VI. Tool Used To Solicit TEPP Members' Proposed Study Ratings via Email and Final Comments on Research Gap List (July 26, 2010) (distributed to TEPP after third conference call)

July 26, 2010

TO: Technical Expert Panel (TEPP) Members

FR: Barbara Mauger Rothenberg, PhD, BCBSA TEC

RE: Follow-up to third conference call, Future Research Priorities in Clinically Localized Prostate Cancer

This is a follow-up to our third conference call. The revised lists of research gaps and projects are attached. AHRQ has asked that we provide sufficient detail on each research project, such as the PICOS (Population, Intervention, Comparator, Outcomes, Setting) elements, so the projects are now presented in that format. We have also attached the final list of published studies since the literature review from the Minnesota EPC was completed and ongoing trials. The second column for new entries is highlighted in yellow.

We are therefore asking you to

1. **Rank the projects listed under each research gap, using the prioritization criteria on p. 3.**
2. **Provide feedback on this pilot project and any suggested improvements.**
3. **Indicate whether you are willing to be listed as an External input on this project at the front of the draft report. Your name, degrees, institution, city, and state would be listed.**

Please provide feedback no later than Friday, July 30th.

We cannot thank you enough for your valuable contribution to this project. It has been a pleasure working with you all.

cc: TEC staff on project; Supriya Janakiraman, M.D.

Attachment: Prioritization criteria
List of research gaps
Response form

RESEARCH GAPS ON TREATMENTS FOR LOCALIZED PROSTATE CANCER

(This page for review only. No response required.)

Gap 1: Identifying which patients to treat

- Identifying which patients to treat (e.g., those most likely to have aggressive cancer) and when
- Understanding of the natural history of localized prostate cancer in the PSA era.
- Identifying biomarkers to provide reliable estimates about prostate cancer aggressiveness and the relative effectiveness of treatments.

Gap 2: Comparative effectiveness of different treatments for localized prostate cancer

- Comparing alternative treatment strategies such as surgery, radiotherapy, androgen deprivation therapy (ADT), or active surveillance.
- Acquiring better evidence on advanced technologies such as IMRT, proton beam radiation, laparoscopic and robotic-assisted prostatectomy, high-intensity focused ultrasound, cryotherapy. Ideally, these should be compared to established treatments.
- Comparing alternative strategies within a given modality, e.g., laparoscopic vs. open prostatectomy or intensity-modulated radiotherapy vs. brachytherapy. (Added by TEPP)
- Obtaining better evidence on outcomes of treatment for patient subgroups (e.g., age, comorbidities, disease characteristics, racial/ethnic groups, including disparities).

Gap 3: Factors with impact on treatment decisionmaking

- Incorporating physician and patient preferences into treatment decisions.
- Investigating treatment patterns by physician characteristics (e.g., specialty, years in practice, volume) or institutional characteristics (e.g., tertiary vs. community hospital).
- Understanding patient psychology in dealing with uncertainty regarding screening, diagnosis, and treatment, especially for active surveillance choice. (Added by TEPP)

Gap 4: Methodologic challenges (NOTE: New addition)

- Exploring approaches to deal with potential "contamination" of RCTs as participants choose screening or treatments over the course of the trial that are not consistent with the arm to which they have been randomized

- Developing and applying more sophisticated statistical and methodologic techniques for dealing with observational data

Prioritization Criteria for Research Studies/Designs to Address Research Gaps
To be used in ranking projects on following document.

Criterion	Elements
Current importance	▪ Incorporates both clinical benefits and harms.
	▪ Represents important variation in clinical care due to controversy/uncertainty regarding appropriate care.
	▪ Addresses high costs to consumers, patients, health-care systems, or payers.
	▪ Utility of available evidence limited by changes in practice, e.g., disease detection or evolution in technology.
Potential for significant health impact	▪ Potential for significant health impact: o To improve health outcomes. o To reduce significant variation related to quality of care. o To reduce unnecessary burden on those with health-care problems.
	▪ Potential for significant economic impact, reducing unnecessary or excessive costs.
	▪ Potential for evidence-based change.
	▪ Potential risk from inaction, i.e., lack of evidence for decisionmaking produces unintended harms
	▪ Addresses inequities, vulnerable populations, patient subgroups with differential impact.
Incremental value	▪ EITHER Adds useful new information to existing portfolio of research on topic
	▪ OR Addresses generalizability of existing research when body of evidence is scant.
Feasibility	▪ Interest among researchers
	▪ Duration
	▪ Cost
	▪ Methodological complexity (e.g., do existing methods need to be refined?)
	▪ Implementation difficulty
	▪ Patient participation
	▪ Facilitating factors
	▪ Potential funders

Proposed Projects to Address Gap 1: Identifying which patients to treat

INSTRUCTIONS: Using the prioritization criteria on p. 3, please rank each project <u>for Gap 1</u> from 1 through 5, with 1 given the lowest priority and 5, the highest. Each rank (i.e., 1, 2, 3, 4, 5) can only be used once for Gap 1. Your comments on the revised project descriptions would be welcomed.

Project 1.1. Identify predictors of disease progression **RANK_____**

<u>Context:</u> As noted below, active surveillance has become a more common option for men recently diagnosed with localized prostate cancer, as it has become clear that many of these cancers are indolent and are unlikely to have a substantial negative impact on a patient's quality of life before that patient dies of other causes. However, there is a subset of patients with aggressive disease for whom postponing treatment might have a strong negative impact and increase the likelihood of death from prostate cancer. The ability to identify those patients a priori is an important precursor of being able to expand substantially the proportion of men with newly diagnosed, low-risk prostate cancer who undergo active surveillance, especially among somewhat younger otherwise healthy men.

<u>Design:</u> Prospective registry with clinical data at diagnosis and treatment, and follow-up outcome data

<u>Population:</u> Patients with localized prostate cancer diagnosed in PSA era

<u>Intervention:</u> Active surveillance

<u>Comparator:</u> None (or other prostate cancer treatments, if registry is broadened to include all newly diagnosed, localized prostate cancer patients)

<u>Outcomes:</u> Timing of treatment; intermediate outcomes such as PSA failure or bone metastases; patient preferences regarding treatment throughout the period; health-related quality of life (HRQOL)

<u>Setting:</u> Multi-institutional

<u>Other:</u> Need to collect comprehensive data on patient risk factors (related to disease, such as perineal invasiion or inflammation, and comorbidities) and preferences, as well as biospecimen repository to allow for analyses of biomarkers in the future (e.g., Oncotype Dx-type study). Might also issue Request for Proposals for ideas on how best to analyze these data.

Project 1.2. Facilitate future research on potential biomarkers to identity patients whose disease is likely to be aggressive **RANK_____**

<u>Context:</u> Although many efforts have been made to predict which patients with localized prostate cancer have aggressive disease, existing tools are inadequate to predict which patient to treat with any high degree of accuracy. With the emergence of

biomarkers in other diseases, such as breast cancer, that have both prognostic and predictive power, the search continues to identify biomarkers that can predict which patients with prostate cancer face a poorer prognosis and may benefit to a greater degree from immediate treatment. Although a number of biomarkers have been explored to data with limited success, the search should continue.

Design: Establish biospecimen repositories with clinical data on diagnosis, treatment, and followup

Population: Patients with localized prostate cancer diagnosed in PSA era

Intervention: Collecting tumor, serum, and urine specimens as well as clinical data

Comparator: None

Outcomes: Time to progression, disease-specific and overall survival

Setting: Prospective studies of localized prostate cancer

Other: Biospecimen repositories are being established for other studies, such as the PROTECT trial in the UK. While expensive to create and maintain, additional repositories would allow for additional biomarker testing (since the tissue specimens are finite and might not accommodate all future biomarker studies). In addition, since studies have different treatment regimens and possibly outcomes, biospecimens from different trials might help address different hypotheses. The National Cancer Institute is in the process of establishing methods for each step of the process for creating and maintaining biospecimen repositories.

Project 1.3. Evaluate whether all patients with elevated PSA scores warrant immediate biopsy **RANK_____**

Context: Concern is increasing about the overtreatment of men with prostate cancer, particularly among older men who may be far more likely to die of other illnesses than prostate cancer. However, once a biopsy is performed and cancer is diagnosed, it is more difficult for patients to forego therapy and choose, for example, active surveillance. A diagnosis of cancer confers a level of anxiety in many patients that is difficult to ignore. Furthermore, although PSA screening has become widely used in the United States for cancer screening, PSA is an indicator of tissue differentiation and not necessarily of prostate cancer. One possible way to address the issue of overtreatment is to delay biopsies rather than acting immediately when PSA-related metrics indicate potential cancer.

Design: Prospective randomized controlled trial

Population: Patients with elevated PSA scores on screening

Intervention: Immediate biopsy

Comparator: Delayed biopsy performed based on PSA velocity. Might also vary PSA cutpoints for making decisions about immediate biopsy or delayed biopsy by adding additional study arms.

Outcomes: Cancer detection, disease progression, patient preferences

Setting: Multi-institutional

Other: Once a person is diagnosed with cancer, it is difficult for them to forego treatment. In other cases in which overtreatment is suspected (e.g., cervical cancer), RCTs have been conducted to gauge the impact of delaying biopsy (e.g., the ALTS trial; see http://dcp.cancer.gov/programs-resources/groups/bgcrg/alts/centers).

Project 1.4. Standardize protocols used for patients on active surveillance **RANK_____**

Context: As the awareness that many men diagnosed with prostate cancer are overtreated and suffer the adverse events associated with prostate cancer therapies with little or no effect on survival, there has been increased interest in the use of active surveillance. Active surveillance differs from watchful waiting in that there may be more frequent follow up with blood tests (to measure PSA), biopsies, and diagnostic imaging, along with an often prespecified threshold for initiating treatment. However, protocols for active surveillance often vary across physicians or institutions. Identifying optimal protocols may benefit patients; introducing consistency across sites will also facilitate the conduct of meta-analyses in the future.

Design: Prospective randomized controlled trials or registries focusing on frequency and timing of followup (e.g., PSA tests, biopsy, imaging), timing and indications for treatment

Population: Patients with localized prostate cancer in PSA era

Intervention: Active surveillance

Comparator: Different active surveillance regimen

Outcomes: Disease progression, time to treatment, treatment outcomes, quality of life, patient preferences.

Setting: Multi-institutional

Other: There appears to be substantial variation in the management of localized prostate cancer patients under active surveillance. Given the apparently increasing number of patients selecting this option, identifying optimal surveillance and treatment has increasing importance. A variety of approaches can be used to investigate the multiple questions that need to be addressed in order to provide the evidence base needed to develop a recommended protocol.

Project 1.5. Investigate more accurate and reliable methods of identifying grade of disease after biopsy **RANK_____**

Context: There appears to be substantial variation in the diagnosis and staging of prostate cancer, as evidence by so-called creep in Gleason scores (with higher scores for the same type of case). The inability to distinguish consistently among patients with newly diagnosed, localized prostate cancer who have indolent versus aggressive disease may also lead to overtreatment of many patients with indolent

disease. Given the substantial adverse events associated with the treatment of prostate cancer, identifying biomarkers or other indicators of indolent disease would enable many more patients to be followed using active surveillance, thus avoiding or postponing the need to undergo treatment.

Design: Observational; may also use specimens from prior randomized controlled trials

Population: Patients undergoing biopsy for possible prostate cancer

Intervention: Alternative metrics for diagnosing prostate cancer, including objective criteria to produce standardized pathology interpretations (to address variation in Gleason scores) and testing biomarkers that may predict disease progression.

Comparator: Current methods for diagnosing prostate cancer

Outcomes: Interrater and interinstitutional reliability, disease progression, treatment outcomes (PFS, OS)

Setting: Multi-institutional

Proposed Projects to Address Gap 2: Comparative effectiveness of different treatment for localized prostate cancer

INSTRUCTIONS: Using the prioritization criteria on p. 3, please rank each project <u>for GAP 2</u> 1 through 3, with 1 given the lowest priority and 3, the highest. Each rank (i.e., 1, 2, 3) can only be used once for Gap 2. Your comments on the revised project descriptions would be welcomed.

Project 2.1. Comparative effectiveness of alternative treatments within a modality such as surgery or radiation therapy **RANK_____**

<u>Context:</u> Large randomized controlled trials comparing surgery, radiotherapy, and either active surveillance or watchful waiting are currently underway. Results are expected in about 1 year for the PIVOT trial and in 5 and 10 years for the PROTECT trial. Given the difficulty of randomizing prostate cancer patients to widely different treatments in the United States and the length of follow-up needed, the TEPP did not recommend the initiation of another trial of this type but rather focused on trials of treatments within a type of therapy (e.g., one type of surgery or radiation versus another over a shorter period of time with a primary focus on HRQOL). Many of these alternative types of surgery and radiation therapy, as well as newer techniques such as cryotherapy or high-intensity focused ultrasound are being used without evidence on comparative effectiveness.

<u>Design:</u> Randomized controlled trial

<u>Population:</u> Patients with recently diagnosed localized prostate cancer

<u>Intervention:</u> Treatments for prostate cancer

<u>Comparator:</u> Alternative treatment within a modality such as surgery (e.g., robotic-assisted laparoscopic prostatectomy vs. open radical prostatectomy) or radiation therapy (e.g., IMRT vs. proton beam).

<u>Outcomes:</u> Adverse events, HRQOL over 5-8 years; time to recurrence (although follow-up unlikely to be long enough to permit reliable estimates); cost-effectiveness of more expensive technologies

<u>Setting:</u> Multi-institutional. Include different types of facilities (e.g., academic medical centers and community hospitals) and physicians with varying experience and training.

Project 2.2. Evaluate frequency of use of ADT for low-risk prostate cancer. **RANK_____**

<u>Context:</u> The use of androgen deprivation therapy is associated with substantial adverse events, including the risk of cardiac disease, and has a negative impact on patients' HRQOL. Evidence has shown that it improves long-term prostate cancer outcomes for patients with intermediate- and high-risk disease but not for those

with low-risk disease. There is concern that low-risk individuals, especially older men, continue to be treated.

Design: Physician survey or analysis of combined registry and claims data

Population: Patients with low-risk, localized prostate cancer

Intervention: ADT

Comparator: No use of ADT

Outcomes: Use of ADT

Setting: Multi-institutional. Include different types of facilities (e.g., academic medical centers and community hospitals) and physicians with varying experience and training, if possible.

Project 2.3. Long-term sequelae of treatments for localized prostate cancer. **RANK_____**

Context: Treatments for localized prostate cancer, including surgery and radiotherapy, can have long-term sequelae independent of the disease itself. These include late radiation effects, second cancers, and adverse effects that interact with consequences of aging or other comorbid disease. While the PIVOT and PROTECT trials will provide some useful information, they do not cover all treatment options (e.g., different types of radiotherapy). Some of these effect may not emerge for 20 years, and widespread use of some of these techniques has not occurred for that long, particularly among PSA-detected cases. But data can soon be collected on 10-year followup.

Design: Longitudinal, cohort study

Population: Patients treated for low-risk, localized prostate cancer

Intervention: Any treatment for prostate localized cancer

Comparator: Other treatments for prostate cancer or active surveillance

Outcomes: Adverse events such as urinary and fecal incontinence, erectile dysfunction, unrelated cancer (which may or may not be related to treatment)

Setting: Multi-institutional. Include different types of facilities (e.g., academic medical centers and community hospitals) and physicians with varying experience and training, if possible.

Proposed Projects to Address Gap 3: Factors with an impact on treatment decisionmaking

INSTRUCTIONS: Using the prioritization criteria on p. 3, please rank each project <u>for GAP 3</u> 1 through 3, with 1 given the lowest priority and 3, the highest. Each rank (i.e., 1, 2, 3) can only be used once for Gap 3. Your comments on the revised project descriptions would be welcomed.

Project 3.1. Evaluate patient preferences and perceptions of risk in selected prostate cancer treatment **RANK_____**

<u>Context:</u> It has long been known that individual's perceptions of risk and decisions made upon them are not purely "rational," in that are not based on a simple calculation of the likelihood and magnitude of risk. In an area like prostate cancer, the issue is complicated by a substantial degree of uncertainty regarding who should be treated and what the outcomes of alternative treatments for a given patient will be. Prostate cancer treatments are now well known to be accompanied by significant morbidities, including incontinence, impotence, and/or rectal disease In addition, all the treatments are associated with side effects that can substantially affect quality of life, with the risk of adverse events and the particular mix varying from treatment to treatment. Because it is not clear whether any treatment is more effective than another in terms of expanding progression-free survival or life expectancy, the role of patient preferences becomes particularly salient. In understanding patients' treatment decisionmaking, it is therefore important to know more about patient preferences and perceptions of risk and how they weigh adverse effects of treatment versus chance for benefit..

<u>Design:</u> Survey pre- and post-treatment

<u>Population:</u> Patients with recently diagnosed localized prostate cancer

<u>Intervention:</u> Any treatment for localized prostate cancer and active surveillance

<u>Comparator:</u> Alternative treatment or active surveillance

<u>Outcomes:</u> Patients' preferences, perceptions of risk, and treatment choices; comparisons of how these may change before and after treatment

<u>Setting:</u> Multicenter with different types of institutions and physicians

Project 3.2. Study the psychological impact of diagnosis and treatment, especially for those under active surveillance. **RANK_____**

<u>Context:</u> Recent studies of men under active surveillance for localized prostate cancer have shown that a number undergo treatment because of personal preference, rather than any sign of disease progression. Some men with elevated PSAs but negative biopsies also have been reported to experience considerable distress. While men

under active surveillance may avoid the potential adverse effects of treatment, they live with the knowledge of having untreated prostate cancer.

Design: Survey pre- and post-treatment (length of follow-up to be specified)

Population: Patients with recently diagnosed localized prostate cancer undergoing treatment or in active surveillance

Intervention: Any treatment for localized prostate cancer and active surveillance

Comparison: Across treatments and active surveillance

Outcomes: Measures of psychological well-being

Setting: Multicenter with different types of institutions

Project 3.3. Increasing use of shared decisionmaking between physicians and patients

RANK_____

Context: A variety of decision aids have been developed and tested for selecting treatments for prostate cancer, due to the uncertainties regarding treatment efficacy and the trade-offs among adverse events associated with different treatments. However, to date, it does not appear that these approaches are used routinely in clinical practice.

Design: Compare different approaches to incorporating decision aids and shared decisionmaking into clinical practice

Population: Clinics treating patients with recently diagnosed localized prostate cancer

Intervention: To be defined

Comparator: To be defined

Outcomes: Use of decision aids and impact on treatment choices

Setting: Multicenter with different types of institutions

NOTE: The TEPP stated that studying variations in geographic, institutional, or physician practice patterns for treating localized prostate cancer is premature, given the lack of consensus on a standard of care for these patients. This presumably would not apply to complication/adverse event rates for a given procedure, however.

Proposed Projects to Address Gap 4: Methodological challenges

INSTRUCTIONS: Using the prioritization criteria on p. 3, please rank each project <u>for GAP 4</u> 1 or 2, with 1 given the lowest priority and 2, the highest. Each rank (i.e., 1, 2) can only be used once for Gap 4. Your comments on the revised project descriptions would be welcomed.

Project 4.1. Applying statistical modeling and other advanced methods to the prostate cancer setting **RANK_____**

<u>Context:</u> It is often difficult to conduct randomized trials on the major questions of interest, because of their cost and complexity, and particularly when there are a variety of questions about a treatment protocol. Statistical work is being done on ways to replicate some of the advantages of a randomized controlled trial using observational data. It is worth exploring whether some of these techniques can be applied to selecting when and how to treat patients with localized prostate cancer. For example, Shepherd et al. have modeled when to initiate antiretroviral treatment for individuals with HIV (Shepherd BE, Jenkins CA, Rebeiro PF, Stinnette SE, Bebawy SS, McGowan CC, Hulgan T, Sterling TR. Estimating the optimal CD4 count for HIV-infected persons to start antiretroviral therapy. Epidemiology 2010 Jun 25 [Epub ahead of print]). The use of similar approaches to understanding when to treat localized prostate cancer can be explored.

<u>Design:</u> Statistical modeling

<u>Population:</u> Patients with newly diagnosed, low-risk prostate cancer

<u>Intervention:</u> Treatment or active surveillance

<u>Comparator:</u> Different treatment choices

<u>Outcomes:</u> Signs of disease progression, treatment among the active surveillance group.

<u>Setting:</u> Multicenter with varying types of institutions and conditions.

Project 4.2. Exploring methods to increase patient adherence with randomization scheme **RANK_____**

<u>Context:</u> Trials of cancer screening (prostate, breast, and colon, for example) in the United States have shown that some individuals in the control group receive screening on their own, during the course of the study. This unplanned crossing over of patients to a different arm of the study weakens the study and makes it more difficult to come to a definitive conclusion on the impact of screening. Similar patterns may occur with treatment trials, in which for example, an individual on active surveillance decides to seek treatment before any signs of disease progression

emerge. Information on why patients change their minds and whether any approaches are effective in reducing this phenomenon are needed.

Design:	Surveys to help understand participants' decisionmaking; measuring the effectiveness of approaches intended to reduce this unplanned crossing over
Population:	Patients with newly diagnosed, low-risk prostate cancer
Intervention:	Treatment or active surveillance
Comparator:	Different treatment choices
Outcomes:	Noncompliance with randomization assignment
Setting:	Multicenter with varying types of institutions and conditions.

Feedback on this Pilot Project on Future Research on Treatments for Localized Prostate Cancer

INSTRUCTIONS: Please let us know below what you thought of this project, its strengths and weaknesses, and any suggestions for future improvements.

Please indicate whether you are willing to be listed as an "External input" to this project in the Acknowledgments section at the front of the draft report. Your name, degrees, institution, city, and state would be listed.

Yes_____ No_____

Thank you very much for your valuable input and cooperation throughout this project.

Please return to Barbara Rothenberg by Friday, July 30.