95% CI):** 100% (75–100) **FPR (95% CI):** 43% (46–40)		

		Reference	
		+	-
Screen	+	13	424
	-	0	569

Study	Participant Characteristics	Screen Characteristics
Rozenberg et al., 2006[62] **Country (# centers):** France (10) **Setting:** Perinatal units (ND) **Study recruitment (timing):** cohort (prospective) **Data collected:** January 2001–December 2002	**Inclusion criteria:** 18 yr or older, 11^{+0}–13^{+6} gestational age, residing in Yvelines, delivering in Yvelines perinatal network, eligible for medical coverage by the regional health system, provide written informed consent **Exclusion criteria:** Multiple pregnancy, pregestational diabetes mellitus, pregnancy from oocyte donor **Screening $N_{analyzed}/N_{screened}$:** 13,384/14,380 **Median maternal age (range):** 30.7 yr (IQR: 28.0–33.9) **Median gestational age (range):** 12^{+3} (IQR: 12^{+0}–12^{+6}) **Pregnancy type:** singleton	**Test:** Combined **Software:** ND **NT training (if applicable):** Sonographers attended training course in FMF standards **Other conditions detected:** Trisomy 13, 16, 18, sex chromosome disjunctions
Screen Performance		
Combined: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 80% (67–90) **FPR (95% CI):** 3% (3–3)		

		Reference	
		+	-
Screen	+	41	370
	-	10	12,963

Study	Participant Characteristics	Screen Characteristics
Sau et al., 2001[63] **Country (# centers):** UK (1) **Setting:** general/community hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** November 1996–November 1998	**Inclusion criteria:** All women booking for prenatal care at Conquest hospital **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 2683/2683 **Median maternal age (range):** 27.53 yr ±5.10 (mean±SD) (for 3185 women enrolled in study) **Median gestational age (range):** ND **Pregnancy type:** ND	**Test:** NT **Software:** FMF software **NT training (if applicable):** Sonographers accredited (ND) in the technique **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** NT > 95 percentile for particular CRL Reference: + / - Screen +: 7 / 52 Screen -: 0 / 2624 **DR (95% CI):** 100% (59–100) **FPR (95% CI):** 2% (1–3)	NT: T18 **Positive test threshold:** NT > 95 percentile for particular CRL Reference: + / - Screen +: 2 / 57 Screen -: 1 / 2623 **DR (95% CI):** 67% (9–99) **FPR (95% CI):** 2% (2–3)	NT: T13 **Positive test threshold:** NT > 95 percentile for particular CRL Reference: + / - Screen +: 1 / 58 Screen -: 1 / 2623 **DR (95% CI):** 50% (1–99) **FPR (95% CI):** 2% (2–3)

Study	Participant Characteristics	Screen Characteristics
Schaelike et al., 2009[64] **Country (# centers):** Germany (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** November 2000–December 2006	**Inclusion criteria:** Singleton pregnancies and patient's consent. **Exclusion criteria:** Multiple gestation, pre-existing diabetes mellitus, vaginal bleeding **Screening $N_{analyzed}/N_{screened}$:** 10,618/11,107 **Median maternal age (range):** 3302 ≥35 yr **Median gestational age (range):** 11^{+0}–13^{+6} wk **Pregnancy type:** singleton	**Test:** NT **Software:** ND **NT training (if applicable):** FMF certification **Test:** Double **Software:** Pia Fetal Database (Viewpoint, Munich, Germany) **NT training (if applicable):** NA **Test:** Combined **Software:** Pia Fetal Database (Viewpoint, Munich, Germany) **NT training (if applicable):** FMF certification **Other conditions detected:** T13, T18
Screen Performance		
NT: T21 **Positive test threshold:** NT>3mm Reference: + / - Screen +: 33 / 546 Screen -: 26 / 10,013 **DR (95% CI):** 56% (42–69) **FPR (95% CI):** 5% (5–7)	Double: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 48 / 1730 Screen -: 11 / 8829 **DR (95% CI):** 81% (69–90) **FPR (95% CI):** 16% (16–17)	Combined: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 52 / 517 Screen -: 7 / 10,042 **DR (95% CI):** 88% (77–95) **FPR (95% CI):** 5% (4–5)

Study	Participant Characteristics	Screen Characteristics
Schielen et al., 2006[65] **Country (# centers):** Netherlands (44) **Setting:** ND **Study recruitment (timing):** cohort (ambispective) **Data collected:** July 2002–May 2004	**Inclusion criteria:** Singleton pregnancies **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 4033/4033 **Median maternal age (range):** 36.5 yr (18–47) **Median gestational age (range):** 11.5 wk (8.0–13.6) **Pregnancy type:** Singleton	**Test:** Combined **Software:** Wallac 1T-risk (version 1.7, PerkinElmer, Turku, Finland) **NT training (if applicable):** FMF certified **Other conditions detected:** T13, T18, triploidies
Screen Performance		
Combined: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 71% (48–89) **FPR (95% CI):** 5% (4–5)		

		Reference	
		+	-
Screen	+	15	190
	-	6	3822

Study	Participant Characteristics	Screen Characteristics
Schmidt et al., 2008[66] **Country (# centers):** Germany (5) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** ND	**Inclusion criteria:** Singleton pregnancies with known fetal outcome **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 10,017/10,017 **Median maternal age (range):** 31.3 yr (mean) (16–43) **Median gestational age (range):** 11^{+0}–13^{+6} **Pregnancy type:** singleton	**Test:** Combined **Software:** PIA Fetal Database (General Electric/ViewPoint, Wessling, Germany) **NT training (if applicable):** FMF certification **Other conditions detected:** Trisomy 13, 18, Turner syndrome, Klinefelter syndrome, other trisomies
Screen Performance		
Combined: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 87% (75–95) **FPR (95% CI):** 7% (6–7)		

		Reference	
		+	-
Screen	+	47	656
	-	7	9307

Study	Participant Characteristics	Screen Characteristics
Scott et al., 2004[67] **Country (# centers):** Australia (1) **Setting:** private obstetric practice **Study recruitment (timing):** cohort (prospective) **Data collected:** July 2000–May 2002	**Inclusion criteria:** All women with a singleton pregnancy referred to Syndey Ultrasound for Women **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 2053/2121 **Median maternal age (range):** 32 yr (15–44), 29%≥35 yr **Median gestational age (range):** 11–14 wk **Pregnancy type:** singleton	**Test:** NT **Software:** FMF software **NT training (if applicable):** FMF certification **Test:** Double **Software:** ND **NT training (if applicable):** NA **Test:** Combined **Software:** ND **NT training (if applicable):** FMF certification **Other conditions detected:** Trisomy 13, 18, 22, triploidies
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 5 / 112 Screen -: 0 / 1936 **DR (95% CI):** 100% (48–100) **FPR (95% CI):** 5% (5–7)	Double: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 4 / 390 Screen -: 1 / 1658 **DR (95% CI):** 80% (28–99) **FPR (95% CI):** 19% (17–21)	Combined: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 5 / 145 Screen -: 0 / 1903 **DR (95% CI):** 100% (48–100) **FPR (95% CI):** 7% (6–8)

Study	Participant Characteristics	Screen Characteristics
Sepulveda et al., 2007[68] **Country (# centers):** Chile (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** January 2003–January 2006	**Inclusion criteria:** Women presenting with a single live fetus with a crown-rump length between 45 mm and 84 mm **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 1287/1287 **Median maternal age (range):** 33 yr (14–47), 35.4%≥35 yr **Median gestational age (range):** 12 wk (11–14) **Pregnancy type:** singleton	Test: NT **Software:** Astraia software (Munich, Germany) **NT training (if applicable):** Obstetricians with FMF certification **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** NT > 95 percentile for gestational age Reference: + / - Screen +: 28 / 82 Screen -: 3 / 1174 **DR (95% CI):** 90% (74–98) **FPR (95% CI):** 7% (5–8)		

Study	Participant Characteristics	Screen Characteristics
Shaw et al., 2010[69] **Country (# centers):** Taiwan (ND) **Setting:** general/community hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** July–December 2008	**Inclusion criteria:** Singleton health pregnancies **Exclusion criteria:** Multiple pregnancies, maternal diabetes or cardiac disease, illiteracy, and known high-risk pregnancies originally referred from a medical centre. **Screening $N_{analyzed}/N_{screened}$:** 21,481/21,481 **Median maternal age (range):** 29.5 yr ±3.6 (mean±SD) **Median gestational age (range):** 15–20 wk **Pregnancy type:** singleton	Test: Quadruple **Software:** Benetech prenatal risk assessment software (Benetech Inc., Toronto, Canada) **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Quadruple: T21 **Positive test threshold:** 1:270 **DR (95% CI):** 82% (48–98) **FPR (95% CI):** 5% (4–5)		

		Reference	
		+	-
Screen	+	9	968
	-	2	20,502

Study	Participant Characteristics	Screen Characteristics
Soergel et al., 2006[70] **Country (# centers):** Germany (3) **Setting:** university/academic hospital (1) and regional private centres (2) **Study recruitment (timing):** cohort (prospective) **Data collected:** June 1998–October 2002	**Inclusion criteria:** All women booking for prenatal prenatal care at participating centres **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 2497/3947 (NT), 2196/3947 (double combined) **Median maternal age (range):** 32.5 yr (16–44), 26.4%≥35 yr **Median gestational age (range):** 11–14 wk **Pregnancy type:** singleton and doubleton	**Test:** NT **Software:** PIA-Fetal Database (Viewpoint, Munich, Germany) **NT training (if applicable):** Sonographers with FMF certification **Test:** Double **Software:** FMF **NT training (if applicable):** NA **Test:** Combined **Software:** PIA-Fetal Database (Viewpoint, Munich, Germany) **NT training (if applicable):** Sonographers with FMF certification **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 82% (48–98) **FPR (95% CI):** 5% (4–6)	Double: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 88% (47–100) **FPR (95% CI):** 15% (14–17)	Combined: T21 **Positive test threshold:** 1:300 **DR (95% CI):** 88% (47–100) **FPR (95% CI):** 4% (3–5)

		Reference	
		+	-
Screen	+	9	128
	-	2	2358

		Reference	
		+	-
Screen	+	7	336
	-	1	1852

		Reference	
		+	-
Screen	+	7	87
	-	1	2101

Study	Participant Characteristics	Screen Characteristics
Stenhouse et al., 2004[71] **Country (# centers):** UK (1) **Setting:** maternity hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** ND	**Inclusion criteria:** All women in the FT attending the Queen Mother's Maternity Hospitals in Glasgow over a 3-yr period with a gestational age of 11–14 wk by ultrasound **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 5000/5000 **Median maternal age (range):** 31.5 yr (14–45), 27.2%≥35 yr **Median gestational age (range):** 93% 11–14 wk **Pregnancy type:** ND	**Test:** Combined **Software:** ND **NT training (if applicable):** FMF certification **Other conditions detected:** Trisomy 13, 18, tripoloidy
Screen Performance		
Combined: T21 **Positive test threshold:** 1:250 Reference: + / -; Screen +: 14 / 283; Screen -: 1 / 4702 **DR (95% CI):** 93% (68–100) **FPR (95% CI):** 6% (5–6)		

Study	Participant Characteristics	Screen Characteristics
Strah et al., 2008[72] **Country (# centers):** Slovenia (2) **Setting:** ultrasound outpatient clinic **Study recruitment (timing):** cohort (retrospective) **Data collected:** November 1999–May 2006	**Inclusion criteria:** All women referred by physician for US examination **Exclusion criteria:** Twin pregnancies **Screening $N_{analyzed}/N_{screened}$:** 7096/7522 **Median maternal age (range):** 28.6 yr (15–42), 2.5%≥36 yr **Median gestational age (range):** 12^{+4} wk (10^{+5}–13^{+6}) **Pregnancy type:** singleton	**Test:** NT **Software:** FMF software **NT training (if applicable):** Experienced sonographers (ND) with FMF certification **Other conditions detected:** T13, T18, triploidies, Turner syndrome
Screen Performance		
NT: T21 **Positive test threshold:** 1:300 Reference: + / -; Screen +: 9 / 162; Screen -: 3 / 6922 **DR (95% CI):** 75% (43–95) **FPR (95% CI):** 2% (2–3)		

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Summers et al., 2003[73]
Country (# centers): Canada (ND)
Setting: ND
Study recruitment (timing): cohort (retrospective)
Data collected: October 1993–September 2000</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 423,895/423,895
Median maternal age (range): 16%≥35 yr
Median gestational age (range): 15–20 wk
Pregnancy type: ND</td><td>Test: Triple
Software: MASFP Expert (Benetech Inc.,ON, Canada)
NT training (if applicable): NA
Other conditions detected: T13, Turner syndrome and other trisomies, NTD (anencephaly, spina bifida)</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Triple: T21
Positive test threshold: 1:385
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>531</td><td>30,703</td></tr>
<tr><td>-</td><td>186</td><td>392,475</td></tr>
</table>
DR (95% CI): 74% (71–77)
FPR (95% CI): 7% (7–7)</td><td>Triple: T18
Positive test threshold: 1:100
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>66</td><td>647</td></tr>
<tr><td>-</td><td>59</td><td>423,123</td></tr>
</table>
DR (95% CI): 53% (44–62)
FPR (95% CI): 0.15% (0.14–0.16)</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Tørring et al., 2009[74]
Country (# centers): Denmark (1)
Setting: university/academic hospital
Study recruitment (timing): cohort (retrospective)
Data collected: November 2003–March 2009</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 3370 (random sample)/44,537
Median maternal age (range): 35 yr (mean)
Median gestational age (range): 7^{+5}–13^{+6}
Pregnancy type: singleton</td><td>Test: Combined
Software: Astraia software Gmbh (Munich, Germany)
NT training (if applicable): FMF certified sonographers
Other conditions detected: T13, T18, triploidies</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Combined: T21
Positive test threshold: 1:300
<table>
<tr><td></td><td></td><td>Reference</td><td></td></tr>
<tr><td></td><td></td><td>+</td><td>-</td></tr>
<tr><td rowspan="2">Screen</td><td>+</td><td>108</td><td>23</td></tr>
<tr><td>-</td><td>12</td><td>3227</td></tr>
</table>
DR (95% CI): 90% (55–100)
FPR (95% CI): 1% (0–1)</td><td></td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Tsai et al., 2001[75]
Country (# centers): Taiwan (1)
Setting: General hospital
Study recruitment (timing): cohort (retrospective)
Data collected: April 1999–September 2000</td><td>Inclusion criteria: Women with singleton pregnancies who received a combined test at the hospital
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 1514/1514
Median maternal age (range): ND
Median gestational age (range): 10–13 wk
Pregnancy type: singleton</td><td>Test: NT
Software: Alpha software (Logical Medical Systems,UK)
NT training (if applicable): FMF-trained sonographers
Test: Combined
Software: Alpha software (Logical Medical Systems,UK)
NT training (if applicable): Trained (ND) sonographers
Other conditions detected: T18, Turner syndrome</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>NT: T21
Positive test threshold: ≥3.0 mm
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>4</td><td>13</td></tr><tr><td>-</td><td>6</td><td>1491</td></tr></table>DR (95% CI): 40% (12–74)
FPR (95% CI): 1% (0–1)</td><td>Combined: T21
Positive test threshold: 1:400
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>9</td><td>88</td></tr><tr><td>-</td><td>1</td><td>1416</td></tr></table>DR (95% CI): 90% (55–100)
FPR (95% CI): 6% (5–7)</td><td></td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Valinen et al., 2007[76]
Country (# centers): Finland (ND)
Setting: public health care centres and maternity clinics
Study recruitment (timing): cohort (Retrospective)
Data collected: 2002–2004</td><td>Inclusion criteria: ND
Exclusion criteria: Samples taken later than 12^{+6} wk and multiple pregnancies
Screening $N_{analyzed}/N_{screened}$: 7534/7534 (serum), 4765/7534 (NT and combined)
Median maternal age (range): 29.6 yr (mean), 18.6%≥35
Median gestational age (range): 10–12^{+6} wk
Pregnancy type: singleton</td><td>Test: Double
Software: LifeCycle risk program (PerkinElmer Life Sciences, Finland)
NT training (if applicable): NA
Test: Combined
Software: LifeCycle risk program (Wallac, Finland)
NT training (if applicable): physicians, nurses, and midwives with formal training
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Double test: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>23</td><td>360</td></tr><tr><td>-</td><td>7</td><td>7144</td></tr></table>DR (95% CI): 77% (58–90)
FPR (95% CI): 5% (4–5)</td><td>Combined: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td rowspan="2">Screen</td><td>+</td><td>21</td><td>232</td></tr><tr><td>-</td><td>3</td><td>4509</td></tr></table>DR (95% CI): 88% (68–97)
FPR (95% CI): 5% (4–6)</td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
von Kaisenberg et al., 2002[77] **Country (# centers):** Germany (8) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** September 1998–November 2001 **Main publication:** Gasiorek-Wiens et al., 2001[25]	**Inclusion criteria:** Women presenting at participating centres at 11–14 wk with single live fetus **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 3551/3864 **Median maternal age (range):** 33 yr (15–46), 35.8%≥35 yr **Median gestational age (range):** 12 wk (11–14) **Pregnancy type:** singleton	**Test:** Combined **Software:** Astraia obstetric and gynecological database, Astraia GmbH, Munich, Germany) **NT training (if applicable):** FMF certified sonographers **Other conditions detected:** Turner's syndrome, other sex chromosome disjunctions, and trisomies
Screen Performance		
Combined: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 16 / 269 Screen -: 3 / 3299 **DR (95% CI):** 84% (60–97) **FPR (95% CI):** 8% (7–8)	Combined: T18 **Positive test threshold:** 1:300 Reference: + / - Screen +: 9 / 264 Screen -: 1 / 3277 **DR (95% CI):** 90% (55–100) **FPR (95% CI):** 7% (7–8)	Combined: T13 **Positive test threshold:** 1:300 Reference: + / - Screen +: 4 / 269 Screen -: 0 / 3278 **DR (95% CI):** 100% (40–100) **FPR (95% CI):** 8% (7–9)

Study	Participant Characteristics	Screen Characteristics
Wald et al., 2009[78] **Country (# centers):** UK (2) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** 2003–2007	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 14,296/14,296 **Median maternal age (range):** 33 yr (15–51), 20%≥37 yr **Median gestational age (range):** 12^{+4}–16^{+1} wk **Pregnancy type:** singleton	**Test:** IPS - ihibin A **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
IPS - ihibin A: T21 **Positive test threshold:** 1:150 Reference: + / - Screen +: 41 / 299 Screen -: 6 / 13,950 **DR (95% CI):** 87% (74–95) **FPR (95% CI):** 2% (2–2)		

Study	Participant Characteristics	Screen Characteristics
Wald et al., 2003[79] **Country (# centers):** United Kingdom (14) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** August 1996–September 2001 **Main publication:** Wald et al., 2003[80]	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 46,193/46,193 **Median maternal age (range):** ND **Median gestational age (range):** 14–22 wk **Pregnancy type:** singleton and doubleton	Test: Quadruple **Software:** ND **NT training (if applicable):** **Other conditions detected:** ND
Screen Performance		
Quadruple: T21 **Positive test threshold:** 1:300 Reference: + / - Screen +: 71 / 3200 Screen -: 17 / 42,905 **DR (95% CI):** 81% (71–88) **FPR (95% CI):** 7% (7–7)		

Study	Participant Characteristics	Screen Characteristics
Wald et al., 2003[80] **Country (# centers):** United Kingdom (25) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** September 1996–May 2001 **Associated publication:** Wald et al., 2003[79]	**Inclusion criteria:** Booked for antenatal care between 8 and 14 wk **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 40,387/47,053 (FT), 37,362/47,053 (ST), 30,375/47,053 (IPS) **Median maternal age (range):** ND **Median gestational age (range):** 10–13 wk (FT), 14–20 wk (ST) **Pregnancy type:** singleton	**Test:** Combined **Software:** ND **NT training (if applicable):** Sonographers received training (ND) **Test:** Triple and quadruple **Software:** ND **NT training (if applicable):** NA Test: Serum IPS **Software:** ND **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 71 / 2015 Screen -: 14 / 38,287 **DR (95% CI):** 84% (74–91) **FPR (95% CI):** 5% (5–5)	Triple: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 66 / 2572 Screen -: 16 / 34,708 **DR (95% CI):** 80% (70–88) **FPR (95% CI):** 7% (7–7)	Quadruple: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 69 / 2125 Screen -: 13 / 35,155 **DR (95% CI):** 84% (74–91) **FPR (95% CI):** 6% (5–6)
Serum IPS: T21 **Positive test threshold:** 1:250 Reference: + / - Screen +: 57 / 1031 Screen -: 8 / 29,279 **DR (95% CI):** 88% (77–95) **FPR (95% CI):** 3% (3–4)		

Study	Participant Characteristics	Screen Characteristics
Wapner et al., 2003[81] **Country (# centers):** USA and Canada (12) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (Prospective) **Data collected:** ND **Associated publication:** Platt et al., 2004[59]	**Inclusion criteria:** Any age with singleton pregnancy between 74 and 97 days gestation (according to CR length) **Exclusion criteria:** Mulitple gestation, recent vaginal bleeding equivalent to a menstrual period, pregestational diabetes milletus, pregnancy from donor oocyte. Patients with indications for prenatal diagnosis other than risk of trisomy also excluded. **Screening $N_{analyzed}/N_{screened}$:** 8216/8514 **Median maternal age (range):** 34.5 yr ±4.6 (mean±SD), 50%≥35 yr **Median gestational age (range):** 12.2 wk ±0.81 (mean±SD) (FT) **Pregnancy type:** singleton	**Test:** Combined **Software:** NTD Laboratories **NT training (if applicable):** Sonographers with FMF certification **Other conditions detected:** ND
Screen Performance		
Combined: T21 **Positive test threshold:** 1:270	Combined: T18 **Positive test threshold:** 1:150	

		Reference	
		+	-
Screen	+	52	770
	-	9	7385

DR (95% CI): 85% (74–93)
FPR (95% CI): 9% (9–10)

		Reference	
		+	-
Screen	+	10	154
	-	1	8051

DR (95% CI): 91% (59–100)
FPR (95% CI): 2% (2–2)

Study	Participant Characteristics	Screen Characteristics
Wayda et al. 2001, 2001[82] **Country (# centers):** Hungary (5) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** 1995–1998	**Inclusion criteria:** ND **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 6841/7044 **Median maternal age (range):** 31 yr (16–46) **Median gestational age (range):** 10–12 wk **Pregnancy type:** unselected	**Test:** NT **Software:** FMF software **NT training (if applicable):** Sonographers with theoretical and practical training (ND) at centre **Other conditions detected:** ND
Screen Performance		
NT: T21 **Positive test threshold:** ≥2.5 mm	NT: T18 **Positive test threshold:** ≥2.5 mm	NT: T13 **Positive test threshold:** ≥2.5 mm

		Reference	
		+	-
Screen	+	17	292
	-	0	6533

DR (95% CI): 100% (80–100)
FPR (95% CI): 4% (4–5)

		Refere ce	
		+	-
Screen	+	8	301
		0	6532

DR (95% CI): 100% (63–100)
FPR (95% CI): 4% (4–5)

		Reference	
		+	-
Screen	+	4	305
	-	0	6532

DR (95% CI): 100% (40–100)
FPR (95% CI): 4% (4–5)

Study	Participant Characteristics	Screen Characteristics
Weingertner et al., 2006[83] **Country (# centers):** France (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** January 2002–December 2004	**Inclusion criteria:** Women with singleton pregnancy between 11–14 wk gestation **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 1260/2044 **Median maternal age (range):** 32 yr (16–47) **Median gestational age (range):** 12.9 wk (10.9–14) **Pregnancy type:** singleton	**Test:** NT **Software:** ND **NT training (if applicable):** Sonographers and physicians experienced in obstetric ultrasound and certified by the French National Society of Ultrasound **Other conditions detected:** Turner syndrome, translocations and other anomalies
Screen Performance		
NT: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 87% (69–96) **FPR (95% CI):** 23% (21–25)		

		Reference	
		+	-
Screen	+	26	463
	-	4	1551

Study	Participant Characteristics	Screen Characteristics
Weisz et al., 2007[84] **Country (# centers):** UK (>1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (retrospective) **Data collected:** January 2003–September 2004	**Inclusion criteria:** Women booked for prenatal care at University College London Hospitals **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 2332/2377 **Median maternal age (range):** 31.7 yr (mean) (15–47) **Median gestational age (range):** 11–$13^{+6/7}$ wk (NT), second component measured at/before 15 wk **Pregnancy type:** ND	**Test:** Full IPS **Software:** Alpha software (Logical Medical Systems, UK) **NT training (if applicable):** Qualified or trained (ND) by study author **Other conditions detected:** ND
Screen Performance		
Full IPS: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 83% (52–98) **FPR (95% CI):** 4% (3–4)	Full IPS: T21 **Positive test threshold:** 1:150 **DR (95% CI):** 44% (17–72) **FPR (95% CI):** 3% (0–8)	

		Reference	
		+	-
Screen	+	10	82
	-	2	2238

		Reference	
		+	-
Screen	+	10	58
	-	2250	2

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Wøjdemann et al., 2005[85]
Country (# centers): Denmark (3)
Setting: university/academic hospital
Study recruitment (timing): cohort (prospective)
Data collected: March 1998–June 2001</td><td>Inclusion criteria: ND
Exclusion criteria: ND
Screening $N_{analyzed}/N_{screened}$: 8662/9941 (NT), 6441/9941 (serum and combined)
Median maternal age (range): 29.3 yr (mean), 10.8%≥35 yr
Median gestational age (range): 10^{+3}–13^{+6} wk
Pregnancy type: singleton</td><td>Test: NT
Software: ViewPoint® (GE Healthcare)
NT training (if applicable): Sonographers and physicians experienced in obstetric ultrasound and FMF certification
Test: Double
Software: ND
NT training (if applicable):
Test: Combined
Software: ND
NT training (if applicable): Sonographers and physicians experienced in obstetric ultrasound and FMF certification
Other conditions detected: ND</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>NT: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>9</td><td>154</td></tr><tr><td></td><td>-</td><td>3</td><td>8496</td></tr></table>DR (95% CI): 75% (43–95)
FPR (95% CI): 2% (2–2)</td><td>Double: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>8</td><td>564</td></tr><tr><td></td><td>-</td><td>3</td><td>5866</td></tr></table>DR (95% CI): 73% (39–94)
FPR (95% CI): 9% (8–9)</td><td>Combined: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>10</td><td>138</td></tr><tr><td></td><td>-</td><td>1</td><td>6292</td></tr></table>DR (95% CI): 91% (59–100)
FPR (95% CI): 2% (2–3)</td></tr>
</table>

<table>
<tr><th>Study</th><th>Participant Characteristics</th><th>Screen Characteristics</th></tr>
<tr><td>Wortelboer et al., 2008[86]
Country (# centers): Netherlands (>1)
Setting: university/academic hospital
Study recruitment (timing): cohort (retrospective)
Data collected: 1991–2005</td><td>Inclusion criteria: ND
Exclusion criteria: Pregnancies with IDDM, multiple pregnancies, and pregnancies with previous Down syndrome
Screening $N_{analyzed}/N_{screened}$: 30,290/42,554
Median maternal age (range): 30.5 yr (1991), 34.5 yr (2005)
Median gestational age (range): 14–23 wk
Pregnancy type: singleton</td><td>Test: Triple
Software: Alpha software (Logical Medical Systems, UK) and Lifecycle™ Elipse (PerkinElmer, USA)
NT training (if applicable): NA
Other conditions detected: Trisomy 13 and 18 and NTD</td></tr>
<tr><td colspan="3">Screen Performance</td></tr>
<tr><td>Triple: T21
Positive test threshold: 1:250
<table><tr><td></td><td></td><td>Reference</td><td></td></tr><tr><td></td><td></td><td>+</td><td>-</td></tr><tr><td>Screen</td><td>+</td><td>85</td><td>3920</td></tr><tr><td></td><td>-</td><td>20</td><td>26,265</td></tr></table>DR (95% CI): 81% (72–88)
FPR (95% CI): 13% (13–13)</td><td></td><td></td></tr>
</table>

Study	Participant Characteristics	Screen Characteristics
Wortelboer et al., 2009[87] **Country (# centers):** Netherlands (>1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** May 2004–July 2006	**Inclusion criteria:** Pregnant women 8–13^{+6} wk **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 20,293/20,293 **Median maternal age (range):** 34.3 yr (final year) (median) (15–48) **Median gestational age (range):** 11.5 wk (final year median) (8–13^{+6}) **Pregnancy type:** singleton	**Test:** Combined **Software:** 1T-risks (version 1.7, PerkinElmer, Turku, Finland) **NT training (if applicable):** FMF-certified sonographers **Other conditions detected:** Trisomy 13 and 18 and triploidy
Screen Performance		
Combined: T21 **Positive test threshold:** 1:250 **DR (95% CI):** 76% (65–84) **FPR (95% CI):** 3% (3–4)		

		Reference	
		+	-
Screen	+	66	677
	-	21	19,529

Study	Participant Characteristics	Screen Characteristics
Xia et al., 2006[88] **Country (# centers):** China (1) **Setting:** university/academic hospital **Study recruitment (timing):** cohort (prospective) **Data collected:** April 2002–March 2005	**Inclusion criteria:** singleton pregnancies 14–20 wk gestation **Exclusion criteria:** ND **Screening $N_{analyzed}/N_{screened}$:** 4680/4680 **Median maternal age (range):** 28.13 yr (19–49) **Median gestational age (range):** 14–20 wk **Pregnancy type:** singleton	**Test:** Triple **Software:** Beckman Coulter Co. **NT training (if applicable):** NA **Other conditions detected:** ND
Screen Performance		
Triple: T21 **Positive test threshold:** 1:384 **DR (95% CI):** 78% (40–97) **FPR (95% CI):** 7% (6–8)	Triple: T18 **Positive test threshold:** 1:384 **DR (95% CI):** 86% (42–100) **FPR (95% CI):** 7% (6–8)	

		Reference	
		+	-
Screen	+	7	325
	-	2	4346

		Reference	
		+	-
Screen	+	6	326
	-	1	4347

Appendix T.D: Methodological Quality of Included Studies

Table T.D.1: Methodological quality for nuchal translucency test for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Audibert 2001[11]	Unclear	Yes	Unclear	Yes	No	Unclear	No	Yes	Yes
Babbur 2005[12]	Yes	Yes	Unclear	No	No	Yes	Unclear	Unclear	Unclear
Chasen 2003[22]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Yes
Gasiorek-Weins 2001[25]	Yes	Unclear	Yes	No	Yes	Yes	No	Yes	Yes
Has 2006[28]	Yes	Yes	Unclear	No	No	Yes	No	Unclear	Unclear
Lam 2002[40]	Yes	Unclear	Unclear	Yes	No	Unclear	No	Yes	Yes
MacRae 2008[44]	Unclear	No	Unclear	Unclear	Unclear	No	No	Yes	
Michailidis 2001[47]	Yes	Yes	Unclear	Yes	No	Unclear	No	Unclear	Yes
Monni 2005[48]	Yes	Yes	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear
Muller 2003[50]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Neimimaa 2001[52]	Yes	No	Unclear	Unclear	No	Unclear	No	Unclear	Unclear
O'Leary 2006[56]	Yes	Yes	Unclear	Unclear	No	Yes	No	Yes	Yes
Panburana 2001[58]	Unclear	No	Unclear	Yes	No	Unclear	Unclear	Unclear	
Sau 2001[63]	Yes	No	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear
Schaelike 2009[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Scott 2004[67]	Yes	Yes	Unclear	Yes	No	Yes	No	Yes	Yes
Sepulveda 2007[68]	Yes	Unclear	Unclear	No	No	Yes	Yes	Unclear	Unclear
Soergel 2006[70]	No	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	Yes
Strah 2008[72]	No	Yes	Unclear	Unclear	No	Unclear	No	Unclear	Unclear
Tsai 2001[75]	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	No	No
Wayda 2001[82]	Unclear	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes
Weingertner 2006[83]	Yes	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes
Wøjdemann 2005[85]	Yes	Unclear	Yes	Yes	No	Yes	No	Yes	Yes

Table T.D.2: Methodological quality for nuchal translucency test for trisomy 18

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Chasen 2003[22]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Yes
Gasiorek-Weins 2001[25]	Yes	Unclear	Yes	No	Yes	Yes	No	Yes	Yes
Has 2006[28]	Yes	Yes	Unclear	No	No	Yes	No	Unclear	Unclear
MacRae 2008[44]	Unclear	No	Unclear	Unclear	Unclear	No	No	Yes	Yes
Panburana 2001[58]	Unclear	No	Unclear	Yes	No	Unclear	Unclear	Unclear	No
Sau 2001[63]	Yes	No	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear
Wayda 2001[82]	Unclear	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes

Table T.D.3: Methodological quality for nuchal translucency test for trisomy 13

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Gasiorek-Weins 2001[25]	Yes	Unclear	Yes	No	Yes	Yes	No	Yes	Yes
MacRae 2008[44]	Unclear	No	Unclear	Unclear	Unclear	No	No	Yes	Yes
Panburana 2001[58]	Unclear	No	Unclear	Yes	No	Unclear	Unclear	Unclear	No
Sau 2001[63]	Yes	No	Unclear	Yes	Unclear	Unclear	No	Unclear	Unclear
Wayda 2001[82]	Unclear	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes

Table T.D.4: Methodological quality for double serum test for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Gysaelers 2004[27]	No	No	No	Unclear	Unclear	Unclear	No	No	No
Muller 2003[50]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Niemimaa 2001[52]	Yes	No	Unclear	Unclear	No	Unclear	No	Unclear	Unclear
O'Leary 2006[56]	Yes	Yes	Unclear	Unclear	No	Yes	No	Yes	Yes
Scott 2004[67]	Yes	Yes	Unclear	Yes	No	Yes	No	Yes	Yes
Schaelike 2009[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Valinen 2007[76]	Yes	Yes	Unclear	Unclear	No	Yes	No	Unclear	Unclear
Wøjdemann 2005[85]	Yes	Unclear	Yes	Yes	No	Yes	No	Yes	Yes

Table T.D.5: Methodological quality for combined screening for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
AHS 2010[9]	Unclear	No	Unclear	Unclear	Unclear	Unclear	No	Unclear	Unclear
Avgidou 2005[7]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Benn 2007[15]	Yes	No	Yes	Yes	Yes	Yes	No	Unclear	Yes
Borrell 2004[19]	Yes	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes
Cocclione 2008[23]	No	No	Yes	Yes	Yes	No	No	Unclear	Unclear
Jaques 2007[32]	Yes	Yes	Unclear	Yes	Unclear	Unclear	No	Yes	Yes
Leung 2009[42]	Yes	No	Unclear	Yes	No	Unclear	Unclear	Yes	Yes
Malone 2005[46]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Montalvo 2005[49]	No	Unclear	Unclear	No	No	Yes	No	No	No
Muller 2003[50]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Neimimaa 2001[52]	Yes	No	Unclear	Unclear	No	Unclear	No	Unclear	Unclear
Nicolaides 2005[51]	Yes	Yes	No	Yes	No	Unclear	Unclear	Yes	Yes
Ochshorn 2001[53]	Unclear	Unclear	Unclear	No	No	Yes	No	Yes	Yes

Okun 2008[55]	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	Yes
O'Leary 2006[56]	Yes	Yes	Unclear	Unclear	No	Yes	No	Yes	Yes
Rozenberg 2006[62]	Yes	Yes	Unclear	Unclear	No	Unclear	No	Unclear	Yes
Schaelike 2009[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schielen 2006[65]	Unclear	Unclear	Unclear	Yes	No	Unclear	No	Yes	Yes
Schmidt 2008[66]	Unclear	No	Unclear	Unclear	No	Yes	No	Yes	Yes
Scott 2004[67]	Yes	Yes	Unclear	Yes	No	Yes	No	Yes	Yes
Soergel 2006[70]	No	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	Yes
Stenhouse 2004[71]	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes
Tørring 2009[74]	Yes	No	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Tsai 2001[75]	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	No	No
Valinen 2007[76]	Yes	Yes	Unclear	Unclear	No	Yes	No	Unclear	Unclear
von Kaisenberg 2002[77]	Yes	Unclear	Yes	No	Yes	Yes	No	Yes	Yes
Wald 2003 (SURUSS)[80]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Unclear
Wapner 2003[81]	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
Wøjdemann 2005[85]	Yes	Unclear	Yes	Yes	No	Yes	No	Yes	Yes
Wortelboer 2009[87]	Unclear	Unclear	No	Yes	Unclear	Yes	No	Yes	Yes

Table T.D.6: Methodological quality for combined test for trisomy 18

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Avgidou 2005[7]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Benn 2007[15]	Yes	No	Yes	Yes	Yes	Yes	No	Unclear	Yes
Borrell 2004[19]	Yes	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes
Jaques 2007[32]	Yes	Yes	Unclear	Yes	Unclear	Unclear	No	Yes	Yes
Leung 2009[42]	Yes	No	Unclear	Yes	No	Unclear	Unclear	Yes	Yes
Montalvo 2005[49]	No	Unclear	Unclear	No	No	Yes	No	No	No
Ochshorn 2001[53]	Unclear	Unclear	Unclear	No	No	Yes	No	Yes	Yes
von Kaisenberg 2002[77]	Yes	Unclear	Yes	No	Yes	Yes	No	Yes	Yes
Wapner 2003[81]	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes

Table T.D.7: Methodological quality for combined test for trisomy 13

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Avgidou 2005[7]	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Benn 2007[15]	Yes	No	Yes	Yes	Yes	Yes	No	Unclear	Yes
Leung 2009[42]	Yes	No	Unclear	Yes	No	Unclear	Unclear	Yes	Yes
Wapner 2003[81]	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes

Table T.D.8: Methodological quality for dual serum test for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Audibert 2001[11]	Unclear	Yes	Unclear	Yes	No	Unclear	No	Yes	Yes
Beaman 2008[14]	Unclear	No	Unclear	Unclear	No	Yes	No	Unclear	Unclear
Garchet-Beaudron 2008[24]	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear
Hsieh 2007[30]	No	Unclear	Unclear	Unclear	No	Yes	No	Unclear	Unclear
Jou 2000[35]	Yes	Yes	Unclear	Yes	No	Yes	Unclear	Yes	Yes
Lam 2002[40]	Yes	Unclear	Unclear	Yes	No	Unclear	No	Yes	Yes
Michailidis 2001[47]	Yes	Yes	Unclear	Yes	No	Unclear	No	Unclear	Yes
Roberts 2000[60]	Yes	Unclear	Unclear	Yes	No	Unclear	No	Yes	Yes

Table T.D.9: Methodological quality for dual serum test for trisomy 18

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Jou 2002[34]	Unclear	No	Unclear	Yes	No	Unclear	No	Unclear	Unclear

Table T.D.10: Methodological quality for triple serum test for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Alvarez-Nava 2008[10]	No	Unclear	Unclear	Unclear	No	Yes	No	Unclear	Yes
Bahado-Singh 2000[13]	No	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Unclear
Cocciolone 2008[23]	No	No	Yes	Yes	Yes	No	No	Unclear	Unclear
Gyselaers 2004[26]	No	No	No	Unclear	Unclear	Unclear	No	No	No
Huderer-Duric 2000[31]	Unclear	No	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Kishida 2000[38]	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Lamlertkittikul 2007[41]	Unclear	Yes	Unclear	No	No	Yes	No	Yes	Yes
O'Connell 2000[54]	Unclear	No	Unclear	No	No	No	No	Yes	Yes

Onda 2000[57]	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Rosen 2002[61]	No	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear
Summers 2003[73]	Yes	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear
Wald 2003 (SURUSS)[80]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Unclear
Wortelboer 2008[86]	Unclear	Yes	No	Unclear	Yes	Yes	No	Unclear	Yes
Xia 2006[88]	Unclear	No	Unclear	Unclear	No	Yes	No	Unclear	Unclear

Table T.D.11: Methodological quality for triple serum test for trisomy 18

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Breathnach 2007[21]	Yes	Yes	Unclear	Yes	No	Yes	No	Yes	No
Hogge 2001[29]	Unclear	No	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear
Kishida 2000[38]	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Onda 2000[57]	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Summers 2003[73]	Yes	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear
Xia 2006[88]	Unclear	No	Unclear	Unclear	No	Yes	No	Unclear	Unclear

Table T.D.12: Methodological quality for triple serum test for spina bifida and anencephaly

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Benn 2000[17]	Unclear	No	Unclear	No	No	Unclear	Unclear	Unclear	No
Onda 2000[57]	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear

Table T.D.13: Methodological quality for quadruple serum test for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Benn 2003[16]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Unclear	Unclear
Jaques 2006[33]	Yes	Unclear	Unclear	Unclear	No	No	No	No	Yes
MacRae 2010[45]	No	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Unclear
Malone 2005[46]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Shaw 2010[69]	Yes	Yes	Unclear	Unclear	No	Yes	No	Unclear	Unclear
Wald 2003 (SURUSS)[80]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Unclear
Wald 2003[79]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Unclear

Table T.D.14: Methodological quality for quadruple serum test for trisomy 18

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Breathnach 2007[21]	Yes	Yes	Unclear	Yes	No	Yes	No	Yes	No
Jaques 2006[33]	Yes	Unclear	Unclear	Unclear	No	No	No	No	Yes

Table T.D.15: Methodological quality for quadruple serum test for spina bifida and anencepaphaly

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Jaques 2006[33]	Yes	Unclear	Unclear	Unclear	No	No	No	No	Yes

Table T.D.16: Methodological quality for full integrated screening for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Benn 2007[15]	Yes	No	Yes	Yes	Yes	Yes	No	Unclear	Yes
MacRae 2010[45]	No	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Unclear
Wald 2003 (SURUSS)[80]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Unclear
Weisz 2007[84]	Unclear	No	No	No	No	Yes	No	Unclear	Unclear

Table T.D.17: Methodological quality for full integrated screening for trisomy 18

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Benn 2007[15]	Yes	No	Yes	Yes	Yes	Yes	No	Unclear	Yes

Table T.D.18: Methodological quality for integrated screening minus inhibin-A for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
MacRae 2010[45]	No	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Unclear
Okun 2008[55]	Yes	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	Yes
Wald 2009[78]	Yes	No	Unclear	Yes	No	Unclear	Yes	Unclear	Yes

Table T.D.19: Methodological quality for serum integrated screening for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Knight 2005[39]	Unclear	Unclear	Yes	Yes	No	Yes	Unclear	Yes	Yes
Wald 2003 (SURUSS)[80]	Yes	Unclear	Unclear	Unclear	No	Yes	No	Yes	Unclear

Table T.D.20: Methodological quality for sequential screening for trisomy 21

Author/year	Spectrum of patients	Selection criteria	Reference standard classification	Whole or random selection receive reference	All pts receive same reference	Index test described in detail	Reference standard described in detail	Uninter-pretable results reported	Withdrawals reported and explained
Malone 2005[46]	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Platt 2004[59]	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	Yes

Appendix T.E: Likelihood Ratios for First and Second Trimester Prenatal Screens

Table T.E.1: Likelihood ratios for nuchal translucency for trisomy 21

Author/year/country	LR+	LR-
Audibert 2001[11] France	16.75	0.34
Babbur 2005[12] United Kingdom	32.00	0.37
Chasen 2003[22] USA	10.38	0.18
Gasiorek-Weins 2001[25] Germany, Switzerland, Austria	6.29	0.14
Has 2006[28] Turkey	14.80	0.27
Lam 2002[40] Hong Kong	13.80	0.33
Michailidis 2001[47] UK	17.40	0.14
MacRae 2008[44] United Kingdom	23.33	0.31
Muller 2003[50] France	12.40	0.40
Neimimaa 2001[52] Finland	5.00	0.45
O'Leary 2006[56] Australia	8.11	0.30

Author/year/country	LR+	LR-
Panburana 2001[58] Thailand	30.86	0.17
Sau 2001[63] United Kingdom	47.35	0.06
Scott 2004[67] Australia	20.0	0.09
Sepulveda 2007[68] Chile	12.86	0.11
Soergel 2006[70] Germany	16.40	0.19
Strah 2008[72] Slovenia	37.50	0.26
Tsai 2001[75] Taiwan	40.00	0.61
Wayda 2001[82] Hungary	37.50	0.26
Weingertner 2006[83] France	3.78	0.17
Wøjdemann 2005[85] Denmark	37.50	0.26

Table T.E.2: Likelihood ratios for nuchal translucency for trisomy 18

Author/year/country	LR+	LR-
Chasen 2003[22] USA	11.25	0.11
Gasiorek-Weins 2001[25] Germany, Switzerland, Austria	6.71	0.07
Has 2006[28] Turkey	16.00	0.21
MacRae 2008[44] United Kingdom	26.67	0.21

Author/year/country	LR+	LR-
Panburana 2001[58] Thailand	30.86	0.17
Sau 2001[63] United Kingdom	33.50	0.34
Wayda 2001[82] Hungary	21.36	0.06

Table T.E.3: Likelihood ratios for nuchal translucency for trisomy 13

Author/year/country	LR+	LR-
Gasiorek-Weins 2001[25] Germany, Switzerland, Austria	6.47	0.04
MacRae 2008[44] United Kingdom	11.0	0.69
Panburana 2001[58] Thailand	27.37	0.26

Author/year/country	LR+	LR-
Sau 2001[63] United Kingdom	25.00	0.51
Wayda 2001[82] Hungary	20.13	0.10

Table T.E.4: Likelihood ratios for double test for trisomy 21

Author/year/country	LR+	LR-
Gysaelers 2004[27] Belgium	12.40	0.40
Muller 2003[50] France	8.63	0.34
Niemimaa 2001[52] Finland	7.50	0.28
O'Leary 2006[56] Australia	7.08	0.17
Scott 2004[67] Australia	4.21	0.25
Soergel 2006[70] Germany	5.87	0.14
Valinen 2007[76] Finland	15.40	0.24
Wøjdemann 2005[85] Denmark	8.11	0.30

Table T.E.5: Likelihood ratios for combined test for trisomy 21

Author/year/country	LR+	LR-
AHS 2010[9] Canada	15.17	0.10
Avgidou 2005[7] UK	11.63	0.08
Benn 2007[15] USA	7.14	0.54
Borrell 2004[19] Spain	29.33	0.12
Cocclione 2008[23] Australia	18.20	0.09
Jaques 2007[32] Australia	22.50	0.10
Leung 2009[42] Hong Kong	15.17	0.10
Malone 2005[46] USA	13.67	0.19
Muller 2003[50] France	14.50	0.28
Neimimaa 2001[52] Finland	10.00	0.22
Montalvo 2005[49] Spain	18.50	0.27
Nicolaides 2005[51] UK	18.60	0.07
Ochshorn 2001[53] Israel	10.82	0.18
Okun 2008[55] Canada	21.0	0.17
O'Leary 2006[56] Australia	20.75	0.18
Rozenberg 2006[62] France	25.67	0.21
Schielen 2006[65] Netherlands	14.20	0.31
Schmidt 2008[66] Germany	12.43	0.14
Scott 2004[67] Australia	14.29	0.09
Soergel 2006[70] Germany	22.00	0.13
Stenhouse 2004[71] UK	15.50	0.07
Tørring 2009[74] Denmark	90	0.10
Tsai 2001[75] Taiwan	15.00	0.11
Valinen 2007[76] Finland	17.60	0.13
von Kaisenberg 2002[77] Germany	10.50	0.17
Wald 2003 (SURUSS)[80] UK	16.80	0l.17
Wapner 2003[81] USA, Canada	9.44	0.16
Wøjdemann 2005[85] Denmark	45.50	0.09
Wortelboer 2009[87] Netherlands	25.33	0.25

Table T.E.6: Likelihood ratios for combined test for trisomy 18

Author/year/country	LR+	LR-
Avgidou 2005[7] UK	11.50	0.09
Benn 2007[15] USA	4.13	0.73
Borrell 2004[19] Spain	25.00	0.26
Jaques 2007[32] Australia	191.43	0.33
Leung 2009[42] Hong Kong	15.50	0.07
Montalvo 2005[49] Spain	19.60	0.17
Ochshorn 2001[53] Israel	6.25	0.54
von Kaisenberg 2002[77] Germany	12.86	0.11
Wapner 2003[81] USA/Canada	45.50	0.09

Table T.E.7: Likelihood ratios for combined test for T13

Study/year/country	LR+	LR-
Avgidou 2005[7] UK	11.13	0.12
Montalvo 2005[49] Spain	14.25	0.45
Ochshorn 2001[53] Israel	8.38	0.36
von Kaisenberg 2002[77] Germany	11.25	0.11

Table T.E.8: Likelihood ratios for dual serum test for trisomy 21

Author/year/country	LR+	LR-
Audibert 2001[11] France	20.00	0.41
Beaman 2008[14] United Kingdom	11.17	0.35
Garchet-Beaudron 2008[24] France	7.40 (sing)	0.29
	5.73 (twin)	0.42
Hsieh 2007[30] Taiwan	10.50	0.39
Jou 2000[35] Taiwan	10.50	0.39
Lam 2002[40] Hong Kong	14.80	0.27
Michailidis 2001[47] United Kingdom	5.56	0.55
Roberts 2000[60] United Kingdom	15.20	0.25

Table T.E.9: Likelihood ratios for triple serum test for trisomy 21

Author/year/country	LR (+)	LR-
Alvarez-Nava 2008[10] Venezuela	11.50	0.33
Bahado-Singh 2000[13] USA	1.57	0.33
Cocciolone 2008[23] Australia	10.71	0.27
Gyselaers 2004[26] Belgium	14.1	0.32
Huderer-Duric 2000[31] Croatia	2.49	0.13
Kishida 2000[38] Japan	2.86	0
O'Connell 2000[54] United Kingdom	15.0	0.42
Onda 2000[57] Japan	5.93	0.20
Rosen 2002[61] Israel	2.33	0
Summers 2003[73] Canada	10.57	0.28
Wald 2003 (SURUSS)[80] United Kingdom	11.43	0.22
Wortelboer 2008[86] Netherlands	6.23	0.22

Lamlertkittikul 2007[41] Thailand	8.33	0	Xia 2006[88] China	11.14	0.24

Table T.E.10: Likelihood ratios for triple serum test for trisomy 18

Author/year/country	LR+	LR-	Author/year/country	LR+	LR-
Breathnach 2007[21] USA	600	0.40	Onda 2000[57] Japan	158	0.21
Hogge 2001[29] USA	67.0	0.33	Summers 2003[73] Canada	265	0.47
Kishida 2000[38] Japan	1.67	0.63	Xia 2006[88] China	12.29	0.15

Table T.E.11: Likelihood ratios for quadruple serum test for trisomy 21

Author/year/country	LR+	LR-	Author/year/country	LR+	LR-
Benn 2003[16] USA	9.67	0.14	Shaw 2010[69] Taiwan	16.40	0.19
Jaques 2006[33] Australia	12.14	0.16	Wald 2003 (SURUSS)[80] UK	14.0	0.17
MacRae 2010[45] Canada	18.0	0.11	Wald 2003[79] UK	11.57	0.17
Malone 2005[46] USA	9.44	0.16			

Table T.E.12: Likelihood ratios for full integrated screening for trisomy 21

Author/year/country	LR+	LR-	Author/year/country	LR+	LR-
Benn 2007[15] USA	14.33	0.15	Wald 2003 (SURUSS)[80] UK	30.33	0.09
MacRae 2010[45] Canada	26.67	0.21	Weisz 2007[84] UK	20.75	0.18

Table T.E.13: Likelihood ratios for ultrasound for spina bifida

Author/year	LR+	LR-	Author/year	LR+	LR-
Anderson 1995	9400	0.06	Levi 1995	3500	0.65
Crane 1994	7000	0.30	Sahinoglu 2001	9500	0.05
Girish 2001	3033	0.09	Stefos 1999	8400	0.16

Table T.E.14: Likelihood ratios for ultrasound for anencephaly

Author/year	LR+	LR-	Author/year	LR+	LR-
Anderson 1995	9700	0.03	Levi 1995	9000	0.10
Crane 1994	8800	0.12	Sahinoglu 2001	9600	0.04
Girish 2001	3067	0.08	Stefos 1999	9000	0.10

SECTION THREE: ECONOMICS ANALYSIS

Anderson Chuck, PhD, MPH, Charles Yan, PhD, Thanh Nguyen, MD, MPH, PhD

Objectives and Policy Questions

The objective of the economic analysis was to estimate the costs and cost effectiveness of various screening strategies. More specifically, the analysis was to address the following questions:

1. To estimate the unit costs, including physician billings, hospitalization or facility operational costs, other service costs and capital costs, for the procedure as well as related health services.
2. To estimate the costs of services avoided within a reasonable period of time.
3. To provide cost-effectiveness comparisons of various FASTS options in the short-term.
4. To estimate patient and public demand, including prevalence and incidence of condition(s) and utilization rates of standard and alternative screening options, where data exist.
5. To estimate the total cost for each option based on utilization estimates.
6. To assess the potential for transfer of service and funds from existing services being replaced or reduced in usage, as well the impact on the health system of such transfers, if possible.

These questions were addressed in both a systematic review of the economic literature and a primary economic analysis which included an economic evaluation which addressed questions 1 to 4, a budget impact analysis to address question 5 and a cost attribution analysis to address question 6.

Methods

Review of economic studies

Search strategy

Selected databases were searched for economic evaluation studies of first and second trimester screening services. Databases searched include Medline EMBASE, CINAHL, Cochrane Database of Systematic Reviews, CRD Databases (DARE, NHS EED, HTA), Web of Science BIOSIS Previews, Biological Sciences, Biotechnology Research Abstracts, Scopus, Econlit. The date restrictions (from 2000 onward) were applied and only English language results were retrieved. To supplement the electronic searches, reference lists of retrieved articles were also reviewed to find further studies. The literature search summary is presented in Appendix E.1.

Selection criteria

The search was limited to human and English language publications. Eligible studies were those that met the following predefined inclusion/exclusion criteria:

Inclusion criteria:

1. Study design: Health technology assessment reports, systematic reviews and economic evaluation studies including studies of cost effectiveness, cost-utility, or cost-benefit
2. Population: pregnant women with singleton gestation
3. Interventions and comparators: various FASTS options

4. Outcomes of interest: Studies are included if they provide cost-effectiveness results that include both costs and health outcomes for each intervention. Health outcomes can include health related quality of life, quality adjusted life years, cases of affected pregnancies correctly identified, cases of correctly identified non-affected pregnancies, and testing-related miscarriages.

Exclusion criteria:

1. Abstracts/summaries, case studies, narrative reviews, comments, letters, and editorials.
2. Economic evaluations that included the lifetime cost of live births. These were excluded because including these costs bias cost effectiveness towards screening algorithms associated with a higher number of abortions but not necessarily to those that have the highest diagnostic precision. Furthermore, such studies fail to incorporate the value of positive contributions of these individuals to society which again bias the cost effectiveness in favour of algorithms associated with a higher rate of abortion[1].
3. Studies that did not conduct an incremental analysis between comparators and did not report totals for costs and outcomes of each comparator to allow for a manual calculation of incremental costs and outcomes.
4. Studies scoring lower than 75 on the Quality of Health Economic Studies (QHES) instrument[2] (see below).

Quality Assessment

A formal quality assessment of economic studies was conducted with the QHES. The instrument is based on criteria adapted from Drummond et al.3 but includes a weighting system to score and aggregate across individual criteria thereby providing a summative index of quality. The quality index ranges from 0 to 100 with a score of 75 or greater indicating acceptable quality.

Data Extraction

Data extracted from studies include study design, objective, perspective, timelines, screening strategy, country, health and cost outcomes, results from the marginal analysis and study conclusions.

Primary economic analysis

The primary economic analysis consisted of an economic evaluation, a cost attribution analysis and a budget impact analysis.

Economic evaluation

Cost effectiveness analysis (CEA) is an analytic approach for comparing the health benefits and resource expenditures associated with competing health technologies. A CEA was conducted to evaluate the cost-effectiveness of alternative FASTS screening strategies in pregnant women with singleton gestation. Specifically, a decision analytic simulation model was developed to comparatively evaluate the alternative screening strategies in terms of both their costs and health outcomes.

The CEA adopted a payer perspective and considered direct medical service costs to the Alberta health system, including costs of physician, outpatient and laboratory services. The time horizon for the analysis considered costs from initial screen to final diagnosis and adopted a constrained program optimization approach. That is, the analysis aims to elucidate the screening strategy that

provides the highest accuracy at the lowest cost to the health system. Furthermore, excluding long term outcomes of live births in economic analyses is supported by relevant research where it has been argued that the inclusion of such costs can result in significantly misleading conclusions[1;4;5]. All analyses were conducted using Microsoft Excel 2003 and TreeAge Pro Suite (TREEAGE software Inc; Williamstown, MA).

Screening algorithms

There were 15 alternative screening strategies evaluated in the CEA (Table E.1) which included various adaptations of first trimester screening (FTS) (e.g. combined testing), second trimester screening (STS), integrated prenatal screenings (IPS), sequential screening, contingent screening, and repeated measure screening described in Tabel T.1 in the T section of this report. All 14 strategies in the T section were considered in the E section, with an addition of the Alberta North strategy. Screening strategies available in Alberta include strategies 1, 3, 6, and 15 (refer to S section for further details).

Figure E.1 shows a simplified flow diagram representing the general structure of the screening algorithms evaluated (refer to Appendix E.2 for detailed diagrams). Women older than 39 years of age can either receive screening or go directly to invasive diagnostic testing (e.g. chorionic villus sampling). Women younger than 40 years of age go directly to screening. For all screening algorithms, except for sequential and contingent screening, a negative screening result requires no further testing, while a positive screening leads to invasive diagnostic testing. In sequential screening, testing in the first trimester is conducted to assess the interim risk where women found to be of high risk may either undergo invasive diagnostic testing whereas women who are found to be of low risk receive testing in the second trimester (regardless of the test result in the first trimester screen). In contingent screening, interim risk is assessed in the first trimester but with the outcome divided into low, intermediate and high risk. Women found to be of low risk do not receive further testing while women found to be of high risk may undergo invasive diagnostic testing and women found to be of intermediate risk are screened in the second trimester (regardless of the testing result in the first trimester screen). In both sequential and contingent screening, women with a negative screen result in the second trimester screen do not require further testing while a positive result could lead to invasive diagnostic testing.

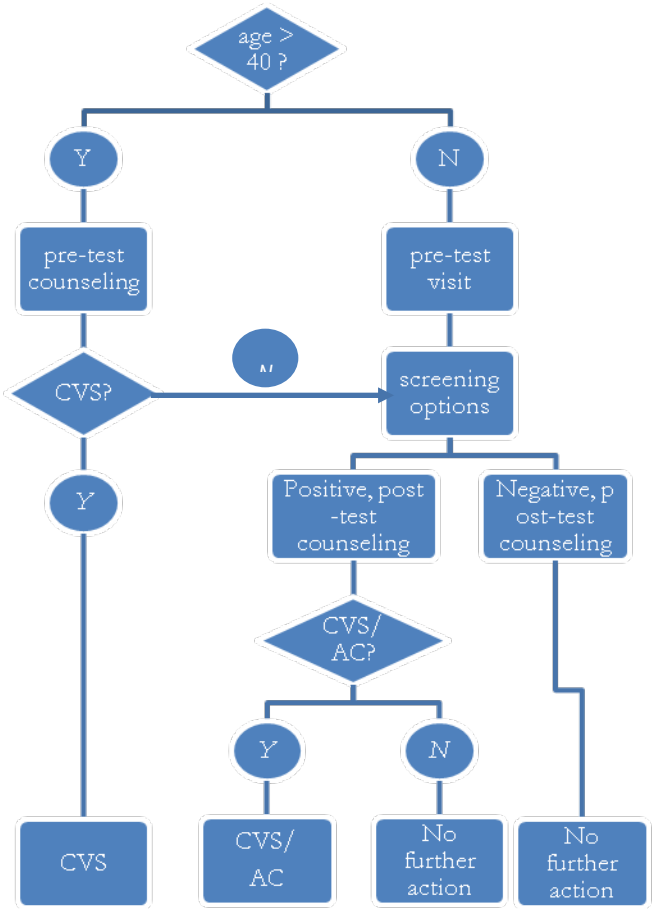
Table E.1: Screening strategy and targeted prenatal abnormality*

Screening strategy			Evidence Available to Population Model					
#	Tri-mester	Tests conducted	T21	T18	T13	Spina bifida	Anencephaly	Encephalocele
1	FTS	NT	✓	✓	✓	×	×	×
2		Double test (PAPP-A and HCG)*	✓	---	---	×	×	×
3		Combined test (NT, free ß-hCG and PAPP-A) – Predominantly utilized in Alberta South	✓	✓	✓	×	×	×
4	STS	Dual (AFP and free ß-hCG)	✓	✓	---	---	---	---
5		Triple (AFP, uE3 and total hCG)	✓	✓	✓	✓	✓	---
6		Quad (AFP, uE3, free ß-hCG, inhibin A) Predominantly utilized in Alberta North	✓	✓	---	✓	✓	---
7		Ultrasound detection of open neural tube defects	NA	NA	NA	✓	✓	---
8	FTS+STS	Full IPS*: FST: NT and PAPP-A; STS: Quad test	✓	✓	---	---	---	---
9		IPS without inhibin A: FST: NT and PAPP-A; STS: Triple test	✓	---	---	---	---	---
10		Serum IPS: FTS: PAPP-A; STS: Quad test	✓	---	---	---	---	---
11		Sequential: FTS: NT, PAPP-A and hCG; STS: Quad or triple test	✓	---	---	---	---	---
12		Contingent: FTS: NT, PAPP-A and hCG; STS: Quad or triple test	✓	---	---	---	---	---
13		Repeated measure 1: FTS: uE3 and PAPP-A; STS: uE3 and PAPP-A	✓	---	---	×	×	×
14		Repeated measure 2: FTS: NT+ uE3 and PAPP-A; STS: uE3 and PAPP-A	✓	---	---	×	×	×
15		Special Case in Alberta North: FTS: combined test STS: AFP	✓	✓	✓	✓	×	×

Note: NA: Not assessed; ×: indicates the conditions for which risk estimate is not generated; ---: indicates conditions for which there is no study reporting the risk estimate, based on the search in T-section

*Of the 15 screening strategies, 1, 3, 6, and 15 are available in Alberta

Figure E.1: Simplified flow diagram of screening algorithm



Note: AC = amniocentesis; CVS = chorionic villus sampling

Targeted prenatal abnormalities

The targeted prenatal abnormalities included trisomy 21, 18, 13, anencephaly, encephaloceles, and spina bifida. However, there were insufficient data available to inform the diagnostic precision of each screening strategy for all of the targeted prenatal abnormalities with complete data only being available for trisomy 21 (Table E.1). Note that this further excludes second trimester ultrasound and the special case in Alberta North because these focus on ONTD only. Consequently, the CEA could only focus on trisomy 21 in the analysis resulting in evaluating 13 of the 15 alternative screening strategies.

Primary analysis

The performance characteristics of the alternative screening strategies in terms of sensitivity and specificity were primary derived from the systematic review conducted in the T-section of this report (Table E.2). However, there was no information available from the T-section that informed the performance characteristics for sequential, contingent and repeated measures screening and the required inputs were derived from mathematical simulations. Mathmatical simulation studies are typically conducted to determine the promise of noval screening strategies followed by empirical studies of those that show promising results. Mathmatical simulation studies can be considered lower level evidence compared to empirical studies. Hence, the primary analysis focuses on those screening strategies that could be populated with empirical evidence generated in the T (i.e. excludes

sequential, contingent and repeated measures) while a secondary analysis was conducted including all screening strategies to examine the potential cost effectiveness of emerging screening strategies.

Model inputs

Epidemiological data including prevalence of the target prenatal abnormalities were derived from Alberta sources (Table E.3). Data on the number of affected pregnancy came from Alberta Congenital Anomalies Surveillance System (ACASS). We analyzed data over 5 years and observed that the rate of affected pregnancy over time was relatively flat. As such, the yearly prevalence was estimated based on the average number of affected pregnancies over the 5-year period of which data was available. Prevalence estimates were calculated by dividing the number of affected pregnancies by the number of live births in Alberta.

Cost data including physician, outpatient, and laboratory services were primarily derived from Alberta sources (Table E.4). Laboratory costs were provided as a cost per test for each of the markers required in the various screening strategies inclusive of labour, equipment, and supplies (i.e. consumables). This data was provided by Calgary Laboratory Services and the AHS Edmonton Zone, UAH laboratory services. Physician service costs included the cost of generic consultation provided by a general practitioner (GP), obstetrician (OB), or midwife, the cost of invasive diagnosis and the cost of pregnancy loss resulting from invasive diagnostic testing. Outpatient services included costs of NT, ultrasound and invasive diagnostic testing. Data for physician services was extracted from the Alberta physician claim database using billing codes listed in the Alberta schedule of medical benefits while data for outpatient services were extracted from the Ambulatory Care Classification System (ACCS), based on the Canadian Classification of Health Interventions (CCI) Code for outpatient services. Note that cost data for nuchal translucency (NT), amniocentesis (AC) and chorionic villus sampling (CVS) were not available in any administrative database and were derived based on available local data within AHS. Costs were converted to 2011 Canadian dollars using the health component of the Canadian Consumer Price Index.

Table E.2: Sensitivity and specificity (95% CI) of the strategies in screening for trisomy 21

Strategy	Tests conducted	Sensitivity*	Specificity*	Source
First Trimester Screening (FTS)				
Nuchal translucency	NT	0.69 [0.51, 0.83]	0.95 [0.95, 0.95]	6
Double test	PAPP-A and HCG	0.62 [0.32, 0.86]	0.95 [0.94, 0.96]	7
Combined test	NT, free ß-hCG and PAPP-A	0.91 [0.84, 0.95]	0.94 [0.94, 0.94]	8
Second Trimester Screening (STS)				
Dual	AFP and free ß-hCG	0.67 [0.57, 0.75]	0.94 [0.94, 0.94]	9
Triple	AFP, uE3 and total hCG	0.74 [0.71, 0.77]	0.93 [0.93, 0.93]	10
Quad	AFP, uE3, free ß-hCG, inhibin A	0.81 [0.71, 0.88]	0.93 [0.93, 0.93]	11
First and Second Trimester Screening				
Full IPS	FST: NT and PAPP-A; STS: Quad test	0.91 [0.81, 0.97]	0.97 [0.97, 0.97]	12
IPS w/o inhibin A	FST: NT and PAPP-A; STS: Quad test	0.88 [0.80, 0.94]	0.97 [0.96, 0.97]	13
Serum IPS	FTS: PAPP-A; STS: Quad test	0.88 [0.77, 0.95]	0.97 [0.96, 0.97]	12
Sequential screening	FTS: NT, PAPP-A	0.655 [0.59, 0.72]	0.995 [0.99, 1.00]	14
	STS: Quad test	0.71 [0.59, 0.80]	0.98 [0.98, 0.98]	14
Contingent screening	FTS: NT, PAPP-A and hCG;	0.655 [0.59, 0.72]	0.995 [0.99, 1.00]	14
	STS: Quad test	0.81 [0.70, 0.89]	0.91 [0.91, 0.91]	14
repeated measure w/o NT	FTS: uE3 and PAPP-A; STS: uE3 and PAPP-A	0.85 (0.15 SD)**	0.995 (0.15 SD)**	15
repeated measure w/ NT	FTS: NT+ uE3 and PAPP-A; STS: uE3 and PAPP-A	0.85 (0.15 SD)**	0.997 (0.15 SD)**	15

Note:
* sensitivity and specificity were assigned beta distribution; **: SD was assumed.
IPS =Integrated Prenatal Screening; 95% CI = 95% confidence interval

Table E.3: Pregnant women, live birth, prevalence and critical assumptions†

M Age	Pregnant women in 2010	Live birth in 2010	Prevalence of Down's Syndrome (DS)*
00-39	67,181	48,660	0.001652
40-99	2105	1525	0.014689

Key assumption‡		
Description	**Value**	**Data Source**
Proportion bypassing screening for women age 40 and over	24.00%	[16]
Proportion bypassing screening for women age under 40	0.00%	Assumption‡
Proportion consenting to invasive diagnosis following positive result	48.50%	[8]
Fetal loss after amniocentesis	0.90%	[17]
Fetal loss after CVS	1.50%	[17]

† data on pregnant women, cases of prenatal abnormality and Alberta live birth were from AHW databases. Alberta live birth and pregnancy data were online available. Available at: http://www.health.alberta.ca/documents/Reproductive-Health-2011.pdf

* prevalence was derived by dividing cases of abnormality by live birth

‡ assumptions were made based on evidence from literature and ERA report

Table E.4: Cost inputs†

Cost item	Mean	Low limit	High limit	Source
Laboratory services				
Inhibin	$26.87	$20.05	$33.69	Calgary Laboratory Services; AHS Edmonton Zone, UAH laboratory services
hCG	$5.12	$2.38	$7.87	
AFP	$8.86	$4.37	$13.36	
UE3	$11.62	$5.96	$17.28	
PAPP-A	$38.23	$35.86	$40.61	
free ß –hCG	$36.26	$34.00	$38.51	
Physician services				
NT measurement	$98.51	$78.81	$118.21	The Alberta Physician Claims database
genetic counseling	$169.63	$152.52	$185.90	
Physician visit	$91.91	$73.53	$110.29	
Amniocentesis	$115.57	$94.79	$204.77	
CVS	$131.26	$94.79	$276.81	
Outpatient services‡				
NT measurement	$64.49	$51.59	$77.39	*
Ultrasound	$380.78	$67.85	$1,624.38	ACCS
Induction of labour	$114.57	$25.14	$416.26	ACCS
Amniocentesis	$450.00	$360.00	$540.00	**
CVS	$550.00	$440.00	$660.00	**

†: All costs were in 2011 price, and assigned Gamma distributions in sensitivity analysis based on the range of variation.
‡: based on AHW administrative databases, majority procedures were performed on outpatient basis. These costs were therefore used to represent hospital costs for the procedures.
*: personal communication with Christine Brake, Manager, ultrasound department, the Royal Alexandra Hospital. The range is based on an assumption of ±20% variation from the mean value.
**: personal communication with Judy Chernos, Director, Cytogenetics Laboratory, Alberta Children's Hospital. The range is based on an assumption of ±20% variation from the mean value.
ACCS provided information related to outpatient procedures including patient specific drug and supply costs, functional centre direct costs such as salaries (excluding physician services), medical and surgical supplies, and functional centre indirect costs such as administration and support services.

Model outputs

The outputs generated from the model are as follows:

- Cases of Down's Syndrome (DS) detected (true positives)
- Total pregnancies correctly identified (true positive and true negative)
- Cases of screening-related miscarriages resulting from invasive diagnostic testing
- Costs of each screening algorithm
- Incremental costs per additional DS detected between screening strategies
- Incremental costs per additional pregnancy correctly identified between screening strategies

A limitation with the available economic evidence was that the main clinical and economic outcome was cases detected which may not represent an assessment of total value because it ignores the value associated with correctly identifying true negatives that do not require confirmatory testing, particularly for conditions with extremely low incidence/prevalence. Hence, the model outputs report both true positive and true negative cases detected and calculates the cost effectiveness of the alternative screening strategies from both clinical (i.e. cost per case detected) and economic (i.e. cost per total correct diagnosis) perspectives.

Criteria for cost-effectiveness

The criteria for concluding that an alternative is cost-effective are as follows:

1. Alternatives that are both more costly and less effective compared to other alternatives are dominated and are considered NOT cost-effective. These are eliminated from further consideration.
2. Alternatives that are less costly and more effective compared to other alternatives are dominant and are considered cost-effective. These are included for further consideration.
3. Alternatives that are both more costly and more effective (or less costly and less effective) are not dominant and their cost-effectiveness is uncertain:
    a. Within these alternatives there can be a situation of extended dominance. That is, among these alternatives there are some alternatives that are more cost efficient than others. Alternatives that are dominated by extension are not considered cost-effective and are excluded from further consideration.
    b. For the remaining alternatives that are not dominated by extension, cost-effectiveness is dependent on whether decision-makers deem the additional effectiveness to be worth the additional costs referred to as the cost effectiveness threshold.

Sensitivity analysis

It is important to provide information regarding the degree of variability (i.e. uncertainty) in potential costs and effectiveness to enable decision makers to evaluate the credible range of potential costs and outcomes. Therefore, a probabilistic sensitivity analysis was conducted using 5000 Monte Carlo simulations using the ranges listed in Tables E.2 through E.4 to generate the distribution of potential costs and effectiveness associated with each alternative screening strategy. Deterministic

one-way sensitivity analysis was also conducted to evaluate the impact of NT on cost effectiveness given its high per unit cost.

Impact of differential timing

Given that all costs and outcomes occur within one year, costs and outcomes are not discounted.

Cost attribution analysis

Alternative health technologies have differential resource implications to disparate health sectors (e.g., costs of laboratory, physician and outpatient services). Differentiating the resource implications of each alternative on disparate health sectors from their total system impact is important for elucidating how available alternatives potentially impact the various sectors of the health system that are relevant to the technology in question. Presenting conventional economic evaluation results (e.g., incremental cost-effectiveness ratio [ICER]) with information generated from a cost attribution analysis would provide decision makers with information that identifies cost-effective alternatives while also providing insight into where resources from within the system can be potentially shifted to facilitate the adoption of the cost-effective alternative.[18] Accordingly, a cost attribution analysis was conducted to differentiate the resource implications to laboratory, physician and outpatient services between the alternative screening algorithms.

Budget impact analysis (BIA)

The BIA was conducted to assess the financial impact of screening strategies on the Alberta health system. The BIA was conducted for the following scenarios:

4. Expanding existing combined screening to the entire province.
5. Expanding existing quad screening to the entire province.
6. Replacing existing combined screening and quad screening with the cost-effective algorithm demonstrated in the CEA using total pregnancies correctly identified as the primary outcome measure.

Quad and combined screening were included in the BIA for two reasons. The first is that they represent the major screening strategies currently available in Alberta and hence represent the reference case with which to determine the budget impact of alternative screening strategies. The second is that it may be difficult to replace existing established services and Alberta may wish pursue the strategies that are already in place.

Cost and clinical inputs applied in the BIA model were identical to the data used in the CEA. The BIA considered a 1-year time horizon. All costs and demand were presented in 2011 data. It is worth mentioning that a BIA is usually conducted over 3 years in an effort to capture economic impact of a health technology. However, here 1-year time horizon is deemed appropriate given that pregnancies resolve within one year.

Results

Review of economic studies

Search results

There were 299 references identified in the literature search. After reviewing the titles and abstracts/summaries, 40 were retrieved for further review. Of the 40 studies, 24 were economic studies of alternative FASTS screening strategies. Of these 24, 12 studies met the final inclusion/exclusion criteria. See Appendix E.4 for data extraction from included studies, Appendix

E.5 for a list of excluded studies, and Appendix E.6 for the quality assessment scores of included studies.

Evidence from literature

Screening for Down syndrome (DS)

Gekas et al.[19] performed computer simulations to compare eight screening options (maternal age, triple test, quad test, integrated test, serum integrated test, combined test, sequential screening, and contingent screening) by applying empirical data from SURUSS trials on the population of 110,948 pregnancies in Quebec, Canada. The author included only the direct costs for screening as well as health services from a public health care perspective. The main outcome was average CER (cost per DS case detected) and ICER (incremental cost per additional DS case detected). The results showed that the most cost effective DS screening strategy was the contingent screening method (CER of Can$26,833 per DS case). Its ICER compared to the second-most cost effective strategy, serum integrated screening, was Can$3815 per DS birth detected. The results also identified the combined test as the screening strategy with the highest CER (Can$47,358) and the highest number of procedure-related euploid miscarriages (n = 71). The authors concluded contingent screening was the most cost effective among the strategies evaluated and the combined test, which is the most popular screening strategy, shows many limitations.

Gekas et al.[20] performed computer simulations using data of 110,948 pregnancies from the SURUSS trials in the province of Québec, Canada to compare rapid aneuploidy diagnosis (RAD) (FISH and QF-PCR) to karyotyping (CVS or AC) following six screening options (quad test, integrated test, serum integrated test, combined test, sequential screening, and contingent screening). The analysis included direct costs for screening and health services from a public health care perspective. The main outcomes included chromosome abnormalities (CA) missed, average CER (cost per DS case detected), and ICER (incremental cost per additional DS case detected). The results showed that among the safer screening strategies, the most cost effective strategy was contingent screening with QF-PCR (CER of $24,084 per DS detected). Using karyotyping, the CER increased to $27,898. QF-PCR missed only six clinically significant CA of which only one was expected to confer a high risk of an abnormal outcome. The ICER of karyotyping to find the CA missed by RAD was $66,608 per CA. The authors concluded that these costs are much higher than those involved for detecting DS cases. As the DS screening programs are mainly designed for DS detection, it may be relevant to question the additional costs of karyotyping.

Gekas et al.[21] performed computer simulations using data of 110,948 pregnancies from the SURUSS trials in the province of Québec, Canada to assess and compare the cost effectiveness of 5 different strategies for prenatal screening for DS (maternal age, triple test, integrated test, sequential screening, and contingent screenings) and to determine the most useful cut-off values for risk. The authors included the direct costs for screening and health services from a public health care perspective. The main outcome measures were average CER (cost per DS case detected), ICER (incremental cost per additional DS case detected), and screening options' outcomes. The results showed that the contingent screening strategy dominated all other screening options: it had the best CER (Can $26,833 per DS case detected) with fewer procedure related euploid miscarriages and unnecessary terminations (respectively, 6 and 16 per 100,000 pregnancies). In terms of ICER, contingent screening was still dominant: compared with screening based on maternal age alone, the savings were Can $30,963 per additional DS birth averted. The authors concluded that contingent screening is the preferred option for prenatal DS screening.

Chou et al.[22] used a decision analytic model to determine the cost effectiveness of screening women < 35 years of age and amniocentesis for women >= 35 years of age with combined testing compared to screening women of all ages. The analysis was conducted from a payer perspective and included the direct costs for screening and associated health services. The main outcome was average CER (cost per DS case averted) and ICER (incremental cost per additional DS case averted). The authors found the average cost per DS case averted for all women screened ranged from US$77,204 to US$98,421, while the cost ranged from US$99,647 to US$116,433 for screening women < 35 years of age and AC for women >=35 years of age. Compared to screening all women with combined testing, screening women < 35 years of age and amniocentesis for women >= 35 years of age with combined screening increased from $2101 in 1995 to $111,368 in 2006. The authors concluded that in an aging population in Taiwan, combined screening should be available for all pregnant women.

Hwa et al.[23] used a decision analytic model to determine the cost-effectiveness of 3 DS screening options: 1) maternal age > = 35; 2) second trimester double test; and 3) triple test in Taiwan. The analysis was taken from a payer perspective including the direct costs of screening and associated health services. The main outcome was the average CER (cost per DS case averted) and ICER (incremental cost per additional DS case averted). The results show that given a cut-off point of 1:270 for the confirmation of DS with AC, the average costs per case averted for the maternal age, double test, and triple test were estimated at US$14,561, US$42,367 and US$37,424, respectively. Compared with maternal age, the incremental costs per case averted for double test and triple test were US$135,950 and US$77,394, respectively. Compared with double test, the incremental cost per case averted for triple test was US$15,199. The authors concluded that the triple test was more cost-effective than the double test.

Chen et al.[24] used a decision analytic model to determine the cost-effectiveness of three prenatal diagnosis options for DS in China, including 1) CVS or AC for women > = 35 years; and 2) second trimester double test. The analysis was taken from a payer and patient perspective including health service costs to both patients and third party payers. Main outcome was the average and incremental CER (cost per case and incremental cost per additional case averted). The results show that in current clinical practice, for a cohort of 10,000 pregnant women, option 1 could detect .67 DS births and option 2 could detect 1.41 DS births. The cost per DS case averted by option 1 and 2 was US$13,091 and US$56,048, respectively. Compared to option 1, the ICER for option 2 was US$94,526 per DS case averted. The authors concluded that although, in general, serum screening has been found to be more cost-effective than maternal age screening, this appears not to be the case in China. The reasons appear to be low uptake rate of the maternal serum strategy, low uptake rate of CVS or AC, and the high price of serum screening. The findings indicate that health system factors concerning technology utilization are important determinants of the technology's efficiency.

Harris[25] used a decision analytic model to determine the cost effectiveness of three DS screening options: 1) second trimester serum screening followed by AC for positive results; 2) NT in the first trimester followed by CVS for positive results; and 3) NT and maternal serum screening in the first trimester, followed by CVS for positive results in 260,000 pregnant women in Australia. The analysis was taken from a payer perspective. The effectiveness of screening options was based on a systematic review of the literature and costs based on current reimbursement fees. The primary outcome was an ICER (incremental cost per additional case detected or avoided). The results show that the incremental cost (in 2001 AU$) for options 2 and 3 (compared with option 1) was about AU$66,300 and AU$105,500 per additional DS case detected; and about AU$301,400 and AU$374,800 per live DS birth avoided, respectively. The author concluded that the

cost-effectiveness of ultrasound screening for DS would appear to be more attractive if it were done at the same time as current dating ultrasound. Any funding mechanism for screening should take this strategy into account by incorporating, as far as possible, provision of NT screening into existing services provided in early pregnancy.

Caughey et al.[26] used a decision analytic model to determine the cost effectiveness of four possible screening options for DS: 1) current second-trimester expanded maternal serum α-fetoprotein test (AFP); 2) first-trimester NT screen; 3) first-trimester serum screen; and 4) combined first-trimester screen with both NT screen and a serum screen. The analysis was taken from a payer perspective. Costs of outcomes and testing were estimated from literature while health utility was measured using standard gamble. Main outcomes included the benefit-to-cost ratios and ICER (incremental cost per additional DS case detected or QALY gained). The authors reported the results with and without the life-time cost of DS separately, so that this study met our inclusive criteria and we just report the results without the life-time cost. Compared to option 1, the ICER were US$128,338 and US$100,437 per QALY gained for option 2 and 4 respectively. With a cost effectiveness threshold of US$100,000/QALY, option 2 and 4 are not cost-effective.

Gilbert et al.[27] used a decision analytic model to determine the cost effectiveness of 10 antenatal screening strategies for DS in the United Kingdom, including: 1) no screening; 2) maternal age and AC; 3) maternal age and CVS; 4) first trimester double test; 5) second trimester double test; 6) NT; 7) second trimester triple test; 8) quad test; 9) first trimester combined test; and 10) integrated test. The analysis was taken from a payer perspective and included direct costs of screening and associated health service costs. The main outcome was an ICER (incremental cost per additional DS birth prevented). The results showed that compared with no screening, the ICER was £22,000 for NT. Compared with NT, the ICER of the integrated test was £51,000. All other strategies were more costly and less effective. However, the first trimester combined test and the quad test may be cost effective depending on the cost of test. The authors concluded that the choice of screening strategies should be between the integrated test, first trimester combined test, quad test, or NT, depending on how much service providers are willing to pay, the total budget available, and values on safety.

Screening for DS and other anomalies (i.e. NTD)

Hoogendoorn et al.[28] used a decision analytic model to determine the cost effectiveness of six screening options for DS and neural tube defects (NTD) in the Netherlands: 1) first trimester double test; 2) NT; 3) first trimester combined double and NT test; 4) triple test; 5) first and second trimester combined test; and 6) invasive testing. Costs of screening and health services were included. The main outcomes included costs, the number of cases detected and screening-related miscarriages. The results showed that the costs per detected case of DS ranged from EUR 98,000 for option 1 to EUR 191,000 for option 6. The ICER was EUR 293,000 per extra DS detected when comparing option 6 to 1 and 4. If NTD detection was included, option 4 had the lowest costs per detected case of DS or NTD at EUR 73,000. The number of screening-related miscarriages due to invasive diagnostic tests varied from 13 per 100,000 women for option 5 to 914 per 100,000 women for 6. The authors concluded that considering screening for both DS and NTD favours the triple test in terms of costs per detected case. Compared to invasive testing, risk assessment tests substantially lowers screening-related miscarriages, which raises the question of whether invasive testing should still be offered in a screening program for DS.

Richie et al.[29] used a discrete event simulation model of 50,000 singleton to determine the most clinically and cost effective policy of scanning and screening for fetal abnormalities in early

pregnancy in Scotland. The authors included six strategies of screening: 1) first trimester combined test and second trimester scan; 2) first trimester combined test; 3) first trimester combined test and second trimester AFP + scan; 4) first trimester combined test and second trimester AFP; 5) first trimester booking scan and second trimester double test + scan; and 6) first trimester booking scan and second trimester double test. Costs of screening and health services were included. The analysis was taken from a payer perspective. The main outcome was an ICER (incremental cost per additional DS case detected). The results showed that compared to option 6, the ICER were £4,790, £8,927, £148,784, £33,472, and £17,525 for option 1, 2, 3, 4 and 5, respectively. The authors found that the option 1 was the most cost effective and recommended this option be offered to all women in Scotland.

Harris et al.[30] used a decision analytic model to determine the economic validity of thresholds based on age (> = 35 years) or risk for offering invasive prenatal diagnosis (CVS and AC) in the US. The analysis was taken from a payer perspective and compared the cost (for screening and health services) and utility of CVS and AC to no invasive testing using data from randomised trials, case registries, and a time trade-off utility assessment of 534 diverse pregnant women aged 16 to 47 years. Compared with no diagnostic testing, AC costs less than US$15,000 per QALY gained for women of all ages and risk levels. The results did not depend on maternal age or risk of DS-affected birth. The cost-utility ratio for any individual woman depended on her preferences for reassurance about the chromosomal status of her fetus, and, to a lesser extent, for miscarriage. The authors concluded that prenatal diagnostic testing can be cost effective at any age or risk level and current guidelines should be changed to offer testing to all pregnant women, not just those whose risk of carrying an affected fetus exceeds a specified threshold.

Summary

There were 25 first and second trimester screening strategies for fetal anomalies that were economically assessed by the reviewed studies including the four screening strategies available in Alberta. The main outcome was incremental cost per case detected, averted or QALY gained. Note that cases detected are equal to case averted if the rate of termination is 100% (Table E.5).

Based on the existing economic evidence, cost effectiveness of specific screening strategies were dependent on a variety of factors and it is unclear which screening algorithm was the most cost effective. Factors affecting cost effectiveness included local context, country of origin, and the specific alternatives included in the comparative analysis. For instance, combined screening was found to be cost effective in three studies[22,25,27] when comparators included no screening and AC but not cost effective in five other studies[18,20,21,26,28,29] where comparators included triple test and contingent screening.

The screening options included in each study are in part dependent on what was available at the time given that new screening strategies developed over time. There were two recent Canadian studies included in our review[19,21] that assessed a greater variety of screening options (maternal age, triple test, quad test, combined first, integrated screening, serum integrated screening, sequential screening, and contingent screening listed in Table E.1). The evidence from these studies suggest that the cost effective strategy was contingent screening (combined screening, then CVS for high, quad for intermediate, and no subsequent testing for women found to be of low risk) either because it was less costly and more effective than the alternatives (maternal age, triple test, quad test, integrated screening, and sequential screening) or because although it was more costly and more effective its ICER was only $3815 per additional case detected (compared to serum integrated screening) which is considered good value for money. It is also worth noting that the combined first strategy

(available in Alberta) was more effective than contingent screening but was associated with an ICER of $369,391 per case detected which is considered not good value for money.

Nevertheless, contingent screening is currently unavailable in Alberta which highlights the importance of determining whether the published economic evidence can be generalized to the Alberta setting. Several factors limit the generalizability of this evidence such as potential differences in the incidence of trisomy 21, the demand for screening services, and the associated health systems cost of screening. It is also noteworthy to mention that the main economic outcome in the studies included in the review focused on cases detected which may not represent an assessment of total value. That is, from an economic value perspective, the most cost effective screening strategy is the one that is the most efficient at identifying both cases that are suitable for subsequent confirmatory testing and non-cases that do not require further testing. In fact, at low incidence rates, specificity will become a bigger driver of cost effectiveness than sensitivity.

Given the limitations in the existing published economic evidence, an economic evaluation contextualized to the Alberta context while also incorporating a broader definition of value is recommended. Indeed, the economic evaluation in the following section below attempts to conduct such an analysis.

Table E.5: Strategies for prenatal screening

No.	Screening strategies	DS									DS+ NTD			No. of studies that include this strategy	No. of studies that recommend this strategy
		Gekas et al. 2011 (a)	Gekas et al. 2011 (b)	Gekas et al. 2009	Chou et al. 2009	Hwa et al. 2008	Chen et al. 2007	Harris 2004	Caughey et al. 2002	Gilbert et al. 2001	Hoogendoorn et al. 2008	Ritchie et al. 2005	Harris et al. 2004		
1	No screening						x	x		x			x	4	0
2	CVS or AC for all												**x**	1	1
3	Maternal age (CVS or AC for >=35 yrs)	x		x		x	**x**			x	x		x	7	1
4*	First trimester NT							x	x	**x**	x			4	1
5	Double1: First trimester PAPP-A + hCG								x	x	x			3	0
6	Double2: Second trimester AFP + hCG					x	x	x		x		x		5	0
7	Triple: AFP + uE3 + hCG	x		x		**x**			x	x	**x**			6	2
8*	Quad: Triple + inhibin A	x	x							**x**				3	1
9*	Combined First: Double1 + NT	x	x		**x**			**x**	x	**x**	x	x		8	3
10	Integrated: NT + PAPP-A + Quad	x	x	x						**x**				4	1
11	Serum integrated: PAPP-A + Quad	x	x											2	0
12	Sequential: Combined First + Quad with results given after each test	x	x	x										3	0
13	Contingent: Combined First, then CVS for high, Quad for intermediate, and no more test for low risk	**x**	x	**x**										3	2
14	Quad + Rapid aneuploidy diagnosis (RAD)		x											1	0
15	Combined First + RAD		x											1	0
16	Integrated + RAD		x											1	0
17	Serum integrated + RAD		x											1	0
18	Sequential:+ RAD		x											1	0

19	Contingent + RAD		**x**										1	1
20	Age+Combined First (AC for >=35 and NT + double1 for <35)				x								1	0
21*	Combined First+AFP											x	1	0
22	Combined First+AFP+genetic sonogram											x	1	0
23	Double2+genetic sonogram											x	1	0
24	Combined First+triple										x		1	0
25	Combined First+genetic sonogram											**x**	1	1
	Study Outcomes													
1	DS cases detected/diagnosed/identified	x	x	x				x	x		x	x	7	
2	DS cases averted/avoided/prevented**				x a	x a	x a	x		x			5	
3	QALY								x				x	2	

"x" indicates included, and the bolded "**x**" indicates cost-effective;

* indicates that the screening algorithm is available in Alberta;

** cases averted = cases detected × uptake rate of termination (all the studies that used cases averted as the outcome used 90% or/and 100%).

a. Indicates a termination rate of 100%. Otherwise, the termination rate was 90%. Cases detected will be equal to case averted if the termination rate is 100%.

Primary economic analysis

Population

Costs and health outcomes are reported per 10,000 pregnant women receiving prenatal screening services in Alberta. All costs are expressed in 2011 Canadian dollars. Note, costs and health outcomes for prenatal abnormalities other than T21 are provided in Appendix E.3 for information purposes only.

Costs

There was wide variation in costs between the 13 alternative screening strategies ranging from $2.75 to $6.85 million (Table E.6). The dual screening strategy was associated with the lowest costs and the contingent screening strategy with the highest costs. NT testing was observed to be a high cost driver given that strategies including NT were > $4 million and those without were below $4 million.

Effectiveness

When adopting effectiveness as the number of DS cases detected, there is a consistent ordering of the screening algorithms based on overall sensitivity (refer to T-section of this report) with combined screening and full IPS screening observed to be the most effective (14 cases detected) and the least effective algorithm being the double test strategy (nine cases detected) (Table E.6). When adopting effectiveness as the number of total pregnancies correctly identified, there is also a consistent ordering of the screening algorithms based on both overall sensitivity and specificity with the repeated measure screening strategy observed to be the most effective (9378 correctly identified pregnancies) and the least effective screening strategy being the triple screening strategy. When observing other outcomes such as false positives and fetal loss, triple testing was observed to have the highest number of false positives and combined testing to have the highest number of fetal loss with repeated measures screening having the lowest number of false positives and fetal loss.

Table E.6: Costs and health outcomes per 10,000 pregnancies*

Screening Algorithm	Total cost, $million	Detected Down's Syndrome	Correctly detected pregnancy†	FP**	Fetal loss
First Trimester Screening (FTS)					
Nuchal translucency (NT)	$4.16	10	8,933	470	4
Double test	$3.32	9	8,933	468	3
Combined test	$4.89	14	8,844	561	4
Second Trimester Screening (STS)					
Dual	$2.75	10	8,857	545	2
Triple	$2.88	11	8,722	681	3
Quad	$3.14	12	8,752	652	3
First and Second Trimester Screening					
Full IPS	$5.03	14	8,776	630	3
IPS without inhibin A	$4.68	14	9,093	312	2
Serum IPS	$3.42	13	9,086	320	2
Sequential screening, FTS	$6.85	14	9,194	212	1

Contingent screening, FTS	$6.85	14	9,178	227	1
repeated measure w/o NT**	$3.41	13	9,378	27	0
repeated measure w/ NT**	$4.95	13	9,378	27	0
* reported health outcomes for some alternative algorithms are the same due to rounding.					
** false positive (FP) indicates healthy pregnancies that are identified as test positive; † sum of affected and healthy pregnancies correctly detected.					

Cost-effectiveness

Figure E.2 shows the relative costs and effectiveness between the 13 screening strategies when defining effectiveness as the number of DS cases detected. The straight line in the figure represents the cost efficiency curve because it is the path that includes the alternatives with the lowest associated ICER (i.e. the most cost efficient path to the alternative that produces the most effectiveness). Strategies lying on the path are considered potentially cost effective while those above the line are not cost effective because they were more costly and less effective compared to those on the line. The path of the cost efficiency curve does not depend on whether the screening strategies of sequential, contingent and repeated measures (secondary analysis) is included given that one of these are on the curve.

The screening strategies lying on the cost efficiency curve including their associated ICER are as follows:

- Moving from dual to triple screening has an ICER = $0.11 million per additional DS detected
- Moving from triple to quad screening has an ICER= $0.26 million per additional DS detected
- Moving from quad to serum IPS has an ICER = $0.25 million per additional DS detected.
- Moving from serum IPS to combined screening has an ICER=$3.07 million per additional DS detected.

Given that combined and quad screening is available in Alberta, decision makers may be interested in comparing these strategies directly to each other. Compared to quad screening, combined screening is associated with an ICER of $1.15 million per additional DS case detected.

Figure E.2: Cost-effectiveness analysis (ICER is in million $ per DS detected)

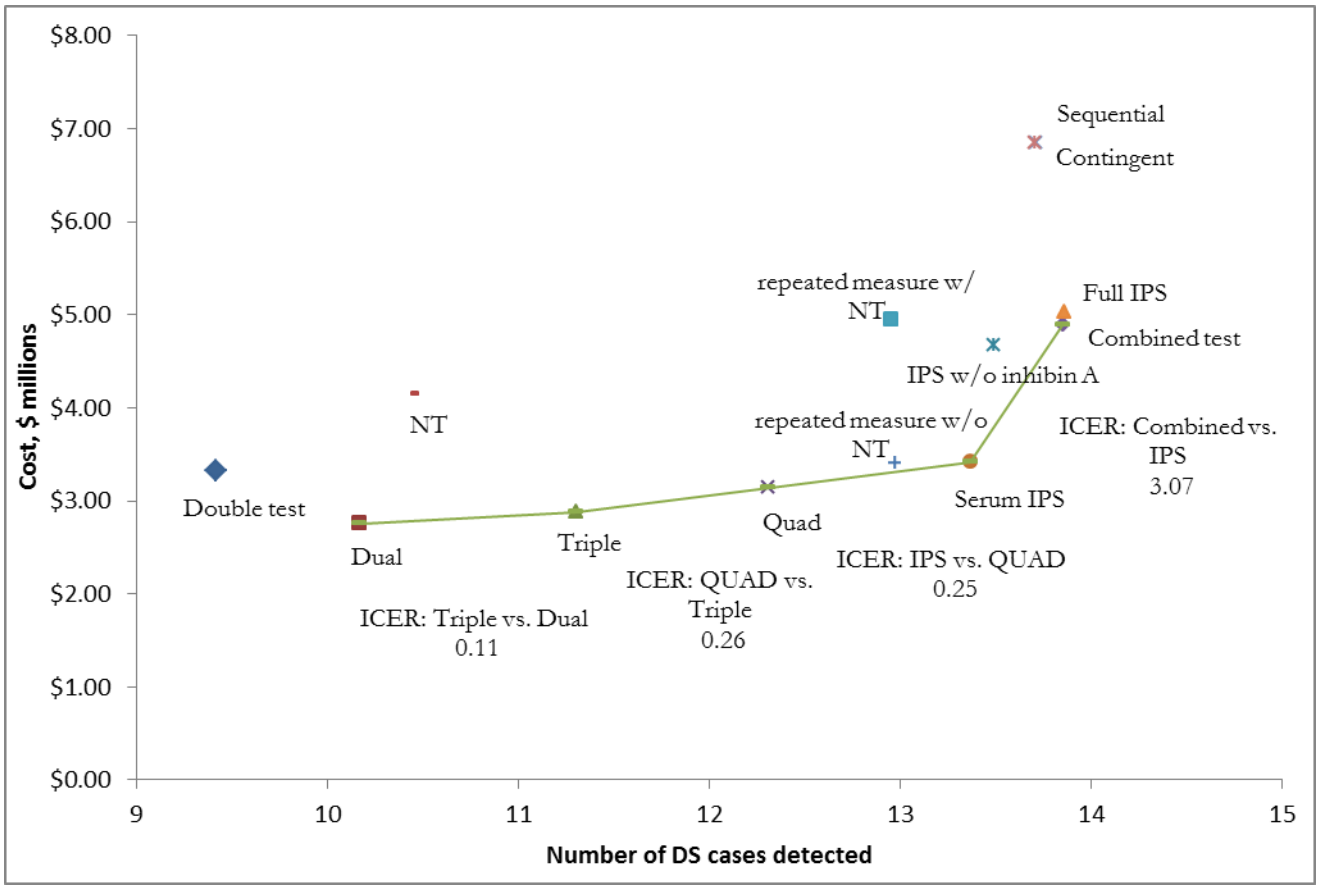
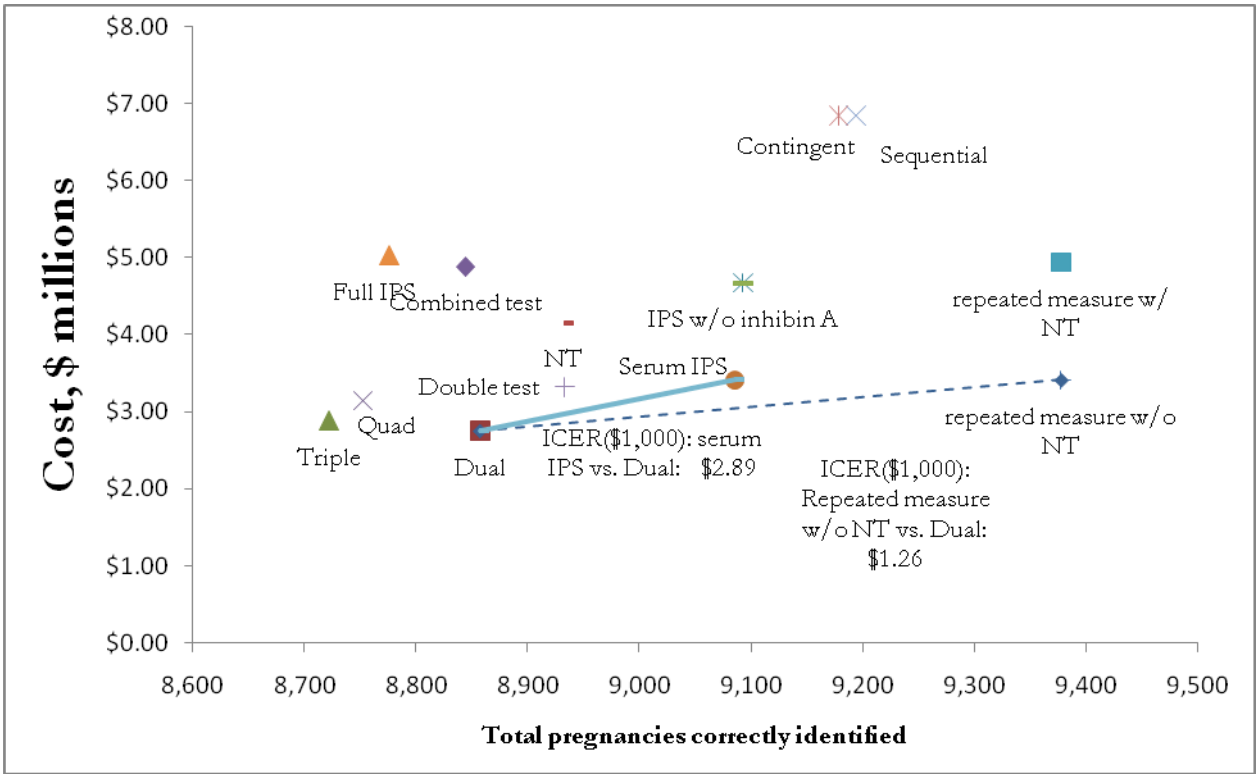


Figure E.3 shows the relative cost-effectiveness between the 13 screening algorithms when defining effectiveness as the total number of correctly identified pregnancies. The path of the cost efficiency curve depends on whether the screening strategies of sequential, contingent and repeated measures (secondary analysis) are included. When excluding these screening strategies (primary analysis) the cost efficiency curve is shown by the solid line and contain dual and serum IPS. The ICER from moving from dual to serum IPS is $2890 per additional correctly identified pregnancy. When including all strategies, the cost efficiency curve is shown by the dotted line and contain dual and repeated measures without NT. The ICER from moving from dual to repeated measures without NT is $1,260 per additional correctly identified pregnancy.

Comparing the strategies within Alberta, compared to quad screening, combined screening is associated with an ICER of $18,900 per additional correctly identified pregnancy. Compared to quad screening, serum IPS is associated with an ICER of $800 per additional correctly identified pregnancy while combined screening is dominated by serum IPS (i.e. serum IPS produces is more effective and less costly).

Figure E.3: Cost-effectiveness analysis (ICER is in 1000 $ per pregnancy corrected identified



Sensitivity analysis

Figure E.4 shows the cost effectiveness frontier which shows the probability of being cost effective at various cost effectiveness thresholds generated from the 5000 Monte Carlo simulations when effectiveness is defined as the number of DS cases detected (refer to Appendix E.7 to view distribution of costs and outcomes). The decrease in probability of being cost effective at higher cost effectiveness threshold suggests that there is a great degree of variation in the cost effectiveness results when varying the inputs in the model. However, up to a threshold of $100,000, the probability of dual screening being cost effective is above 50%.

Figure E.5 shows the cost effectiveness frontier which shows the probability of being cost effective at various cost effectiveness thresholds generated from the 5000 Monte Carlo simulations when effectiveness is defined as the number of total pregnancies correctly identified. At a cost effectiveness threshold between $0 and $2500, the dual screening remains the most cost effective with a probability of 100%. Between $2500 and $3300, there is a 50% probability that a dual or serum IPS is the most cost effective. At greater than $3300 serum IPS is the most cost effective with a 100% probability.

The deterministic sensitivity analysis on the cost of NT showed that the results were not sensitive to the cost of NT with the ordering of the screening strategies being stable at a range of costs (refer to Appendix E.7).

Figure E.4: Cost effectiveness frontier with effectiveness defined as DS cases detected

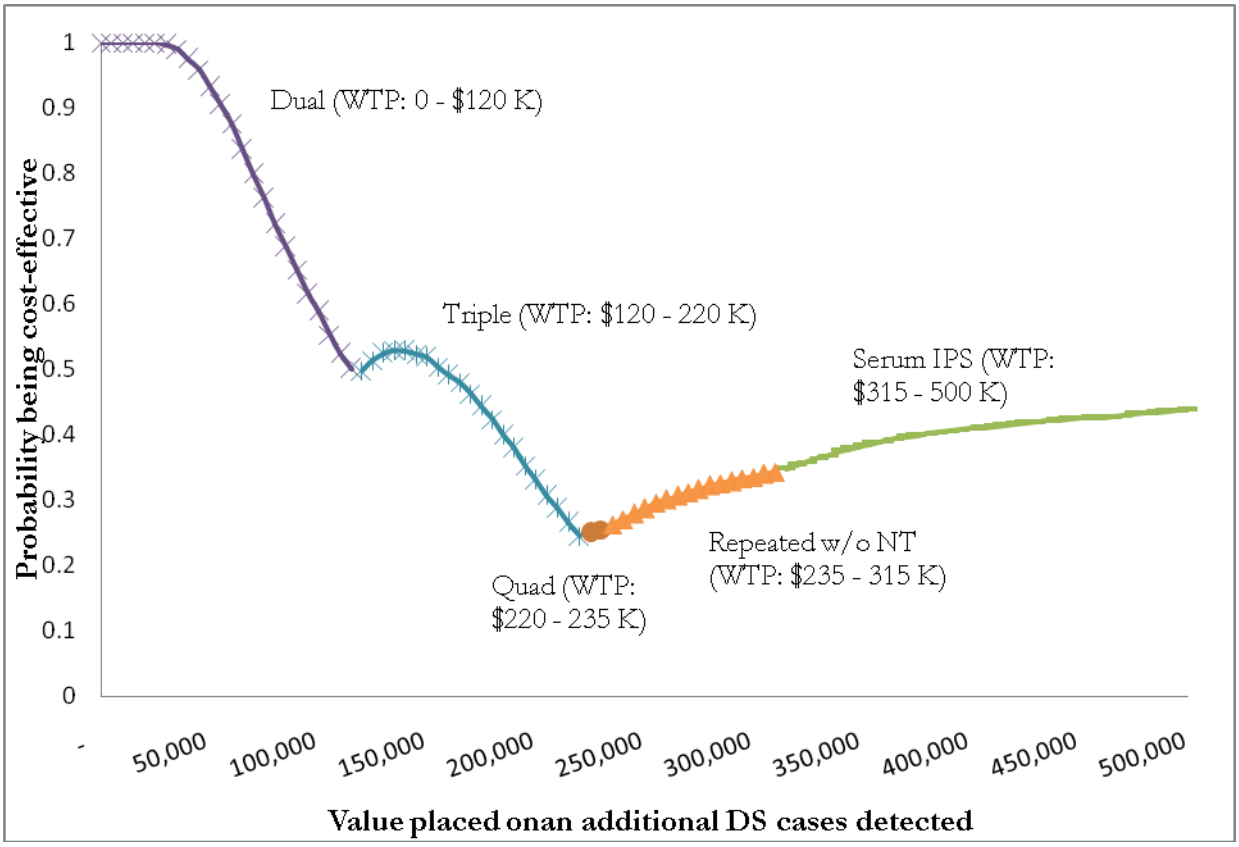
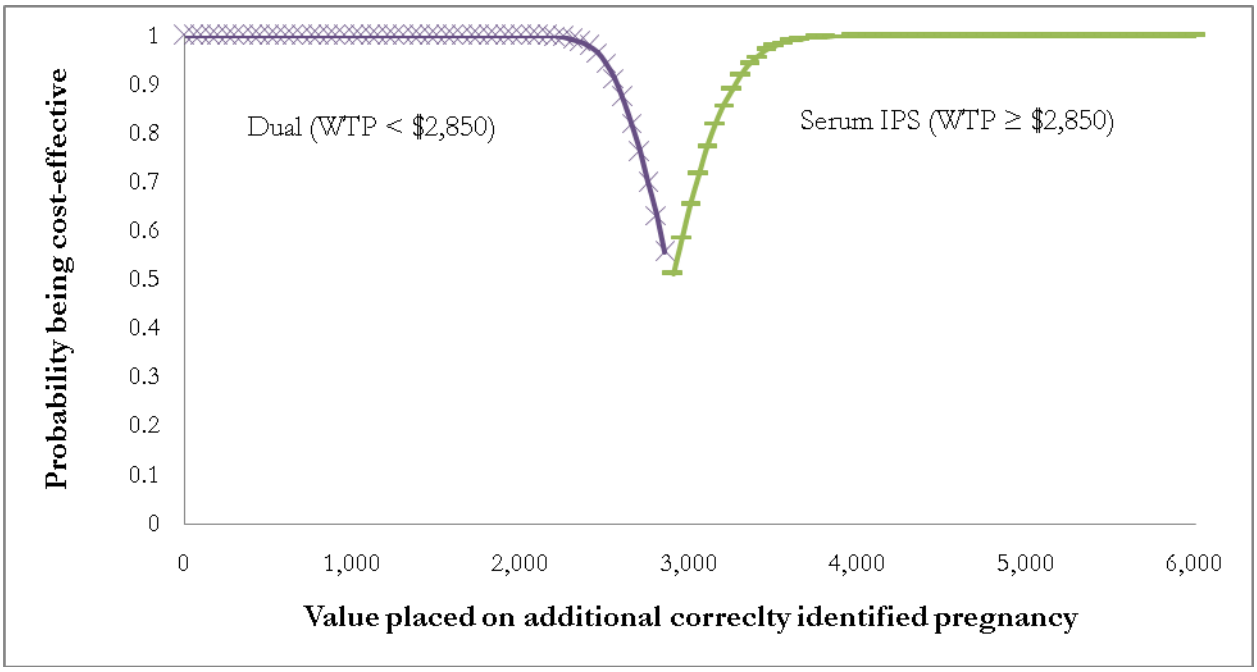


Figure E.5: Cost effectiveness frontier with effectiveness defined as the number of pregnancies correctly identified



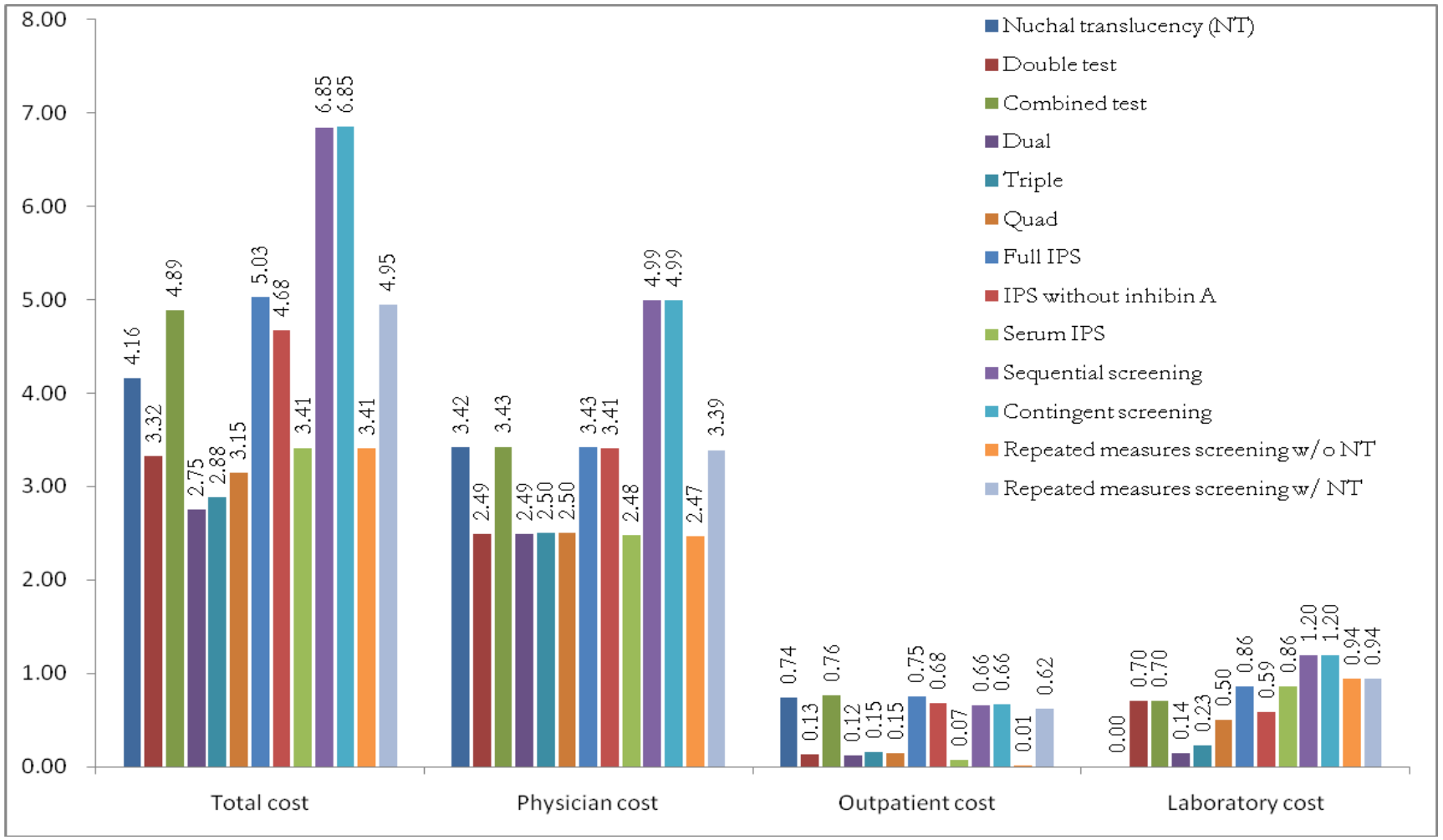
Cost attribution

Figure E.6 shows the costs of the 13 alternative screening strategies, separated into three cost categories of physician, outpatient and laboratory services. Costs of physician services account for over 70% of total costs across all strategies.

Comparing the screening strategies available in Alberta and those with acceptable ICER from the CEA, the associated cost impact to the disparate health sectors are as follows:

- When compared to quad screening, combined screening was associated with a net total cost 1.55 times larger, resulting from by 1.37 times in physician services, 5.21 times in outpatient services and 1.41 times in laboratory services.
- When compared to quad screening, serum IPS was associated with a net total cost 1.09 times larger, resulting from 0.99 times in physician services, 0.51 times in outpatient services and 1.72 times in laboratory services.
- When compared to serum IPS, combined screening was associated with a net total cost 1.43 times larger, resulting from by 1.38 times in physician services, 10.29 times in outpatient services and 0.82 times in laboratory services.
- When compared to quad screening, repeated measures without NT was associated with a net total cost 1.08 times larger, resulting from by 0.99 times in physician services, 0.07 times in outpatient services and 1.88 times in laboratory services.
- When compared to repeated measures without NT, combined screening was associated with a net total cost 1.43 times larger, resulting from by 1.39 times in physician services, 75 times in outpatient services and 0.75 times in laboratory services.

Figure E.6: Costs of alternative algorithms ($ millions)



Budget impact analysis

The scenarios for the BIA were as follows:

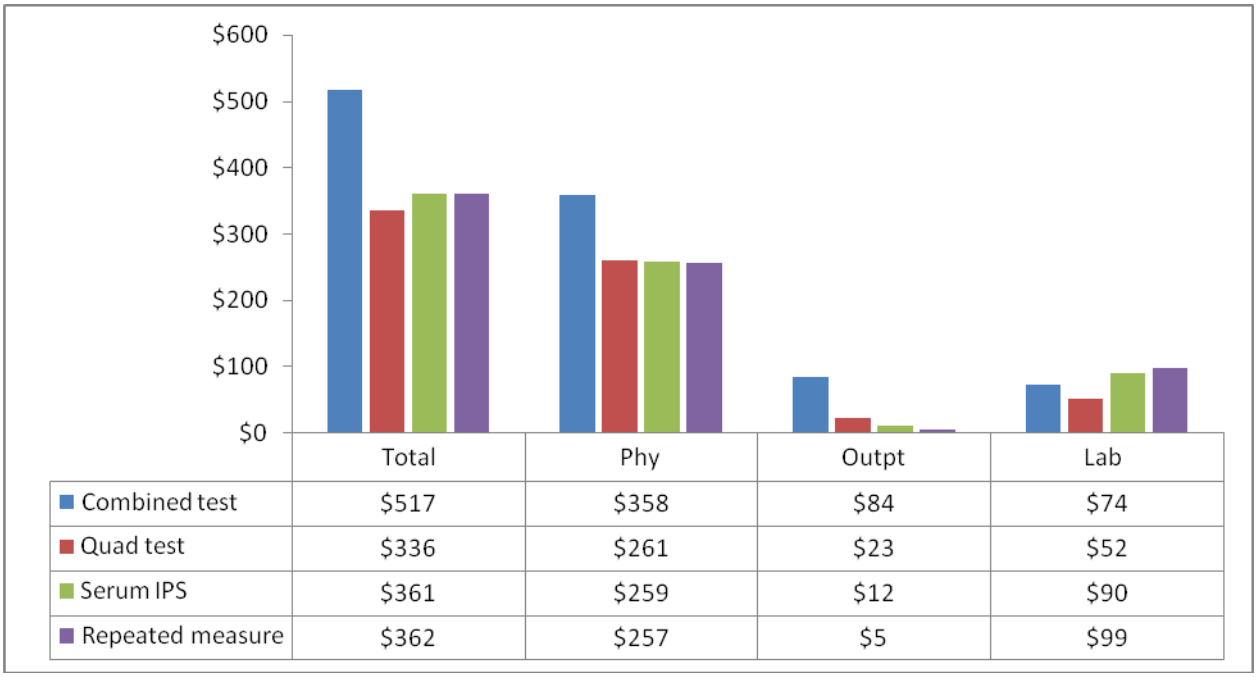
- Scenario 1: expanding current combined screening to the province. This scenario was include because combined screening is an available screening strategy in Alberta.
- Scenario 2: expanding current quad screening to the province. This scenario was include because quad screening is an available screening strategy in Alberta.
- Scenario 3: Replacing combined and quad screening with serum IPS in Alberta. Serum IPS' cost per additional correctly identified pregnancy was low relative to the other alternative screening strategies in the primary analysis indicating it is the most cost effective screening strategy. As previously defined, the primary analysis excludes sequential, contingent and repeated measures screening.
- Scenario 4: Replacing combined and quad screening with repeated measure screening without including NT in Alberta. Repeated measures screening without NT's cost per additional correctly identified pregnancy was low relative to the other alternative screening strategies in the secondary analysis indicating it is the most cost effective screening strategy.

Demand for prenatal screening was estimated based on 2010 volumes. The volume of combined and quad screening was derived from data provided by Calgary Laboratory Services and AHS Edmonton Zone, UAH laboratory services. There were approximately 12,543 combined tests (including 9743 conducted in southern and 2800 in northern Alberta) and 12,062 quad tests (1062 in the southern and 11,000 in the northern) conducted across Alberta accounting for approximately 35.5% of 69,286 [b] pregnancies in 2010.

The BIA is calculated at the current coverage rate in Alberta but also at increased rates of 50%, 70%, and 100% of unscreened pregnancies (i.e. of the remainder) to explore the cost impact of expanding screening services to all singleton pregnancies in Alberta. The additional volumes of pregnancies screened at 50%, 70% and 100% of unscreened pregnancies were 10,038, 23,895 and 44,681 respectively. The BIA for the four scenarios were estimated using unit costs per women screened derived using the data described in the CEA multiplied by the volume of screening services. Figure E.7 shows the unit costs for the four algorithms inclusive of physician, laboratory and outpatient services from the time of screen to final diagnosis. Total costs per pregnant women screened were estimated to be $517, $336, $361 and $362 for the combined, quad, serum IPS and repeated measure without NT screening, respectively.

[b] Data on pregnancy came from "Alberta Reproductive Health Pregnancies & Births". Access on September 2011. http://www.health.alberta.ca/documents/Reproductive-Health-2011.pdf

Figure E.7: Costs per women screened by services ($)



	Total	Phy	Outpt	Lab
Combined test	$517	$358	$84	$74
Quad test	$336	$261	$23	$52
Serum IPS	$361	$259	$12	$90
Repeated measure	$362	$257	$5	$99

Table E.7 shows the budget impact of the four scenarios over the range of specified coverage rates. As shown in column 2, the cost at current volumes was $6.48 million for combined screening and $4.05 million for quad screening. At current volumes, replacing quad screening with combined screening resulted in a cost increase of $2.18 million with costs potentially rising to $25.3 million if volumes increased to 100% of all pregnancies in the province. Replacing combined screening with quad screening resulted in cost savings of $2.27 million at current volumes but could potentially cost up to $12.7 million if volumes increased to 100% of all pregnancies in the province. Replacing both combined and quad screening with serum IPS resulted in a cost saving of $1.66 million at current volumes with costs potentially rising to $14.5 million if volumes increased to 100% of all pregnancies in the province. Replacing both combined and quad screening with repeated measures without NT resulted in a cost saving of $1.63 million at current volumes with costs potentially rising to $14.5 million if volumes increased to 100% of all pregnancies in the province.

Table E.7: Budget impact for each scenario by coverage rate (× $1000) in 2011 cost

	Column A: Cost of base case at current volumes*	Column B: Cost of replacing existing volume of services	Cost of expanding volumes			**Budget Impact**		
			Col C: 50%	Col D: 70%	Col E: 100%	**50% (B+C)**	**70% (B+D)**	**100% (B+E)**
Scenario 1: expanding current combined to the rest of the province	$6,480	Cost of replacing quad = $2,185	$5,186	$12,345	$23,084	**$7,371**	**$14,530**	**$25,268**
Scenario 2: expanding current quad to the rest of the province	$4,047	Cost of replacing combined = -$2,272	$3,368	$8,017	$14,991	**$1,096**	**$5,745**	**$12,719**
Scenario 3: applying serum IPS to the province	Not currently available	Cost of replacing combined and quad = -$1,656	$3,619	$8,615	$16,109	**$1,989**	**$6,985**	**$14,479**
Scenario 4: applying repeated measure screening to the province	Not currently available	Cost of replacing combined and quad = -$1,630	$3,630	$8,641	$16,157	**$2,000**	**$7,011**	**$14,527**

* This is the cost of existing service volumes and is not included in the BIA because the BIA represents the additional cost of service.

Discussion

Value for money

The relative ordering between screening strategies in terms of their effectiveness were consistent with the sensitivity and specificity from the extant evidence (consistent with T section) suggesting a high level of face validity to the economic model.[c] The cost effectiveness of the 13 alternative screening strategies varied depending on how effectiveness was defined.

When defining effectiveness as the number of DS cases detected, there was no single strategy that dominated (i.e. detected more cases of DS at a lower cost) in terms of cost effectiveness. Determining that a strategy is cost effective depends on whether the additional effectiveness is considered to be worth the additional cost. The results indicate that there were five strategies that are potentially cost effective including dual, triple, quad, serum IPS and combined screening (presented in order of increasing effectiveness). The ICER to move from dual to combined screening ranged from $110,000 to $3 million per additional DS case detected. When focusing only on the screening strategies available in Alberta compared to quad, combined screening was associated with $9.16 million per additional DS case detected suggesting that quad screening is more

[c] Test accuracy was taken from individual studies identified in the systematic review that were selected based on those deemed most transferrable and relevant to the Alberta setting (e.g. used results from Early Risk Assessment Program in Calgary.

cost effective than combined screening because the additional cost for the additional number of cases detected is too great.

When defining effectiveness as the number of pregnancies correctly identified (i.e. includes both true positive and true negative cases detected) there were two strategies that were potentially cost effective which were dual and serum IPS. The ICER to move from dual to serum IPS was $2890 per additional correctly identified pregnancy respectively. When focusing only on the screening strategies available in Alberta (acknowledging that neither combined nor quad is the optimal strategy because they aree more costly and less effective than dual, serum IPS), compared to quad, combined screening was associated with $18,900 per additional correctly identified pregnancy.

The difference in CEA depending on how effectiveness is defined raises two important questions. The first is: what is accounting for the divergent results when focusing on cases identified opposed to total correct pregnancies identified. The second is: what does the CEA tell us about the screening strategies for Alberta? The answer to the first question resides in the incidence of DS in Alberta (i.e. underlying probability of having DS). In Alberta, for every 10,000 pregnancies there will be approximately three true cases and 9997 non cases of DS. Hence, a 1% improvement in specificity will have a larger impact than a 1% improvement in sensitivity if the definition of effectiveness includes all benefits and not simply the number of cases detected. Thus, when defining effectiveness as the number of DS cases detected, cost effectiveness favoured screening strategies with high sensitivity but when defining effectiveness as the number of total correct pregnancies identified, cost effectiveness favoured screening strategies with both higher sensitivity and specificity with higher specificity being a stronger driver of cost effectiveness given the disproportionately larger number of non-DS cases (if the incidence of DS were high, we would expect the opposite trend).

The answer to the question of what does the CEA tell us about the screening strategies for Alberta requires a decision about the appropriate definition of effectiveness. This was included because it is a common measure of effectiveness used in the available research literature. Defining effectiveness as the number of DS cases detected was included because it is a common measure of effectiveness used in the availale research literature. It must be recognized however that this definition creates a framing bias in that it favors screening strategies with higher sensitivity but ignores specificity. Consequently, a screening strategy with a higher number of cases detected but also a high number of FP could be considered cost effective (note that the economic analysis does not consider any psychological harm caused to women/families with false positive test results). Defining effectiveness as the number of correctly identified pregnancies was included because it captures the total overall benefit. From an economic perspective, the most cost effective strategy is the one that is the most efficient at identifying cases that are suitable for confirmatory testing and non-cases that do not require further testing particularly at lower rates of incidence where specificity can become a stronger driver of cost effectiveness than sensitivity. Hence arguments of efficiency favour a definition of effectiveness that better captures the total value of a screening strategy particularly in light of an already constrained health system where the opportunity cost of investing in one area of the system resulting in the disinvestment in another area is often unknown and unquantifiable.

If effectiveness is defined as the total number of correct pregnancies incorporating both true cases and true non-cases detected, then the current evidence suggests that the screening strategy that offers the best value for money at current Alberta DS incidence rates is serum IPS. To illustrate, compared to quad, serum IPS detected one more case of DS per 10,000 women and resulted in 332 less false positives and 2 less iatrogenic fetal losses. Compared to combined, serum IPS detected one less case of DS per, 10,000 women but resulted in 242 less false positives and three less iatrogenic fetal losses.

Still, given that quad and combined screening is already provided in Alberta, determining which of these screening strategies is cost effective may be of intest to decision makers. When effectiveness is defined as the total number of correctly identified pregnancies, the results suggest that combined screening may be more cost effective than quad if the value placed on an additional correctly identified pregnancy is greater than $18,900. That is the amount of foregone net health benefit from instead investing those resources in the next best alternative in the health system (e.g. alcohol counseling for pregnant women) is greater than $18,900 then combined is cost effective compared to quad.

Insights from cost attribution analysis

A cost attribution analysis was conducted to provide deeper insight into the resource implications on various sectors of the health system that are associated with FASTS screening strategies. There were differential and systematic resource impacts to laboratory, physician, and outpatient services. Physician services accounted for 70% of all health system costs across all screening strategies. Compared with quad screening, combined screening was associated with a net total cost 1.55 times larger than quad which was driven by increases in physician services, outpatient services, and laboratory services. Combined screening was associated with a net total cost 1.43 times larger than serum IPS driven by increases in physician services and outpatient services; although there was a decrease in laboratory services. Serum IPS was associated with a net total cost 1.09 times larger than quad driven by an increase in laboratory services; although there was a decrease in outpatient services. Physician costs between serum IPS and quad screening were similar.

Insights from budget impact analysis

A budget impact analysis was conducted to assess the potential financial impact of specific alternative screening strategies including expanding quad screening, expanding combined screening and replacing quad and combined with repeated measures without NT. At current volumes, replacing quad screening with combined screening resulted in a cost increase of $2.18 million with costs potentially rising to $25.3 million if volumes increased to 100% of all pregnancies in Alberta. Replacing combined screening with quad screening resulted in cost savings of $2.27 million at current volumes but could potentially cost up to $12.7 million if volumes increased to 100% of all pregnancies in Alberta. Replacing both combined and quad screening with serum IPS resulted in a cost saving of 1.7 million at current volumes with costs potentially rising to $14.5 million if volumes increased to 100% of all pregnancies in Alberta.

Increasing the coverage rate implies that additional capacity would be needed to accommodate the increased volumes. It should therefore be noted that resources needed to increase capacity (e.g. infrastructure, training and education) are not included in the BIA due to unavailability of data and uncertainty in how screening services would be operationalized across the province. Furthermore current capacity varies across Alberta. In southern Alberta, existing laboratory capacity can conduct up to 70,000 screens per year for first trimester screens and no issues of capacity for second trimester screens (personal communication, Calgary Laboratory Services). Laboratory service capacity in northern Alberta in contrast is already at capacity for performing first trimester screens require more staff and equipment to accommodate higher volumes of screens and can increase second trimester screening volumes by 20% at current capacity (personal communication, Edmonton Zone, UAH laboratory services). Yet, the volumes of first trimmest combined screening are increasing in northern Alberta where there were approximately 2800 combined screens in 2010, and a projected 4400 in 2011 (personal communication, Edmonton Zone, UAH laboratory services).

Other cost components not included in the BIA are program based resources. These include costs of administrative and nursing staff to support the management of care for women receiving screening services. These are important cost considerations for screening services given the time required for activities such as obtaining patient consent, explaining and providing educational materials, and patient coordination through the health system. The Early Prenatal Risk Assessment (ERA) Program in Calgary estimated that administrative costs including salaries, benefits, allowances and severances were $133,000 for a screening volume of approximately 7000 women in 2008.

Strengths

Several approaches were adopted to increase the validity of results of the analysis for Alberta decision-makers:

1. The analysis incorporates Alberta-relevant data associated with prenatal screening programs, health service utilization, health services costs and epidemiology.
2. A probabilistic sensitivity analysis was conducted to evaluate the confidence (i.e., the degree of uncertainty) in the results by elucidating how the extent of variability in the evidence (i.e., in the model inputs) affected the resulting costs and effectiveness for each of the algorithms evaluated. A one-way sensitivity analysis was conducted on costs of NT, a main cost driver, to elucidate its impact on cost effectiveness between screening strategies.
3. A cost attribution analysis was conducted to not only report the cost impact in terms of total health system costs but to also identify, more specifically, the cost impact to disparate health system sectors that included laboratory, physician and outpatient services.
4. Cost effectiveness analysis was conducted using a broader definition of effectiveness capturing a better assessment of value compared to existing economic research.

Caveats

No model can perfectly capture what is or will be observed in reality, and the findings should be evaluated in light of the following caveats:

1. The results are founded on the screening and testing strategies outlined in this report. Although in actual conditions there will be variation in how these tests are used depending on clinical presentation and patient history, the screening/testing algorithms outlined in this report should be adhered to the greatest extent permissible in order to achieve the economic and health outcomes described.
2. The CEA focused on T21 which ignores any value associated with detecting other abnormalities (e.g. ONTD). Quad screening has the added benefit of detecting T18, spina bifida and anencephaly, while combined screening has the added benefit of detecting T18 and T13. Serum IPS does not detect additional conditions to T21. However, the relevance of these other conditions from a clinical and health outcome perspective is uncertain. These conditions are also much less frequent than T21 (e.g. 159 DS cases per 10,000 live births versus 18 ONTD cases in Alberta in 2010).
3. The primary analysis focused on those screening strategies whose effectiveness was informed with empirical studies while the secondary analysis included screening strategies whose effectiveness was informed from mathematical simulations which are considered lower in quality compared to empirical studies. While the primary analysis suggests that serum IPS is the most cost effective screening strategy the secondary analysis suggests that

repeated measures without NT is even more effective and less costly. Hence, while the evidence around the test performance of repeated measures is in the early stages, repeated measures without NT has the potential to be the most cost effective algorithm.

4. Costs associated with additional infrastructure requirements, capital purchases, impact of software selection, nursing and other staff including training and education were not included in the CEA or the BIA due to lack of data and uncertainty regarding how FASTS screening services are to be provided across the province.
5. The economic analysis focused on the efficiency of various screening alternatives and identified those that provided the highest accuracy at the lowest cost to the health system and therefore adopted time frame from pregnancy until final diagnosis. Hence the analysis does not evaluate the screening strategies in terms of their impact on abortions and excludes costs associated with abortions, delivery and long term health outcomes of infants with congenital abnormalities. While it is acknowledged that the analysis will ignore the fact that timing of screening tests can impact health care costs in terms of early vs. later intervention (i.e. abortion) these costs are beyond the scope of the analysis.
6. Individuals undergoing screening may not receive any benefit and may be exposed to iatrogenic health risks (e.g. unnecessary invasive follow-up procedures resulting from false positive test results). Any emotional harm associated with false positive test results were not considered in the analysis.
7. A cost attribution analysis was conducted to elucidate the resource implications of each alternative on various sectors of the health system that are associated with prenatal screening. It is important to be clear that this information is from an overall perspective, which is not the same as information generated from a detailed local micro costing.

Conclusion

Identifying the screening strategy that provides the best balance between costs and improvements in the precision of information for women undergoing screening requires careful consideration of not only the test characteristics and precision of the specific strategies, but considers these characteristics within the context of baseline risk (i.e. incidence) and the resulting impact on the health system in terms of what additional value is achieved for the additional resources invested. From an overall value perspective, serum IPS provides the most value for money among the 13 strategies evaluated. Within the screening strategies available in Alberta, combined screening is associated with additional benefit and costs compared to quad screening and its cost effectiveness is dependent on whether the additional benefit is determined to be worth the additional cost by decision makers and the health system. The cost impact of establishing a systematic province wide screening program with increased coverage of pregnancies will result in net budget increases to physician, outpatient and laboratory services.

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Appendices

Appendix E.1: Literature Search Summary

The literature search was conducted by the IHE Research Librarian for publications published between 2000 and September 20, 2010. A search update was performed on March 8th, 2011 to catch any recent publications. The search was further limited to Publication type and was developed and carried out prior to the study selection process. In addition to the strategy outlined below, reference lists of retrieved articles were reviewed for potential studies.

Database	Edition or date searched	Search Terms ‡‡
The Cochrane Database of Systematic Reviews http://www.thecochranelibrary.com	2000- Sept 20, 2010	#1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester):ti,ab,kw #2 MeSH descriptor Mass Screening, this term only #3 MeSH descriptor Genetic Testing explode all trees #4 MeSH descriptor Prenatal Diagnosis, this term only #5 (screen* or diagnos* or test or tests or testing):ti #6 ("maternal age"):ti,ab,kw #7 MeSH descriptor Amniocentesis, this term only #8 MeSH descriptor Chorionic Villi Sampling, this term only #9 MeSH descriptor Ultrasonography, Prenatal, this term only #10 (ultrasound* or ultrason* or sonogra*):ti,ab,k #11 (amniocentes* or chorionic vill* or cvs):ti,ab,kw #12 MeSH descriptor Nuchal Translucency Measurement, this term only #13 ("nuchal translucency"):ti,ab,kw #14 ("maternal serum" or "serum marker"):ti,ab,kw #15 MeSH descriptor Biological Markers, this term only #16 ((biochemical or serum or soft) NEAR/1 marker*):ti,ab,kw #17 MeSH descriptor Chorionic Gonadotropin, this term only #18 MeSH descriptor Chorionic Gonadotropin, beta Subunit, Human, this term only #19 ((chorionic NEAR/2 gonadotrop*) or hcg):ti,ab,kw #20 (PAPP A):ti,ab,kw #21 MeSH descriptor Pregnancy-Associated Plasma Protein-A, this term only #22 MeSH descriptor alpha-Fetoproteins, this term only #23 (afp or alpha fetoprotein*):ti,ab,kw #24 MeSH descriptor Estriol, this term only #25 (uE3 or estriol):ti,ab,kw #26 (inhibin*):ti,ab,kw #27 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) #28 MeSH descriptor Aneuploidy, this term only #29 (aneuploid*):ti,ab,kw #30 MeSH descriptor Neural Tube Defects explode all trees #31 (neural tube defect* or ancephal* or encephalocele* or "spina bifida"):ti,ab,kw #32 ((down* or patau or edwards) NEXT syndrome):ti,ab,kw #33 MeSH descriptor Down Syndrome, this term only #34 (Trisom*):ti,ab,kw #35 MeSH descriptor Trisomy, this term only #36 MeSH descriptor Congenital Abnormalities, this term only #37 MeSH descriptor Chromosome Disorders, this term only #38 ((congenital or chromosom* or anatomic*) NEXT anomal*):ti,ab,kw #39 ((chromosom* or anatomic*) NEXT abnormalit*):ti,ab,kw

		#40 (#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39) #41 (cost* OR economic* OR expenditures OR fiscal OR pharmacoeconomic):ti,ab,kw #42 (#1 AND #27 AND #40 AND #41) 0 Results
MEDLINE (includes in-process and non-medline citations) OVID Licensed Resource	2000 – August 9, 2010	Search Strategy: # Searches Results 1. (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester).sh,ti. 2. mass screening/ or genetic testing/ 3. prenatal diagnosis/ 4. (screen* or diagnos* or test or tests or testing).ti 5. maternal age.tw. 6. amniocentesis/ or chorionic villi sampling/ or ultrasonography, prenatal/ 7. (ultrasound* or ultrason* or sonogra*).tw. 8. (amniocentes* or chorionic vill* or cvs).tw. 9. Nuchal Translucency Measurement/ 10. nuchal translucency.tw. 11. (maternal serum or serum marker*).tw. 12. biological markers/ 13. ((biochemical or serum or soft) adj marker*).tw. 14. Chorionic Gonadotropin/ or Chorionic Gonadotropin, beta Subunit, Human/ 15. ((chorionic adj2 gonadotrop*) or hcg).tw. 16. PAPP A.tw. 17. Pregnancy-Associated Plasma Protein-A/ 18. Alpha-Fetoproteins/ 19. (afp or alpha fetoprotein*).tw. 20. exp Estriol/ 21. (uE3 or estriol).tw. 22. inhibin*.mp. 23. or/2-22 24. Aneuploidy/ 25. aneuploid*.tw. 26. exp Neural Tube Defects/ 27. (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw. 28. ((down* or patau or edwards) adj syndrome).tw. 29. Down syndrome/ 30. Trisom*.tw. 31. Trisomy/ 32. congenital abnormalities/ 33. Chromosome Disorders/ 34. ((congenital or chromosom* or anatomic*) adj anomal*).tw. 35. ((chromosom* or anatomic*) adj abnormalit*).tw. 36. or/24-35 37. exp "Costs and Cost Analysis"/ 38. (economic adj1 (evaluat* or analys* or study or studies or assess* or consequence*)).tw. 39. (cost-benefit or benefit-cost or cost effectiv* or cost utility).tw. 40. (cost minimization or cost minimisation or cost consequence* or cost offset*).tw. 41. ((cost or costs) adj2 analys*).tw. 42. "cost of illness".tw. 43. (cost* or economic* or expenditures or fiscal or pharmacoeconomic or spending).ti. 44. or/37-43 45. 1 and 23 and 36 and 44

		46. limit 45 to (english language and yr="2000 - 2010") **110 results**
EMBASE Licensed Resource (Ovid Platform)	2000-Sept 27, 2010	1. (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester).sh,ti. 2. mass screening/ or genetic screening 3. prenatal diagnosis 4. (screen* or diagnos* or test or tests or testing).ti. 5. maternal age.tw. 6. amniocentesis/ or chorion villus sampling/ or ultrasonography, prenatal/ 7. (ultrasound* or ultrason* or sonogra*).tw. 8. (amniocentes* or chorionic vill* or cvs).tw. 9. Nuchal Translucency Measurement/ 10. nuchal translucency.tw. 11. (maternal serum or serum marker*).tw. 12. biological marker 13. ((biochemical or serum or soft) adj marker*).tw. 14. Chorionic Gonadotropin/ 15. ((chorionic adj2 gonadotrop*) or hcg).tw. 16. PAPP A.tw. 17. Pregnancy Associated Plasma Protein A/ 18. alpha fetoprotein/ 19. (afp or alpha fetoprotein*).tw. 20. Estriol/ 21. *(uE3 or estriol).tw. 22. inhibin A/ 23. inhibin*.tw. 24. or/2-23 25. Aneuploidy/ 26. aneuploid*.tw. 27. exp Neural Tube Defect/ 28. (neural tube defect* or ancephal* or encephalocele* or spina bifida).tw. 29. ((down* or patau or edwards) adj syndrome).tw. 30. patau syndrome/ 31. edwards syndrome/ 32. Down syndrome/ 33. Trisom*.tw. 34. exp Trisomy/ 35. congenital disorder/ 36. Chromosome Disorder/ 37. ((congenital or chromosom* or anatomic*) adj anomal*).tw. 38. ((chromosom* or anatomic*) adj abnormalit*).tw. 39. or/25-38 40. "COST"/ 41. exp Economic Evaluation/ 42. health economics/ 43. PHARMACOECONOMICS/ 44. ((economic or cost*) adj2 (evaluat* or analys* or study or studies or assess* or consequence*)).tw. 45. ((cost-benefit or benefit-cost or cost effectiv* or cost utility) adj2 (analys* or evaluat* or assess* or study or studies)).tw. 46. (cost minimization or cost minimisation or cost consequence* or cost offset*).tw. 47. "cost of illness".tw. 48. or/40-47 49. 1 and 24 and 39 and 48 50. limit 49 to (english language and yr="2000 - 2011") **140 results**

CRD Databases (DARE, HTA & NHS EED) http://nhscrd.york.ac.uk		#1 pregnan* OR fetal OR prenatal OR perinatal OR antenatal OR antepartum OR maternal OR trimester #2 MeSH Mass Screening # 3 MeSH Genetic Screening #4 MeSH Prenatal Diagnosis #5 screen* OR diagnos* OR test OR tests OR testing #6 "maternal age" #7 MeSH Amniocentesis #8 MeSH Chorionic Villi Sampling #9 MeSH Ultrasonography, Prenatal #10 ultrasound* OR ultrason* OR sonogra* #11 amniocentes* OR chorionic AND vill* #12 MeSH Nuchal Translucency Measurement #13 "nuchal translucency" #14"maternal serum" OR serum AND marker* #15 MeSH Biological Markers #16 (biochemical AND marker*) OR (serum AND marker) OR (soft AND marker*) #17 (biochemical AND marker*) OR (serum AND marker*) OR (soft AND marker*) #18 MeSH Chorionic Gonadotropin #19 MeSH Chorionic Gonadotropin, beta Subunit, Human #20 ((chorionic AND gonadotrop*) OR hcg) #21 PAPP AND A #22 MeSH Pregnancy-Associated Plasma Protein-A # 23 MeSH alpha-Fetoproteins # 24 afp OR alpha AND fetoprotein* #25 MeSH Estriol EXPLODE 1 2 #26 uE3 OR estriol #27 inhibin* #28 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 #29 Aneuploidy #30 Aneuploid* #31 MeSH Aneuploidy #32 MeSH Neural Tube Defects EXPLODE 1 2 #33 neural AND tube AND defect* OR ancephal* OR encephalocele* OR spina AND bifida #34 (down*AND syndrome) OR (Patau AND syndrome) OR (Edwards AND syndrome) #35 MeSH Down Syndrome EXPLODE 1 2 3 4 #36 Trisom* #37 MeSH Trisomy EXPLODE 1 2 3 #38 MeSH Congenital Abnormalities #39 MeSH Chromosome Disorders #40 (congenital NEAR anomal*) OR (chromosom* NEAR anomal*) OR (anatomic* NEAR anomal*) #43 (chromosom* NEAR abnormalit*) OR (anatomic* NEAR abnormalit*) #44 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 or #38 or #39 OR #40 OR #41 OR #42 OR #43 #45 #1 AND #28 AND #44 #46 cost* OR economic* OR expenditures OR fiscal OR pharmacoeconomic #47 #45 AND #46 RESTRICT YR 2000 2010

Web of Science ISI Interface Licensed Resource	2000- Sept 272010	#1 TS=(pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester) #2 TS=(screen* or diagnos* or test or tests or testing) #3 TS=("maternal age" or ultrasound* or ultrason* or sonogra*or amniocentes* or chorionic vill* or cvs or "nuchal translucency" or "maternal serum" or serum marker* or biological marker*or biochemical marker*or soft marker* or chorionic gonadotrop*or hcg or " PAPP A" or "Pregnancy Associated Plasma Protein A" or afp or alpha fetoprotein or uE3 or estriol or inhibin*) #4 #2 or #3 #5 TS= (aneuploid* or neural tube defect* or ancephal* or encephalocele* or spina bifida or down* syndrome or patau syndrome or edwards syndrome or trisom*) #6 TS=(congenital abnormalit* or chromosom* abnormalit* or anatomic* abnormalit* or congenital anomal* or chromosom* anomal* or anatomic* anomal* or chromosome disorder*) #7 #5 or #6 #8 #1 and #4 and #7 #9 #8 Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2000-2010 #10 TI=(cost* OR economic* OR expenditures OR price OR fiscal OR pharmacoeconomic OR spending) #11 #10 and #9 **36 results**
Biosis Previews ISI Interface Licensed Resource		#1 TS=(pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester) #2 TS=(screen* or diagnos* or test or tests or testing) #3 TS=("maternal age" or ultrasound* or ultrason* or sonogra*or amniocentes* or chorionic vill* or cvs or "nuchal translucency" or "maternal serum" or serum marker* or biological marker*or biochemical marker*or soft marker* or chorionic gonadotrop*or hcg or " PAPP A" or "Pregnancy Associated Plasma Protein A" or afp or alpha fetoprotein or uE3 or estriol or inhibin*) #4 #2 or #3 #5 TS= (aneuploid* or neural tube defect* or ancephal* or encephalocele* or spina bifida or down* syndrome or patau syndrome or edwards syndrome or trisom*) #6 TS=(congenital abnormalit* or chromosom* abnormalit* or anatomic* abnormalit* or congenital anomal* or chromosom* anomal* or anatomic* anomal* or chromosome disorder*) #7 #5 or #6 #8 #1 and #4 and #7 #9 #1 and #4 and #7 AND Language=(English) AND Taxa Notes=(Humans) Databases=PREVIEWS Timespan=2000-2010 #10 TI=(cost* OR economic* OR expenditures OR price OR fiscal OR pharmacoeconomic OR spending) AND Language=(English) AND Taxa Notes=(Humans) #11 #10 AND #9 **14 results**
Biological Abstracts	Sept 28, 2010	(pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester) and((DE="genetic screening") or(DE=("prenatal diagnosis" or "amniocentesis")) or(DE=("ultrasonography" or "ultrasound")) or(DE="genetic markers") or(TI=(screen* or diagnos* or test or tests or testing)) or(maternal age or chorionic vill* sampling or amniocentes* or ultrasound* or ultrason* or sonogra* or "nuchal translucency" or "maternal serum" or serum marker* or biochemical marker* or soft marker* or chorionic gonadotrop* or hcg or PAPP A or Pregnancy Associated Plasma Protein A or afp or alpha fetoprotein* or

		uE3 or estriol or inhibin*)) and((DE=("neural tube defects" or "anencephaly" or "spina bifida" or "aneuploidy")) or(DE="downs syndrome") or(DE="trisomy") or(DE=("chromosome aberrations" or "edward s syndrome" or "patau s syndrome")) or(aneuploid* or neural tube defect* or ancephal* or encephalocele* or "spina bifida" or down* syndrome or "patau syndrome" or "edwards syndrome" or trisomy or(congenital anomal*) or (chromosom* anomal*) or (anatomic*anomal*) or(chromosom* abnormalit*) or (anatomic* abnormalit*))) and((DE=("cost benefit analysis" or "costs")) or(DE=("economics" or "economic importance")) or(TI=(cost* OR economic* OR expenditures OR fiscal OR pharmacoeconomic))) **18 results**
Biotechnology Abstracts		(pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester) and ((TI=(screen* or diagnos* or test or tests or testing)) or(maternal age or chorionic vill* sampling or amniocentes* or ultrasound* or ultrason* or sonogra* or "nuchal translucency" or "maternal serum" or serum marker* or biochemical marker* or soft marker* or chorionic gonadotrop* or hcg or PAPP A or Pregnancy Associated Plasma Protein A or afp or alpha fetoprotein* or uE3 or estriol or inhibin*)) and(aneuploid* or neural tube defect* or ancephal* or encephalocele* or "spina bifida" or down* syndrome or "patau syndrome" or "edwards syndrome" or trisomy or(congenital anomal*) or (chromosom* anomal*) or (anatomic*anomal*) or(chromosom* abnormalit*) or (anatomic* abnormalit*))and((TI=(cost* OR economic* OR expenditures OR fiscal OR pharmacoeconomic))) **2 results**
Econlit		S1 pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester S2 TI screen* or diagnos* or test or tests or testing S3 maternal age or amniocentes* or chorionic vill* sampling or ultrasound* or ultrason* or sonogra* or "nuchal translucency" or "maternal serum" or serum marker* or biochemical marker* or soft marker* or (chorionic W/2 gonadotrop*) or hcg or "PAPP A" or Pregnancy Associated Plasma Protein A or afp or alpha fetoprotein* or uE3 or estriol or inhibin* S4 S2 or S3 S5 aneuploid* or neural tube defect* or ancephal* or encephalocele* or spina bifida or down* syndrome or patau* syndrome or edwards syndrome or trisomy or congenital anomal* or chromosom* anomal* or anatomic* anomal* or chromosom* abnormalit* or anatomic* abnormalit* or chromosom* disorder* S6 S1 and S4 and S5 **0 results**
Clinical Practice Guidelines		
AMA Clinical Practice Guidelines http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines.html	April 8, 2010	Browsed lists of guidelines **2 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	April 8, 2010	Browsed lists of guidelines **5 results**

National Guideline Clearinghouse http://www.ngc.gov	April 7, 2010	Prenatal or antenatal or trimester or fetal or maternal or pregnancy AND Diagnosis or Screening **11 results**
NICE Guidance http://guidance.nice.org.uk/	April 7, 2010	Browsed lists of guidelines **No results**
Health Regulatory sites		
Alberta Health and Wellness http://www.health.gov.ab.ca	Sept 22, 2010	Browsed list of publications **7 results**
Health Canada (http://www.hc-sc.gc.ca) Medical Devices active license listing (MDALL) http://webprod.hc-sc.gc.ca/mdll-limh/index-eng.jsp	Sept 22, 2010	down's-syndrome OR down-syndrome OR aneuploidy OR aneuploidies OR spina-bifida OR neural-tube-defects site:http://www.hc-sc.gc.ca **0 Results**
CDC – Centers for Disease Control and Prevention http://www.cdc.gov/obesity/index.html	Sept 22, 2010	Browsed topics list **11 results**
Aetna Clinical Policy Bulletins http://www.aetna.com/about/cov_det_policies.htm	Sept 22, 2010	Browsed topics list **4 results**
MHRA http://www.mhra.gov.uk/index.htm		**NA**
Library Catalogues		
NEOS (Central Alberta Library Consortium) http://www.library.ualberta.ca/catalogue	Sept 22, 2010	"neural tube defect*" OR Any field "down* syndrome" OR Any field "aneuploid* or trisom*" OR Any field "prenatal screening" OR Any field "prenatal diagnosis" OR Any field "(antenatal screening) or (antenatal diagnosis)" **291 results**
AMICUS http://www.nlc-bnc.ca/amicus (Command search interface)		**NA**
LocatorPLUS (National Library Medicine US) http://locatorplus.gov/		**NA**
Theses Canada Portal http://www.nlc-bnc.ca/thesescanada		**NA**
Proquest Dissertations and Theses Full Text Licensed Resource (Proquest Interface)	Sept 22, 2010	neural tube defect* or down* syndrome or aneuploid* or spina bifida) OR (trisom* or "prenatal screening" or "prenatal diagnosis" or "antenatal screening" or "antenatal diagnosis" or trimester screen or trimester screening or trimester testing or "prenatal testing") OR (amniocentes* or chorionic vill* sampling or "maternal serum" or "nuchal translucency") AND PDN(>10/4/2000) or congenital abnormalit* or chromosomal abnormalit* or congenital anomal* or chromosomal anomal* or chromosome disorder*) AND PDN(>10/4/2000)

		1000 results
Internet Search Engine		
Google http://www.google.ca	October 20, 2010	7. down's-syndrome OR down-syndrome 8. aneuploidy OR aneuploidies OR spina-bifida OR 9. neural-tube-defects or trisomy 10. congenital-abnormality OR congenital-abnormalities OR chromosomal-abnormality OR chromosomal-abnormalities OR congenital-anomaly OR congenital-anomalies OR chromosomal-anomaly OR chromosomal-anomalies OR chromosome-disorder OR chromosome-disorders 11. prenatal-screening OR prenatal-diagnosis OR antenatal-screening OR antenatal-diagnosis OR trimester-screen OR trimester-screening OR trimester-testing OR prenatal-testing 12. amniocenteses OR amniocentesis OR chorionic-villi-sampling OR chorionic-villus-sampling OR maternal-serum OR nuchal-translucency *6 separate searches **42 results**
Grey Literature Sources		
Intute http://www.intute.ac.uk/healthandlifesciences/nursing/	Sept 20, 2010	Browsed lists of publications under MESH headings : prenatal diagnosis, down syndrome, Amniocentesis, Chronic villi sampling, chromosome abberations **8 relevant results**
Centre for Health Economics and Policy Analysis http://www.chepa.org	Oct. 1, 2010	Prenatal or antenatal or trimester or amniocentesis or chorionic or maternal or downs syndrome or spina bifida or neural tube or congenital or chromosomal or chromosome or aneuploidy or nuchal **2 results**
NLH (National Library for Health) http://www.library.nhs.uk/Default . aspx	Sept 22, 2010	pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or trimester OR (((down* or patau or edwards) NEAR syndrome) or (spina bifida) or Trisom*) or (aneuploid* or ((congenital or chromosom* or anatomic*) NEAR anomal*) or ((chromosom* or anatomic*) NEAR abnormalit*)) or (neural tube defect*) OR Amniocentesis or chorionic vill* sampling or maternal serum or nuchal translucency In title **12 results**
AETMIS: http://www.aetmis.gouv.qc.ca/site / home.phtml	October 1, 2010	Browsed list of publications **2 results**
CADTH: http://www.cadth.ca	October 1, 2010	Prenatal or antenatal or trimester or amniocentesis or chorionic or maternal or downs syndrome or spina bifida or neural tube or congenital or chromosomal or chromosome or aneuploidy or nuchal **2 results**
Health Technology Assessment Unit at McGill: http://www.mcgill.ca/tau	October 1, 2010	Browsed list of publications **No results**
Institute for Clinical and Evaluative Sciences (ICES) http://www.ices.on.ca	October 1, 2010	Browsed list of publications **2 results**
EuroScan: http://www.euroscan.bham.ac.uk	October 1, 2010	Browsed list of publications **3 results**

ASERNIP-S: http://www.surgeons.org/asernip-s	October 1, 2010	Browsed list of publications **0 results**
Society of Obstetricians and Gynaecologists of Canada	October 1, 2010	Browsed list of publications **2 results**

Note:

†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Appendix E.2: Screening Algorithms

Prenatal screening algorithms and resource use for fetal aneuploidy

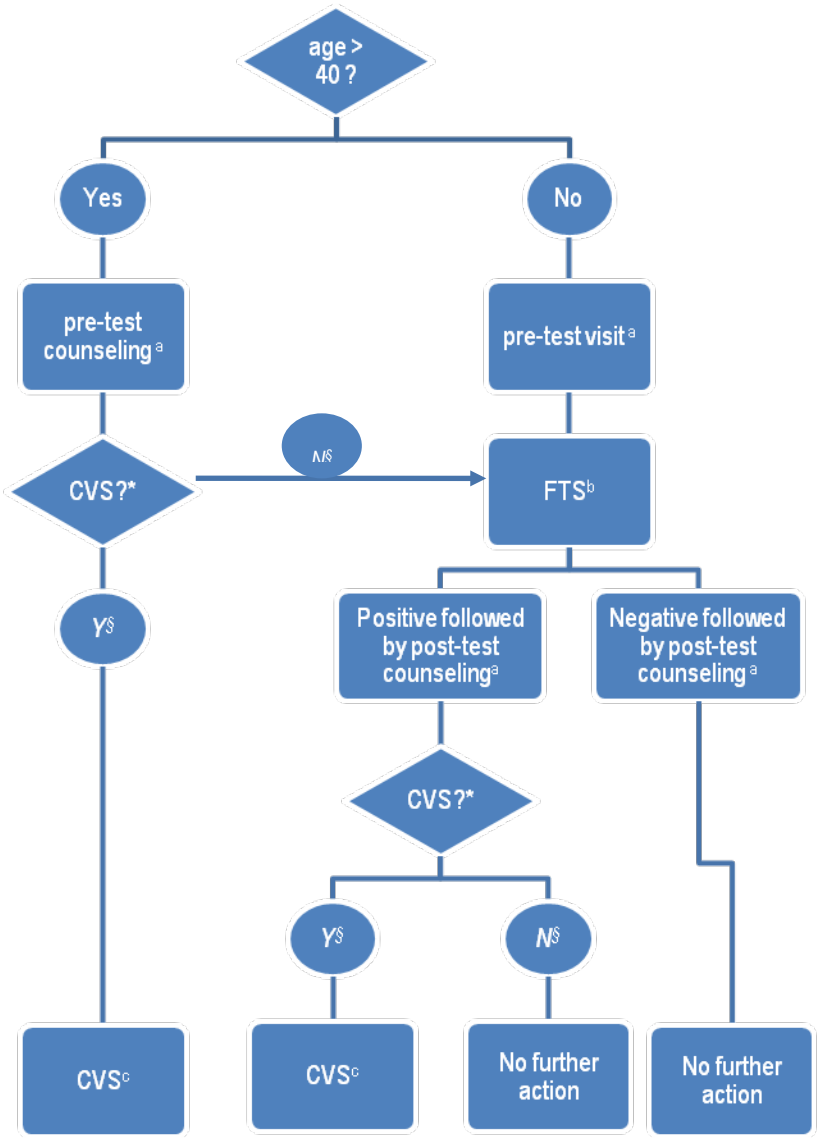
Note:

1. The analysis is to determine the screening algorithm(s) that provides the highest accuracy at lower cost prior to the decision on whether or not terminating pregnancy. So the time horizon is from pre-test counseling to final diagnosis (e.g. CVS or amniocentesis).
2. Specific options may be dependent on the software package used for the screening analysis.
3. The screening options listed below are based on the project charter for the First and Second Trimester Screening. The option of Ultrasonography was adapted from the SOGC practice guidelines.
4. The maternal age cut-off in the algorithms is 40 years, which is based on the SOGC practice guidelines.

1. First trimester screening (FTS)

Options:

1. NT
2. Double test (PAPP-A and HCG)
3. Combined test (NT, free ß-hCG and PAPP-A)



Note:

*: Patients are provided the option of CVS

§: Denotes patient choice

a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

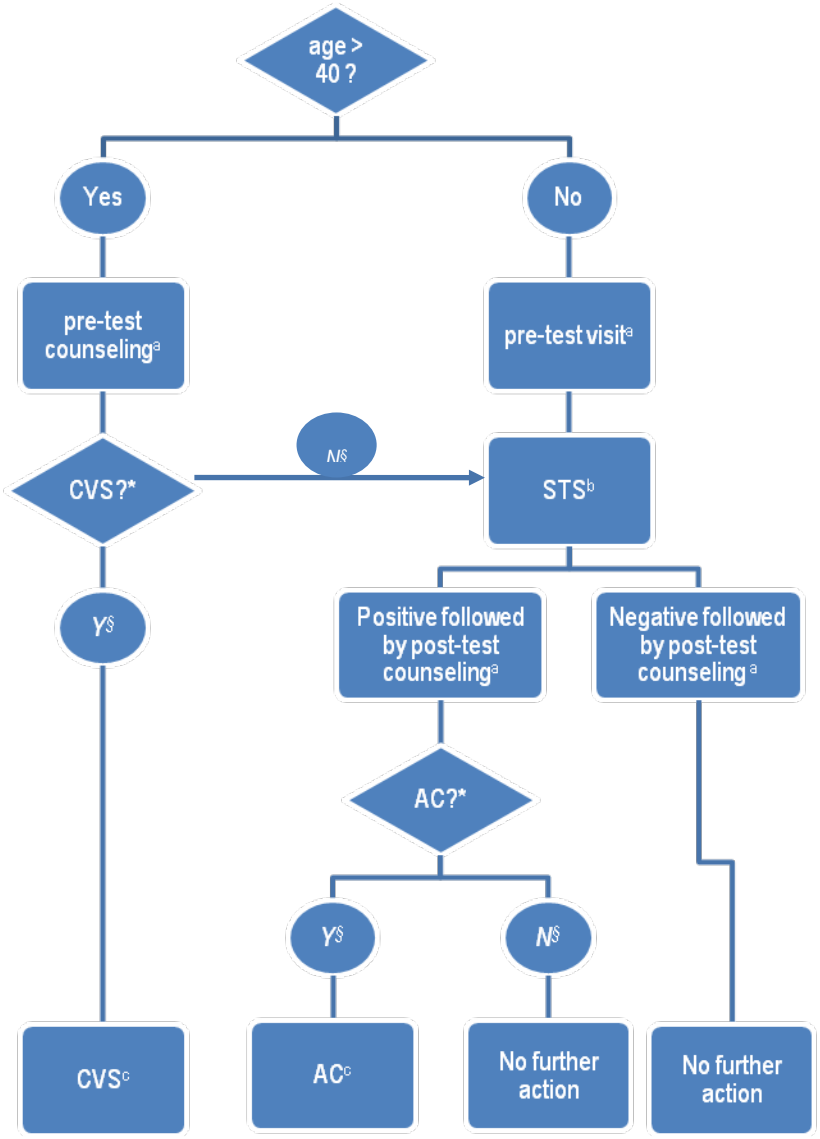
b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

2. Second trimester screening (STS)

Options:

1. Dual (AFP and free ß-hCG)
2. Triple (AFP, uE3 and total hCG)
3. Quad (AFP, uE3, free ß-hCG, inhibin A)
4. Ultrasonography



Note:

*: Patients are provided the option of CVS

§: Denotes patient choice

a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

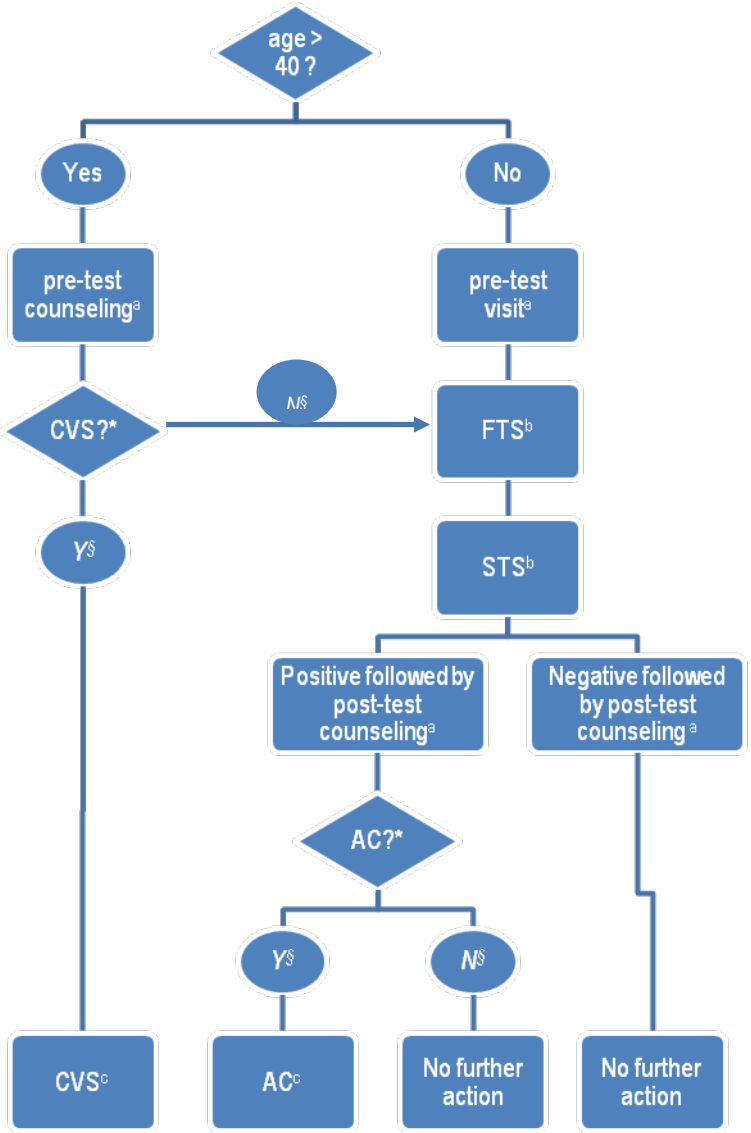
b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

3. Integrated prenatal screening (IPS)

Options:

1. Full IPS: FST: NT and PAPP-A; STS: Quad test
2. IPS without inhibin A: FST: NT and PAPP-A; STS: Triple test
3. Serum IPS: FTS: PAPP-A; STS: Quad test



Note:

*: Patients are provided the option of CVS

∫: Denotes patient choice

a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

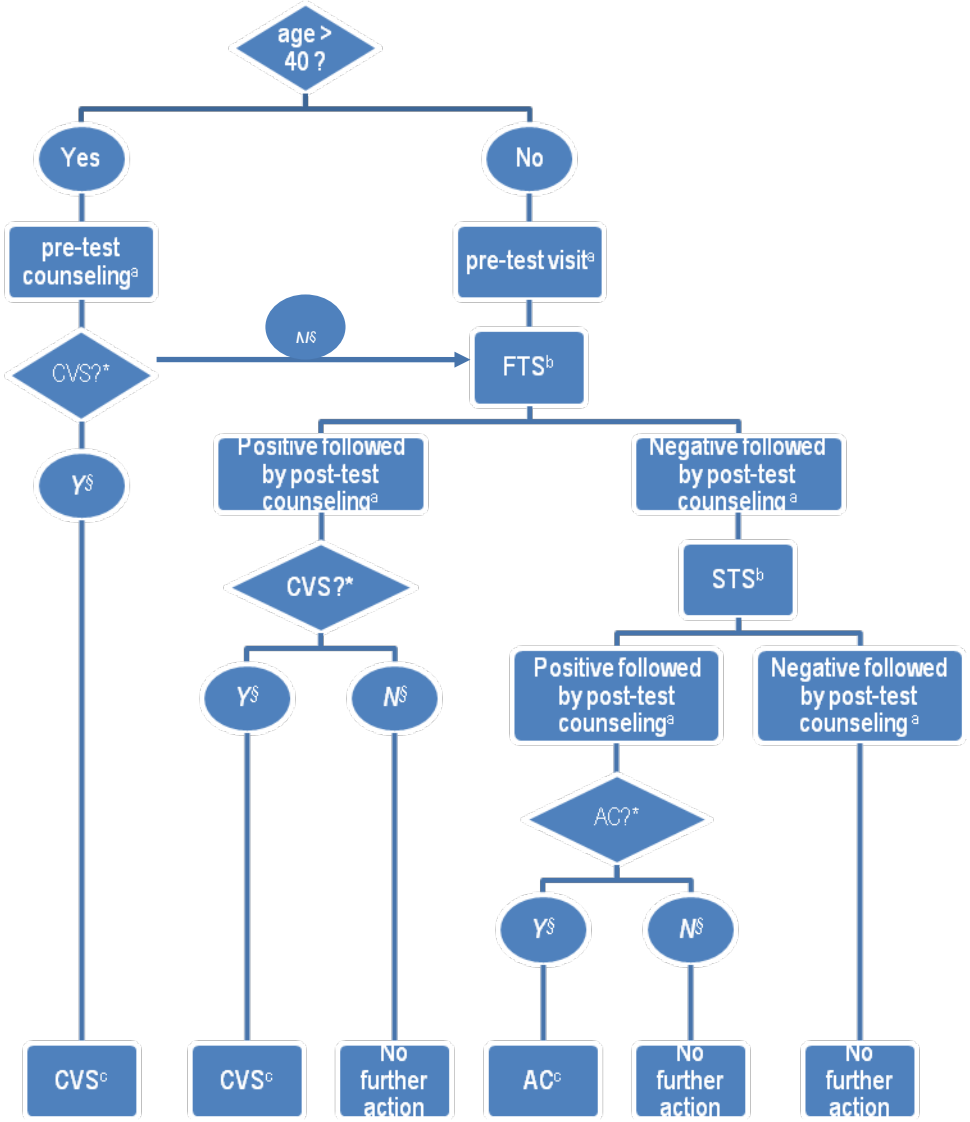
b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

4. Sequential screening

Options:

FTS: NT, PAPP-A and hCG; STS: Quad or triple test



Note:

*: Patients are provided the option of CVS/AC

∫: Denotes patient choice

a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

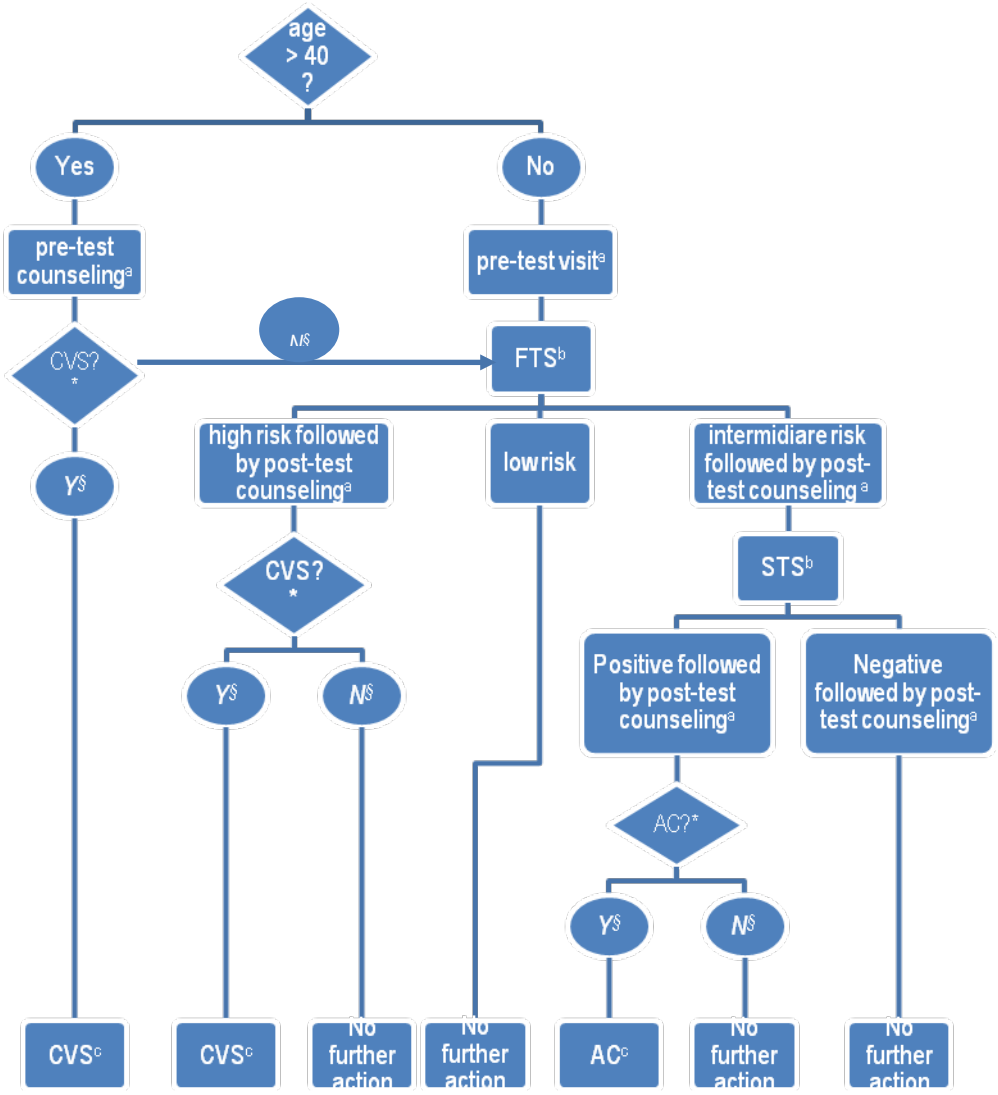
b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

5. Contingent screening

Options:

FTS: NT, PAPP-A and hCG; STS: Quad or triple test



Note:

*: Patients are provided the option of CVS/AC

§: Denotes patient choice

a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

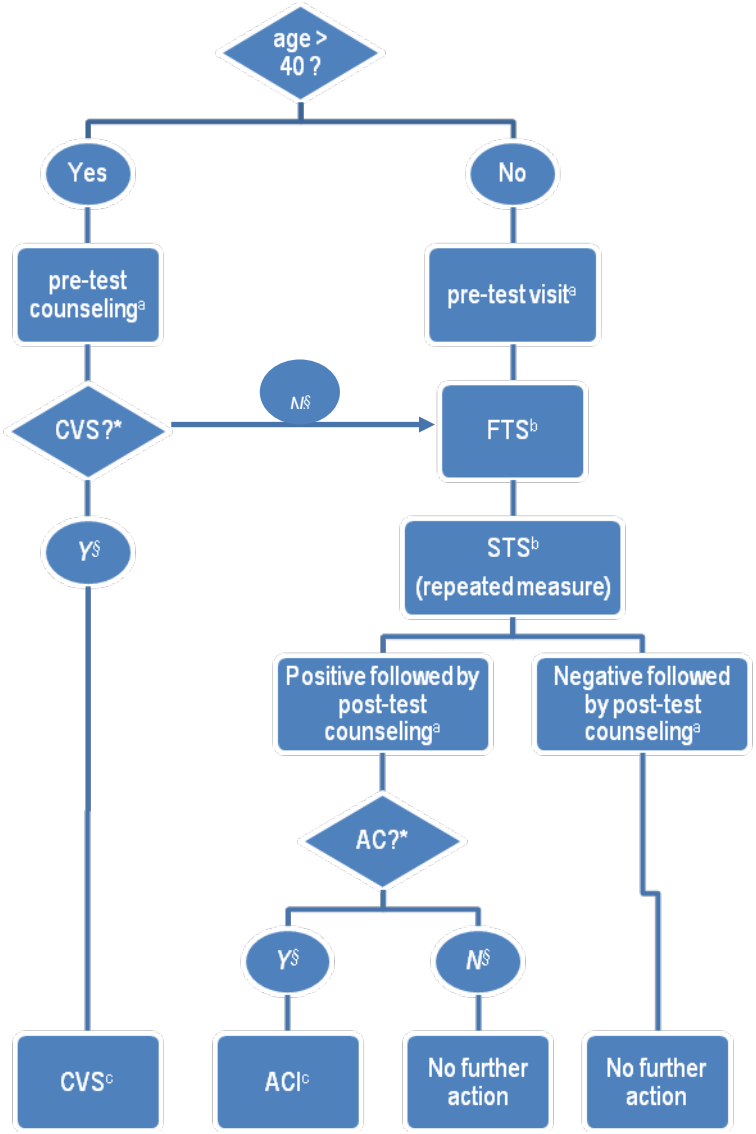
b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

6. Repeated measures screening

Options:

1. FTS: uE3 and PAPP-A; STS: uE3 and PAPP-A
2. FTS: NT+ uE3 and PAPP-A; STS: uE3 and PAPP-A



Note:

*: Patients are provided the option of CVS/AC

§: Denotes patient choice

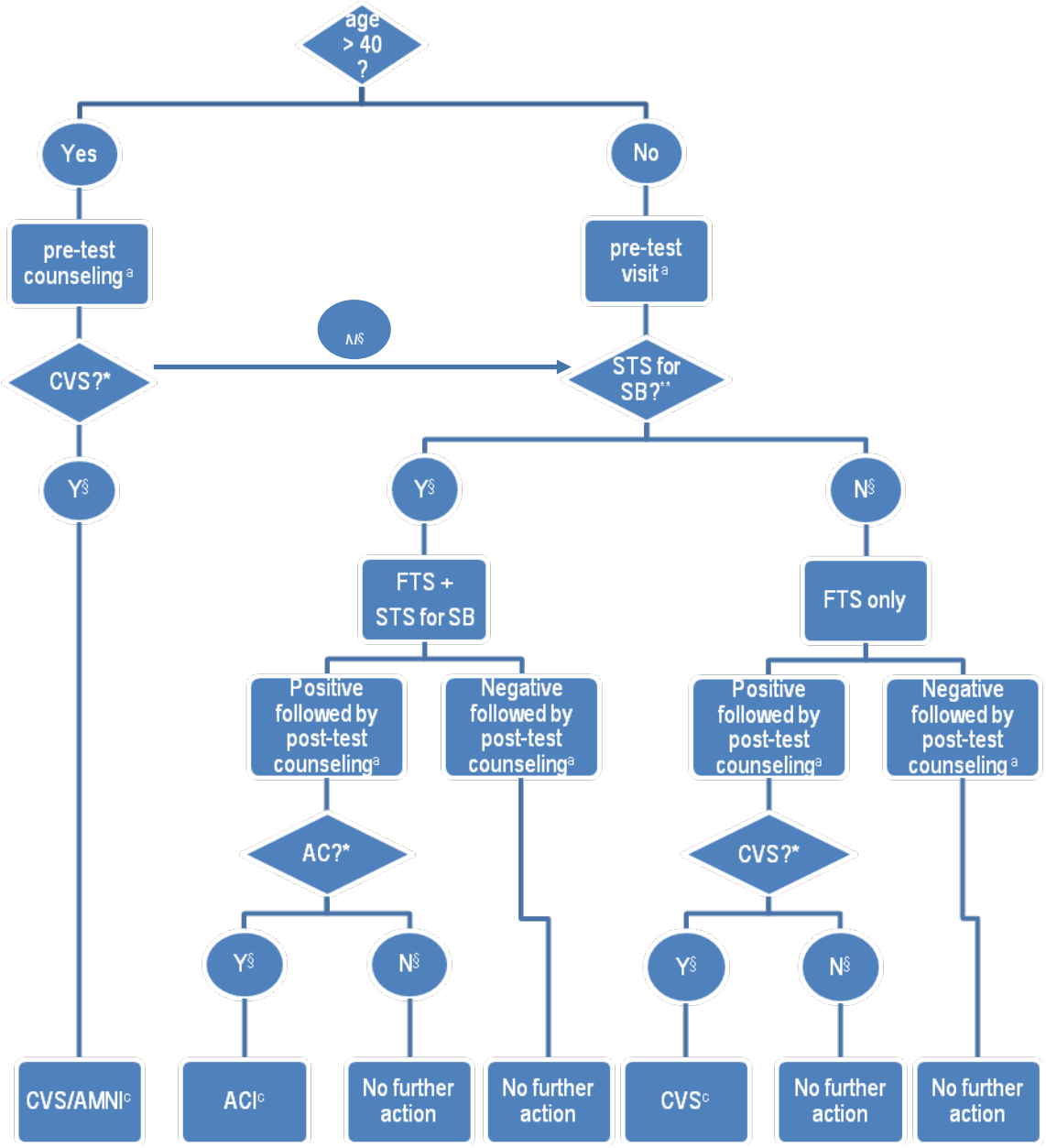
a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

7. 1st and partial 2nd screening (Alberta North)

Options: FTS: Combined test (NT, free ß-hCG and PAPP-A); STS (AFP) for spina bifida



Note:

*: Patients are provided the option of CVS/AC

**: SB = spina bifida

∫: Denotes patient choice

a: Provided by a general practitioner (GP), obstetrician (OB) or midwife

b: Lab services, equipment, labour, software and supplies

c: GP, inpatient, or outpatient

Appendix E.3: Cost and Health Outcomes in Screening for Trisomy 13 and 18, Anencephaly, Encephaloceles, and Spina Bifida

Table E.A.1: Costs (in $million) and health outcomes for the study cohort (n=52,500)

Algorithm	Total cost, $million	Affected pregnancy detected	Correctly identified pregnancy	FP*	Fetal loss
Screening for trisomy 18					
Nuchal translucency	$23.31	20	42,341	7045	52
Combined test	$25.63	20	46,452	2934	22
Dual	$14.11	19	47,684	1701	8
Triple	$14.14	13	49,309	70	1
Quad	$15.61	9	49,134	241	1
Full IPS	$26.31	21	46,407	2980	13
Screening for trisomy 13					
Nuchal translucency	$23.37	12	42,193	7193	53
Combined test	$26.03	11	45,277	4108	30
Triple	$18.99	7	31,693	17,687	77
Screening for anencephaly					
Triple	$14.53	9	47,995	1392	6
Quad	$15.72	10	48,859	528	3
Ultrasonography	$31.78	10	49,387	0	0
Screening for spina bifida					
Triple	$14.20	18	49,126	261	1
Quad	$15.69	9	48,849	529	3
Ultrasonography	$31.70	14	49,383	0	0
Combined plus AFP	$32.62	8	23,752	941	4
*: false positive (FP) indicates healthy pregnancies that are identified as test positive.					

Table E.A.2: Sensitivity and specificity (95% CI) of the strategies in screening for trisomy 18, 13, anencephaly, spina bifida, and encephalocele

#	Strategy	T18		T13		Anencephaly		Spina bifida		Encephalocele		Source
		Sen.	Spe.	Sen.	Spe.	Sen.	Spe.	Sen.	Spe.	Sen.	Spe.	
1	NT	0.94 [0.88, 0.97]	0.86 [0.85, 0.86]	0.97 [0.82, 1.00]	0.85 [0.85, 0.86]	-	-	-	-	-	-	31
2	Double test	-	-	-	-	-	-	-	-	-	-	-
3	Combined test	0.93 [0.68, 1.00]	0.94 [0.94, 0.95]	0.89 [0.71, 0.98]	0.92 [0.91, 0.92]	-	-	-	-	-	-	32,33
4	Dual	0.89 [0.52, 1.00]	0.97 [0.96, 0.97]	-	-	-	-	-	-	-	-	34
5	Triple	0.60 [0.32, 0.84]	1.00 [1.00, 1.00]	0.50 [0.01, 0.99]	0.64 [0.61, 0.67]	0.90 [0.70, 0.99]	0.97 [0.97, 0.97]	1.00 [0.16, 1.00]	0.99 [0.99, 1.00]	-	-	35-38
6	Quad	-	-	-	-	1.00 [0.54, 1.00]	0.99 [0.99, 0.99]	0.50 [0.16, 0.84]	0.99 [0.99, 0.99]	-	-	39
7	Ultrasonography	-	-	-	-	1.00 [0.29, 1.00]	1.00 [1.00, 1.00]	0.75 [0.19, 0.99]	1.00 [1.00, 1.00]	-	-	40
8	Full IPS	1.00 [0.29, 1.00]	0.94 [0.93, 0.95]	-	-	-	-	-	-	-	-	41
9	IPS without inhibin A	-	-	-	-	-	-	-	-	-	-	-
10	Serum IPS	-	-	-	-	-	-	-	-	-	-	-
11	Sequential	-	-	-	-	-	-	-	-	-	-	-
12	Contingent	-	-	-	-	-	-	-	-	-	-	-
13	Repeated w/o NT	-	-	-	-	-	-	-	-	-	-	-
14	Repeated w/ NT	-	-	-	-	-	-	-	-	-	-	-
15	AFP for spina bifida	-	-	-	-	-	-	0.89 [0.52, 1.00]	0.96 [0.96, 0.97]	-	-	42

Table E.A.3: Prevalence of prenatal abnormalities*

M Age	Anencephaly	Encephalocele	Spina Bifida	Trisomy 13	Trisomy 18
00-39	0.00020	0.00012	0.00037	0.00026	0.00043
40-99	0.00051	0.00013	0.00051	0.00128	0.00307

*: Data on cases of prenatal abnormality were from ACASS, and prevalence was derived by dividing cases of abnormality by live birth

Appendix E.4: Data Extraction and Included Studies

Author/ Country	Study Type	Objective/ Perspective	Target population/ Price year/ Assumption	Intervention/ comparator	Results			Conclusion
					Cost	Outcome	Marginal analysis	
Screening for Down syndrome (DS)								
Gekas et al. 2011[19] / Canada	CEA	To analyse the CE and performances of commonly used prenatal DS screening strategies	110,948 pregnancies in the SURUSS trials / 2007 CAD / 5%FPR&90%DR	1. Contingent screening 2. Serum integrated test 3. Sequential screening 4. Integrated test 5. Combined test(5%) 6. Quadruple test 7. Triple test 8. AC>=35 years old	2.86m 2.79m 3.74m 3.26m 4.16m 3.44m 3.83m 4.15m	106.5 detected 88.9 106.3 90.4 114.0 88.2 87.5 56.1	$3815 (comp. to 2) $369,391 (comp. to 1)	Contingent screening is the best choice. The combined test which is the most popular screening strategy shows many limitations.
Gekas et al. 2011[20] / Canada	CEA	To compare the CE of rapid aneuploidy diagnosis (RAD: FISH or QF-PCR) vs. karyotyping (CVS or AC) following the 6 screening strategies and to evaluate the clinically significant missed chromosomal abnormality (CA)	110,948 pregnancies / 2007 CAD / 8.4%FPR&90%DR	1. Integrated 2. Sequential 3. Contingent 4. Serum integrated 5. Quadruple 6. Combined (8.4%)	+QF-PCA $34,293 $33,227 $24,084 $24,103 $23,754 $24,853	1 DS detected	Karyotyping vs. RAD $59,377 $71,646 $66,608 $59,034 $59,077 $125,278	Among the safer, the most cost-effective strategy was contingent screening with QF-PCR. QF-PCR missed one CA expected to confer a high risk. ICER was $66,608 per CA. It may be relevant to question the additional costs of karyotyping

Gekas et al. 2009[21] / Canada	CEA	To assess and compare the cost effectiveness of three different strategies for prenatal screening for DS and to determine the most useful cut-off values for risk	Model 100.000 women Computer simulations to study integrated, sequential, and contingent screening strategies with various cut-offs leading to 19 screening algorithms / 2007 CA$	1. AC for women>=35yrs 2. contingent: the first trimester (NT+PAPP-A) used to categorise pregnant women as high, low, or intermediate risk. The high risk are offered CVS, the low risk receive no further screening, the intermediate risk undergo the second trimester quadruple test. 3. sequential: the first trimester (NT+PAPP-A) performed, if positive, the mothers are offered CVS, if not positive, the second trimester quadruple test is performed 4. integrated test: First trimester (NT+PAPP-A) + Second trimester quadruple test (AFP+estriol+ free β-hCG+inhibin A) + maternal age (integrated into a single test result) 5. Triple test: Second trimester screening (AFP+HCG+unconjugated estriol)	$4.1549m $2.7529m to $4.1999m for cut-offs from 1/6 to 1/307 $3.6265m to $5.0960m for cut-offs from 1/6 to 1/307 $3.3944m $3.8324	56.1 DS detected 101.4 to 112.7 100.9 to 112.5 87.2 87.5	Reference -$30,963 to $795 -$11,805 to $16,704 -$24,502 -$10,285	Contingent screening, with a first trimester cut-off value for high risk of 1 in 9, is the preferred option for DS prenatal screening
Chou et al. 2009[22] / Taiwan	CEA	To test if the first trimester DS screening of women <35 yrs and women >=35 yrs routinely receiving AC is cost-effective compared to all pregnant women screened with this test	10811 singleton women <35yrs / 1999-2007 US$ / Cut-off point for positive: 1 in 270	1. first trimester screening (NT+ PAPP-A+ β-hCG) for women <35yrs and AC for women>=35yrs 2. first trimester screening (NT+ PAPP-A+ β-hCG) for all women	$99,647-$116,433 $77,204-$98,421	1 DS prevented	$2101 in 1995 to $111,368 in 2006	The first trimester screening for DS should be implemented for all pregnant women

Hwa et al. 2008[23] / Taiwan	CEA	To assess the cost effectiveness of adding uE3 in maternal serum screening for DS / Society (health care and patient out of pocket	5057 women / USD in ??? / Cut-off 1:270 Acceptance rate of AC for a positive screen: 100%	1. maternal age>=35 2. double test (AFP+hCG) 3. triple test (AFP+hCG+uE3)	$14,561 $42,367 $37,424	1 case averted - -	Reference $139,590 $77,394 Compared to double test: $15,199 $20,980 (if the AC accepted rate=80%)	Triple test is more effective and more cost effective than double test
Chen et al. 2007[24] / China	CEA	To assess the cost-effectiveness of prenatal diagnosis intervention for DS / Societal perspective	10,000 pregnant women / 2004 US$ / DS incidence: All: 0.1117% >=35: 0.532% <35: 0.088%	1. No screening at all 2. CVS or AC for >=35 yrs 3. AFP+hCG double test in second trimester then the diagnostic test only for high-risk women	$0 $8,705 ($13,091) $78,884	.00 DS prevented .67 (1.00) 1.41	reference $94,526/DSprevented	Option 3 is not cost-effective in China because of low uptake rate and high price of serum screening
Harris 2004[25] / Australia	CEA	The cost effectiveness of NT ultrasound screening was compared to alternative screening strategies for DS	Model 260,000 women / 2001 AUS$	1. No screening 2. Serum screening in second trimester followed by AC for positive results 3. NT in first trimester followed by CVS for positive results 4. NT and maternal serum screening in the first trimester followed by CVS for positive results 5. NT and maternal serum screening for high risk women (age related) in the first trimester, with maternal serum screening in the second trimester for other women	- $21.3m $33.8m $48.1m ?	0 detected; 416 DS live born 346 detected 212 DS live born 534 detected 171 DS live born 599 detected 141 DS live born	Reference for 2) $61.700/detected $104.800/avoided Reference for 3) & 4) $66,300/detected $301,400/DS avoided 105,500/detected 374,800/DS avoided	The cost effectiveness of ultrasound screening for DS would appear to be more attractive if it was done at the same time as current dating ultrasound. NT should be incorporated into existing services provided in early pregnancy

Caughey et al. 2002[26] / USA	CEA, CUA, CBA	To perform a CEA tat compared the first- and second-trimester screening tools for DS / Societal perspective / Lifetime cost per DS case: $577,248, (exclusion of the lifetime cost results in blanket)	General population, 4 million births per year in the US / 2002 / First-(second-) trimester risk of DS: 1:500 (1:714) Amniocentesis loss rate: 1:200, Acceptance rate of amniocentesis for a positive screen: 70% (range 50%-100%)	1. Current second-trimester expanded AFP (estriol+free β-hCG+ AFP) 2. First-trimester NT screen 3. First-trimester serum screen (PAPP-A+free β-hCG) 4. Combined first-trimester NT and serum screens (NT+ PAPP-A+free β-hCG)	1,088 million 1,183 million 1,176 million 1,532 million	2446 detected 3413 detected 2993 detected 3833 detected	Reference $98,381/detected; B-C ratio=5.21; $86,566/QALY (128,338/QALY) $160,266/detected;B-C ratio=4.85 319,934/detected; B-C ratio=1.57; $76,552/QALY ($100,437/QALY)	First-trimester screening for DS with NT screening alone or with serum markers is more clinically effective and cost-effective than the current second-trimester expanded AFP screen. If the lifetime cost was excluded, they are not cost-effective
Gilbert et al. 2001[27] / UK	CEA	To compare the effects, safety, and cost effectiveness of antenatal screening strategies for DS / Health care /	10000 women with age distribution of women delivering in England and Wales 1995 / 1998 / Cut-off point for positive: 1 in 300 Amniocentesis (>=15w): 100% Chorionic villus sampling (11-14w): 100% False positive rate: 5%	1. No screening 2. Maternal age and AC 3. Maternal age and CVS 4. First trimester double test (PAPP-A+hCG) 5. Second trimester double test (AFP+hCG 6. NT 7. Second trimester triple test (AFP+hCG+ uE3) 8. Quadruple test (AFP+hCG+uE3+inhibin A) 9. First trimester combined test (NT+PAPP-A+hCG 10. Integrated test (First trimester: NT+PAPP-A; Second trimester: Quad test)	0 £164,000 £195,000 £256,000 £245,000 £171,000 £234,000 £241,000 £238,000 £276,000	16.2 affected 12.0 12.0 9.0 8.9 8.6 8.5 7.7 7.4 6.6	Reference Extended dominance Dominance Dominance Dominance £22,000/prevented Extended dominance Extended dominance Extended dominance £51,000/prevented	NT, Quad, first trimester combined, and integrated represent the best options in terms of effectiveness, cost-effectiveness, and safety. The choice between the four options depends on how much service providers are willing to pay to prevent 1 affected baby, on the total budget available for screening, and on how much the providers value safety.

Screening for DS and others (i.e. neural tube defects (NTD))								
Hoogendoorn et al. 2008[28] / The Netherlands	CEA	To evaluate prenatal screening methods for DS and NTD / Health care	Model 100,000 / EU in 2003 / Cut-off: 1:250 for DS; 2.5 MoM (multiple of the median given the gestation age) for NTD	1. first trimester double test 2. NT 3. first trimester combined double and NT test 4. triple test 5. first and second trimester combined test 6. invasive testing	€100,000 €176,000 €176,000 €100,000 €190,000 €190,000	1 DS detected. If NTD included 73,000/detected 141,000/detected 151,000/detected	293,000 per extra DS detected if compared 6) to 1) and 4)	Considering screening for both DS and NTD favours the triple test in terms of cost per detected case
Richie et al 2005[29] / UK (Scotland)	CEA	To determine the most clinically and cost effective policy of ultrasound scanning and screening for fetal abnormalities (trisomy 21 and 18 and NTD) in early pregnancy / Health care	Model 50,000 singleton pregnancies during the first 24 weeks of gestation / Year? / Cut-off: 1:250 for DS	1. first trimester NT+hCG+PAPP-A and second trimester scan 2. first trimester NT+hCG+PAPP-A 3. first trimester NT+hCG+PAPP-A and second trimester AFP+scan 4. first trimester NT+hCG+PAPP-A and second trimester AFP 5. first trimester booking scan and second trimester AFP+hCG+scan 6. first trimester booking scan and second trimester AFP+hCG	£22,909 £26,574 £25,017 £27,339 £25,162 £28,222	1 case detected	£4,790 £8,927 £148,784 £33,472 £17,525 reference	The preferred strategy includes both first and second trimester ultrasound scans and a first trimester screening test for chromosomal abnormalities

Harris et al. 2004[30] / USA	CUA	To assess the economic validity of thresholds based on age or risk for offering invasive prenatal diagnosis of trisomies 13, 18 and 21 / Society / Lifetime cost per case: $228,400 in sensitivity analysis	Model / 2003 USD /	*20 years 1. CVS 2. AC 3. No screening *35 years 1. CVS 2. AC 3. No screening *44 years 1. CVS 2. AC 3. No screening	 $54,180 $54,080 $52,940 $61, 590 $61,490 $60,360 $59,020 $59,020 $57,890	 24.13 QALY 24.16 24.08 20.35 20.39 20.30 17.03 17.08 16.98	 Dominated $14,200 Dominated $12,600 Dominated $11,300	Prenatal diagnosis testing should be offered to pregnant women irrespective of maternal age or risk, and guidelines should emphasize the important role of individual preference.

Appendix E.5: Excluded Studies (listed in alphabetical order)

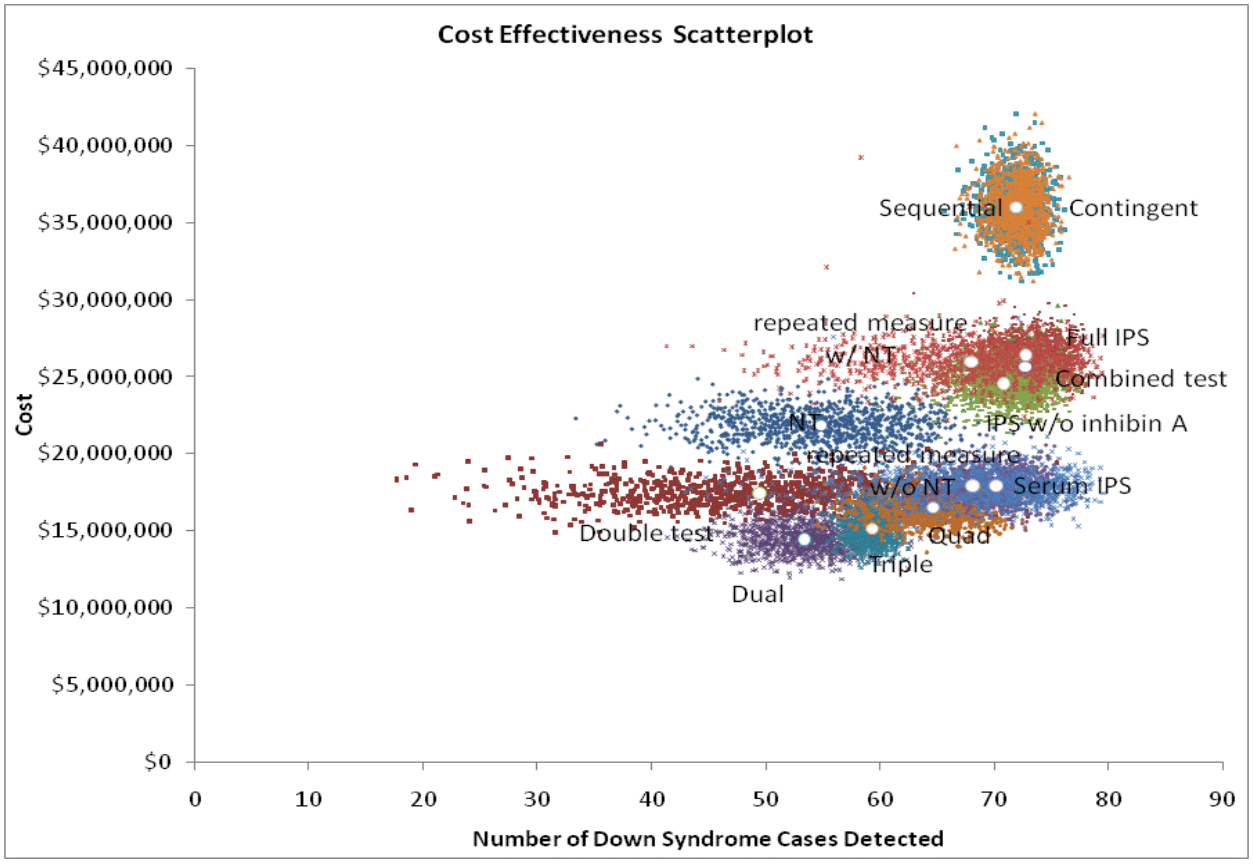
Studies	Reasons for exclusion
Ball RH, Caughey AB, Malone FD et al. First- and second-trimester evaluation of risk for Down syndrome. Obstetrics & Gynecology 2007;110(1):10-17.	Including the lifetime cost of children born with abnormalities
Biggio JR, Morris CT, Owen J, Stringer JSA. An outcomes analysis of five prenatal screening strategies for trisomy 21 in women younger than 35 years. Am J Obstet Gynecol 2004;190:721-9.	Including the lifetime cost of children born with abnormalities
Cusick W, Buchanan P, Hallahan TW et al. Combined first-trimester versus second-trimester serum screening for Down syndrome: A cost analysis. Am J Obstet Gynecol 2003;188(3):745-51.	Including the lifetime cost of children born with abnormalities
Christiansen M and Larsen SO. An increase in cost-effectiveness of first trimester maternal screening program for fetal chromosome anomalies is obtained by contingent testing. Prenat Diagn 2002;22:482-6.	Including the lifetime cost of children born with abnormalities
Hartnett J, Borgida AF, Benn PA et al. Cost analysis of Down syndrome screening in advanced maternal age. The Journal of Maternal-Fetal and Neonatal Medicine 2003;13:80-84.	Including the lifetime cost of children born with abnormalities
Kott B and Dubinsky TJ. Cost-effectiveness model for first-trimester versus second-trimester ultrasound screening for Down syndrome. J Am Coll Radiol 2004; 1:415-21.	Neither reporting ICER nor total cost and total outcome for each option
Odibo AO, Stamilio DM, Nelson DB, Sehdev HM, Macones GA. A cost-effectiveness analysis of prenatal screening strategies for Down syndrome. Obstet Gynecol 2005;106:562-8.	Including the lifetime cost of children born with abnormalities
Roberts T, Henderson J, Mugford M et al. Antenatal ultrasound screeing for fetal abnormalities: a systematic review of studies of cost and cost effectiveness. BOJC 2002; 109: 44-56	Reviewing old economic evaluations (before 2000)
Vintzileos AM, Ananth CV, Smulian JC et al. Cost-benefit analysis of prenatal diagnosis for Down syndrome using the British or the American approach. Obstet Gynecol 2000;95:577-83.	Including the lifetime cost of children born with abnormalities
Vintzileos AM, Ananth CV, Smulian JC, Beazoglou T, Knuppel RA. Routine second-trimester ultrasonography in the US: A cost-benefit analysis. Am J Obstet Gynecol 2000;182:655-60	Including the lifetime cost of children born with abnormalities
Wald NJ, Rudnicka AR and Bestwick JP. Sequential and contingent prenatal screening for Down syndrome. Prenat Diagn 2006; 26: 769-77.	Neither reporting ICER nor total cost and total outcome for each option
Wald NJ, Rodeck C, Hackshaw AK, et al. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Journal of Medical Screening 2003;10(2): 56-104.	Neither reporting ICER nor total cost and total outcome for each option

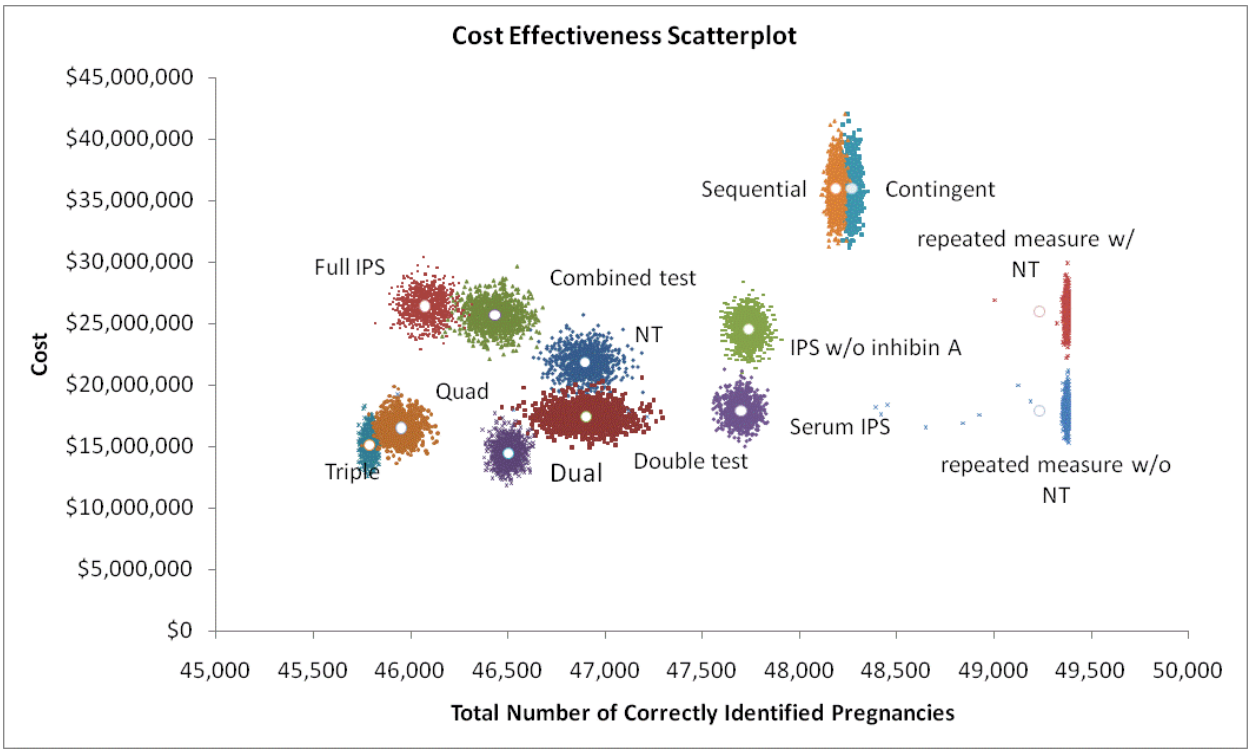
Appendix E.6: Quality Assessment of Included Studies (QHES Instrument)

	Questions	Pts	Gekas et al. 2011 (a)	Gekas et al. 2011 (b)	Gekas et al. 2009	Chou et al. 2009	Hwa et al. 2008	Chen et al. 2007	Harris 2004	Caughey et al. 2002	Gilbert et al. 2001	Hoogendoorn et al. 2008	Ritchie et al. 2005	Harris et al. 2004
1	Was the study objective presented in a clear, specific, and measurable manner?	7	7	7	7	7	7	7	7	7	7	7	7	7
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4	4	4	4	2	2	4	2	4	4	2	4	2
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?	8	8	8	8	4	5	4	4	8	8	8	4	8
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1												
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9	7	7	9	9	9	5	9	9	9	9	1	9
6	Was incremental analysis performed between alternatives for resources and costs?	6	6	6	6	4	6	6	6	6	6	3	6	6
7	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	5	5		0	5	0	0	0	0	5	0	5

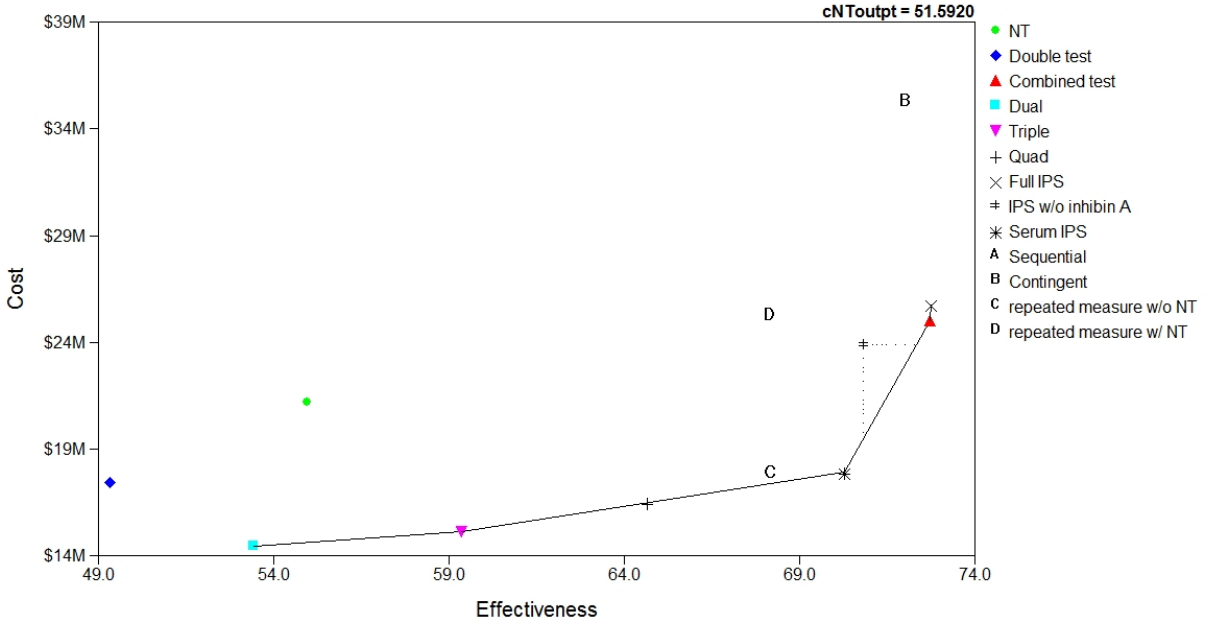
8	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	7	7	7	4	2	7	2	7	7	7	5	5
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	8	8	8	8	6	8	8	8	8	8	8	8
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term was justification given for the measures/scales used?	6	6	6	6	6	6	6	6	6	6	6	6	6
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7	7	7	7	7	7	7	7	7	7	7	7	7
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	8	8	8	8	8	8	8	8	8	8	8	8
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	8	8	7	4	5	4	7	7	7	7	6	7
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	6	6	6	6	4	4	3	6	6	2	6	6
15	Were the conclusions/recommendations of the study justified and based on the study results?	8	8	8	8	8	8	8	8	8	8	6	8	8
16	Was there a statement disclosing the source of funding for the study?	3	0	0	3	0	0	3	0	3	3	3	0	3
	TOTAL POINTS	**100**	**95**	**95**	**94**	**77**	**80**	**81**	**77**	**94**	**94**	**88**	**76**	**95**

Appendix E.7: Results from Sensitivity Analysis

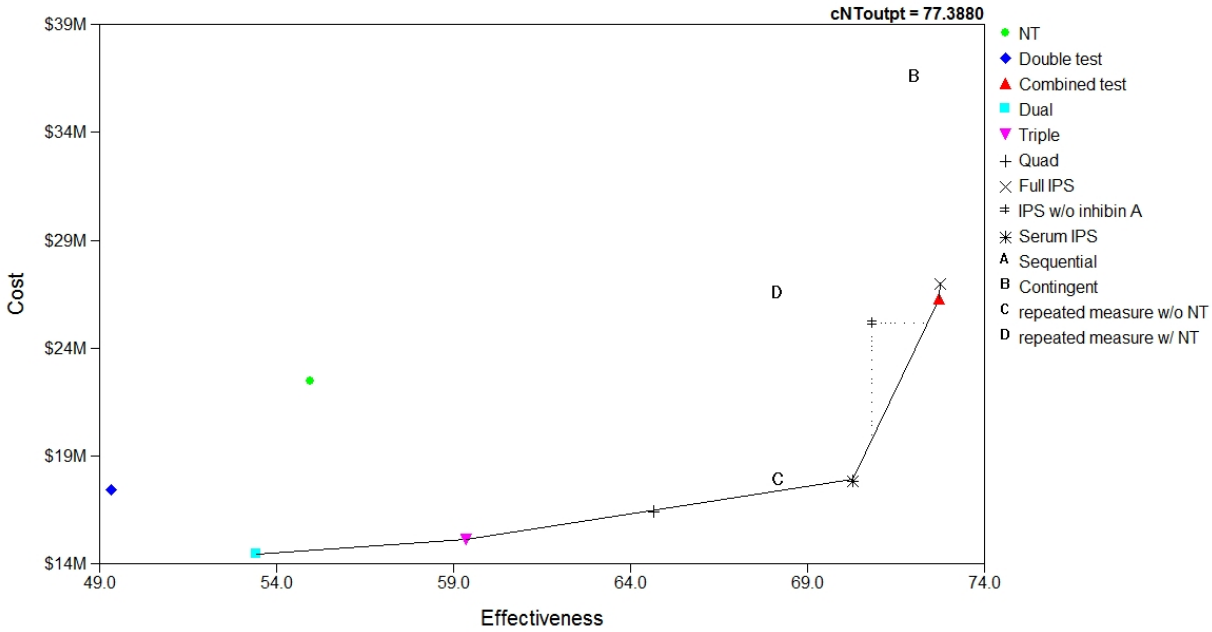


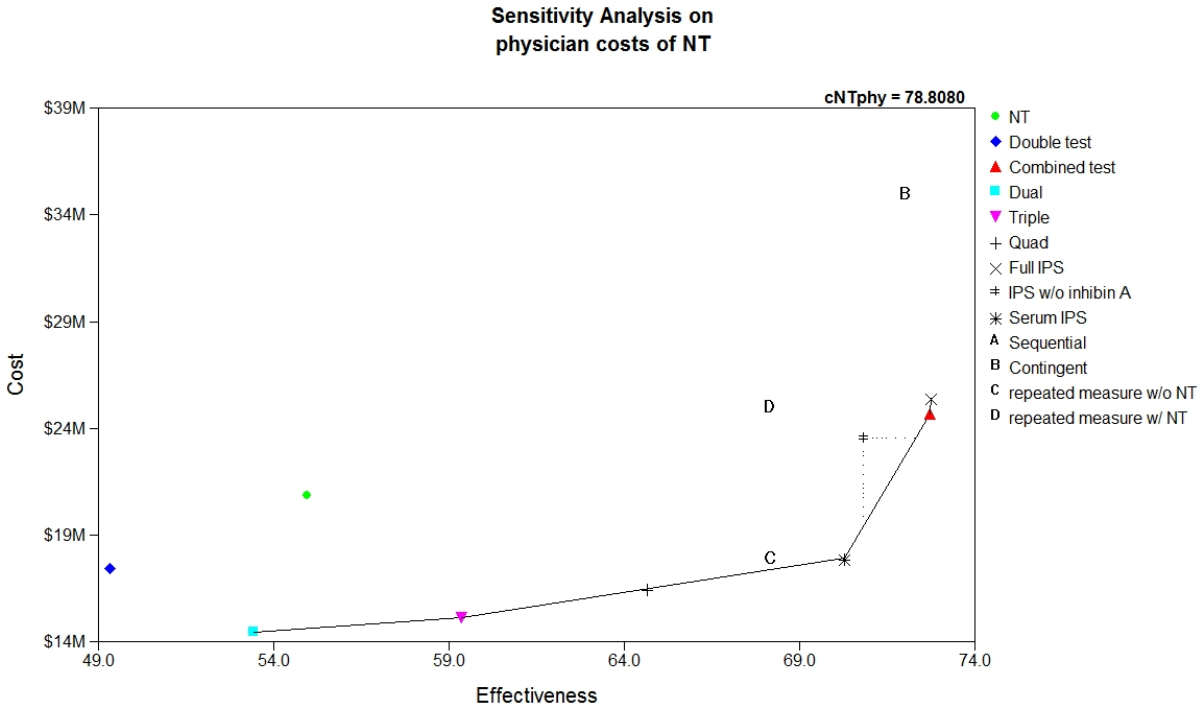


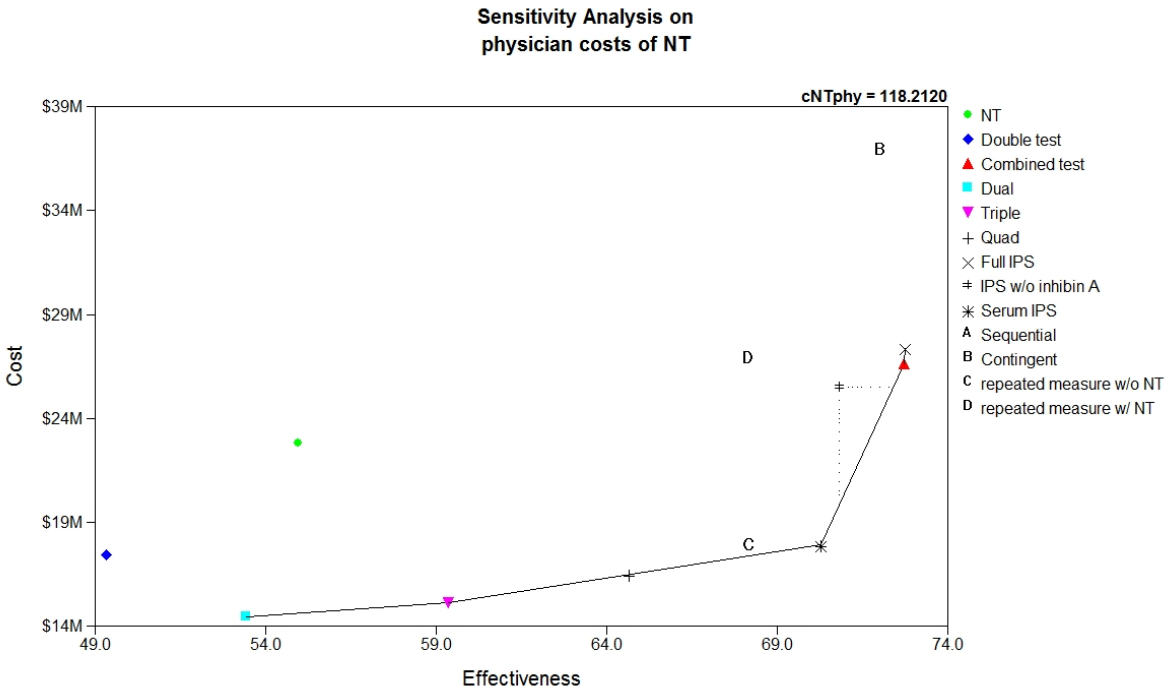
Sensitivity Analysis on outpatient cost of NT



Sensitivity Analysis on outpatient cost of NT




Sensitivity Analysis on
physician costs of NT
cNTphy = 78.8080
$39M
$34M
$29M
$24M
$19M
$14M
Cost
49.0
54.0
59.0
64.0
69.0
74.0
Effectiveness
B
D
C
NT
Double test
Combined test
Dual
Triple
Quad
Full IPS
IPS w/o inhibin A
Serum IPS
A Sequential
B Contingent
C repeated measure w/o NT
D repeated measure w/ NT


Sensitivity Analysis on
physician costs of NT
cNTphy = 118.2120
$39M
$34M
$29M
$24M
$19M
$14M
Cost
49.0
54.0
59.0
64.0
69.0
74.0
Effectiveness
B
D
C
NT
Double test
Combined test
Dual
Triple
Quad
Full IPS
IPS w/o inhibin A
Serum IPS
A Sequential
B Contingent
C repeated measure w/o NT
D repeated measure w/ NT

Author Contribution Statements

Maria Ospina contributed to study conception and design, data analysis and interpretation, and approved the final version for publication.

Ken Bond contributed to study conception and design, data analysis and interpretation, and approved the final version for publication.

Carmen Moga contributed to study conception and design, data analysis and interpretation, and approved the final version for publication.

Christa Harstall contributed to study conception and design, revision of manuscript for critical content, and approved the final version for publication.

Charles Yan contributed to study conception and design, statistical analysis, economic expert review of the literature, revision of manuscript for critical content, and approved the final version for publication.

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Dagmara Chojecki developed and executed the literature search.

This report provides an epidemiological profile of fetal aneuploidy and open neural tube defects (ONTD); describes the patterns of care, utilization trends, and factors affecting the provision of first and second trimester screening (FASTs) services for fetal aneuploidy and ONTD; performs an evaluation of the scientific evidence on the performance of available first and second trimester screening tests (FASTs) for Trisomy 21, 18,13, and open neural tube defects (specifically spina bifida, anencephyaly, encephalocele, collectively refererred to as ONTDs); and provides an estimation of the costs and cost effectiveness of various screening strategies.

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