Prenatal Diagnosis through Next Generation Sequencing (NGS)

SBU ASSESSMENTS | ASSESSMENT OF METHODS IN HEALTH CARE AND SOCIAL SERVICES

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Executive summary

Conclusions

NGS for targeted analysis

- There is insufficient scientific data to assess the reliability of non-invasive prenatal testing (NIPT) using NGS analysis for detecting trisomies other than trisomy 13, 18 or 21, or sex chromosome aneuploidies. Conducted studies includes few events, and the sensitivity of the method varies significantly between studies in the case of monosomy X.
- Because of heterogeneity in the studies, it is not possible to combine the results. However, the identified studies show that false positives occur to a greater extent than false negatives.
- There is insufficient scientific data to assess the reliability of NIPT using NGS for detecting microdeletions or microduplications associated to known syndromes.
- Analysis of the entire genetic makeup of the fetus can be included in some analysis packages, even if the primary issue relates to a specific abnormality. This could potentially become an ethical problem if the woman and her partner are not given the opportunity to decide whether they want these analyses.

NGS for whole genome sequencing

- There is insufficient evidence to draw any conclusions on the reliability of whole genome sequencing using NGS on whether additional genetic changes affecting anatomy, function or development can be detected with the method.
- NGS enables detailed analysis of the entire genetic makeup of a fetus based on a blood sample from the pregnant woman. Since the method can provide information down to the smallest genetic detail, it has the potential to provide more detailed information than is necessary.
- While NGS could ultimately lead to early detection and treatment of some conditions, it also involves such extensive mapping of all of the fetus' genes that difficulties to interpret the information will occur. This raises questions regarding which genetic changes should be identified and how the results should be reported. There are also important issues related to how the genetic information should be handled within the healthcare sector and by commercial organisations. There is a need for a thorough ethical analysis regarding the management and possible regulation of how the information generated by NGS should be used.

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Background

Next generation sequencing (NGS) is the collective term for some new methods developed in recent years that makes it possible to analyse large amounts of genetic material within the same analysis.

NGS can be used to analyse the presence of a number of predetermined genetic changes, referred to as targeted analysis. NGS can also be used to analyse an individual's entire genome, referred to as whole genome sequencing. When used for whole genome sequencing, NGS can identify genetic changes without any predetermined objective.

Targeted analysis with NGS can focus on trisomies (where an individual has three copies of a chromosome instead of the normal two), sex chromosome aneuploidies (one, three, or more sex chromosomes instead of two), microdeletions (where a copy of a chromosomal region is missing), or microduplications (one or more extra copies of a chromosomal region). Fetal DNA analysis with NGS can be performed on a blood sample taken from the pregnant woman, referred to as non-invasive prenatal testing or NIPT. In Sweden, targeted NGS analysis of NIPT samples to detect trisomy 13, 18, 21 or sex chromosome aneuploidy is offered in a few regions.

Objective and method

This report evaluates the reliability of the results obtained through NGS of noninvasive samples compared to karyotyping, QF-PCR or FISH analysis for trisomies (other than trisomy 13, 18 or 21), sex chromosome aneuploidies, microdeletions and microduplications.

The report also evaluates the reliability of the results obtained when NGS is used for whole genome sequencing of both invasive (amniotic fluid or placenta samples) and non-invasive samples.

The report highlights ethical aspects of using NGS for prenatal diagnosis, and how expectant parents perceive the value of the information. Health economic aspects are not addressed in this report.

This evaluation was performed following SBU's method.

Ethical and social aspects

Prenatal diagnosis involves issues relating to human dignity, parental autonomy, and the health of both the fetus and the parents. This SBU report presents some of the ethical issues associated with the NGS analysis method as compared to karyotyping.

The main advantage to using NGS for prenatal diagnosis is that NGS can be used to analyse non-invasive samples. Another possible advantage is the ability to detect microdeletions and other smaller chromosomal abnormalities.

An ethical problem with NGS is that it is often provided in the form of a predesigned analysis package that includes elements that may not be of interest. For instance, this packaging has led to NGS already being used to analyse the incidence of sex chromosome aneuploidies in conjunction with analysis for trisomy 13, 18 and 21. Since NGS of non-invasive samples does not increase the risk of miscarriage, expectant parents could perceive it as difficult to turn down. Depending on which genetic changes are included for analysis in the future, use of the method may contribute to a shift of focus to include low or medium-level indications, i.e. that healthcare professionals will gradually begin to look for what are currently perceived as less serious conditions. NGS could also contribute to the stigmatisation of individuals with conditions linked to genetic abnormalities that can be identified using NGS.

An introduction of NGS for prenatal whole genome sequencing may introduce ethical problems regarding how to sufficiently explain the method and the expected results, how to determine who should be analysed and what kind of information should be provided to whom.

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