Effective Health Care Program

Future Research Needs Paper
Number 4

Future Research Needs for Comparative Effectiveness of Treatments of Localized Prostate Cancer

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Future Research Needs for Comparative Effectiveness of Treatments of Localized Prostate Cancer

Identification of Future Research Needs from Comparative Effectiveness Review No. 13

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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Rockville, MD 20850
www.ahrq.gov

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Prepared by:
Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center (BCBSA TEC EPC)
Chicago, IL

Investigators
Barbara Mauger Rothenberg, Ph.D.
Anne Marbella, M.S.
Suzanne E. Belinson, Ph.D., M.P.H.
David J. Samson, M.S.
Claudia J. Bonnell, B.S.N., M.L.S.
Kathleen M. Ziegler, Pharm.D.
Naomi Aronson, Ph.D.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

As part of a new effort in 2010, AHRQ has supported EPCs to work with various stakeholders, including patients, to further develop and prioritize the future research needed by decisionmakers. The Future Research Needs products are intended to inform and support researchers and those who fund research to ultimately enhance the body of comparative effectiveness evidence so that it is useful for decisionmakers.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative effectiveness reviews will be updated regularly.

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External Inputs

The following individuals served as members of the Technical Expert and Patient Panel described in this report. Their contributions were invaluable. They have not reviewed this report and will be given the opportunity to do so when it is released publicly by AHRQ.

Peter C. Albertsen, M.D., M.S., University of Connecticut Health Center, Farmington, CT
Otis Webb Brawley, M.D., American Cancer Society, Atlanta, GA
Robert Carey, RPC Associates/Consulting Services, John's Creek, GA
William L. Dahut, M.D., National Cancer Institute, Bethesda, MD
Barnett S. Kramer, M.D., M.P.H., National Institutes of Health, Bethesda, MD
Michael L. LeFevre, M.D., M.S.P.H., University of Missouri School of Medicine, Columbia, MO
Max Robinowitz, M.D., U.S. Food and Drug Administration, Silver Spring, MD
Chris Saigal, M.D., UCLA/RAND, Santa Monica, CA
Bryan Shepherd, Ph.D., Vanderbilt University School of Medicine, Nashville, TN
Michael J. Zelefsky, M.D., Memorial Sloan-Kettering Cancer Center, New York, NY
Anthony L. Zietman, M.D., Massachusetts General Hospital, Boston, MA

AHRQ Contacts

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality

Supriya Janakiraman, M.D., M.P.H.
Project Officer
Agency for Healthcare Research and Quality

Contents

Executive Summary ES-1
Objective 1
Background 2
    Burden of Illness 2
    2008 Comparative Effectiveness Review 2
    Research Gaps 4
Methods 8
    Identifying Recently Published and Ongoing Studies 8
    Role and Composition of the Technical Expert and Patient Panel 9
    Process for Establishing Future Research Priorities 10
    Engaging Stakeholder, Researchers, and Funders 14
    Handling Conflicts of Interest 15
Results 16
    Recently Published Studies and Ongoing Trials 16
    Prioritization of Research Gaps 18
    Recommended Research Studies 19
Discussion 31
Conclusions 34
References 36
Abbreviations 38

Tables

Table 1. Research gaps identified in Minnesota EPC CER, as selected and categorized by the BCBSA TEC EPC 6
Table 2. Initial inclusion criteria for published studies and ongoing clinical trials 9
Table 3. Prioritization criteria for research gaps and proposed research studies 13
Table 4. Prioritized list of research gaps on treatments for localized prostate cancer, 2010 18
Table 5. Potential research studies, prioritized for each research gap (n=11 of 11) 19
Table A-1. Recently published studies A-1
Table A-2. Ongoing trials A-20

Figures

Figure 1. Analytic framework for comparative effectiveness of treatments for clinically localized prostate cancer 5
Figure 2. Process chart for pilot project on future research on treatments for localized prostate cancer 12
Figure 3. Revised analytic framework for comparative effectiveness of treatments for clinically localized prostate cancer 30

Appendixes

Appendix A. List of Recently Published and Ongoing Studies
Appendix B. Prioritization Tools
Appendix C. Interim List of Potential Research Studies

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its comparative effectiveness reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Background

The objective of this project is to pilot an approach for developing future research priorities and suggesting specific projects to address evidence gaps. The topic of this pilot project, the Comparative Effectiveness of Treatments for Localized Prostate Cancer, was selected because of its importance. The project is based on a comparative effectiveness review (CER) by the Minnesota Evidence-based Practice Center (EPC).

About 1.8 million men living in the United States have a diagnosis of prostate cancer, with about 218,890 men diagnosed each year. Approximately 90 percent of men with prostate cancer have disease considered confined to the prostate gland (i.e., clinically localized disease). If left untreated, men frequently die with, rather than from, prostate cancer. Considerable overdetection and treatment may exist. However, there are no reliable ways to determine who has aggressive cancer. All treatments for prostate cancer have risks of complications, although their frequency and severity may vary.

Key questions and results from the Minnesota report are as follows:

Key Question	Summary Results
1. What are the comparative risks, benefits, short- and long-term outcomes of therapies for clinically localized prostate cancer?	• No preferred therapy; weak body of evidence. • Differences in adverse events, convenience, costs.
2. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression), affect the outcomes of these therapies, overall and differentially?	• Weak evidence on impact of treatments by race/ethnicity and age. • One randomized, controlled trial (RCT) suggested survival benefits of radical prostatectomy versus watchful waiting may be limited to men younger than 65 years.

Key Question	Summary Results
3. How do provider/hospital characteristics affect outcomes overall and differentially (e.g., geographic region and volume)?	• Results from administrative databases and surveys suggest that provider/hospital characteristics affect outcomes. • No information was found on volume and outcomes for brachytherapy, cryotherapy, or external beam radiotherapy. • Higher volume surgeons tend to have fewer surgery-related complications. • Higher volume hospitals tend to have lower surgery-related mortality, fewer late urinary complications, shorter hospital stays. • Clinicians are more likely to recommend procedures they perform, regardless of tumor grade and prostate-specific antigen (PSA) level.
4. How do tumor characteristics, e.g., Gleason score, tumor volume, screen versus clinically detected tumors, affect the outcomes of these therapies, overall and differentially?	• Few data on comparative effectiveness of treatments by tumor characteristics. • Estimated that PSA increases the time of detection by 5–15 years. Men with PSA-detected tumors likely to have better 20-year disease-specific survival.

The Minnesota CER concluded that more RCTs are needed to reliably assess the comparative effectiveness and adverse effects of alternative treatments. The research gaps and methodologic needs are summarized below:

Category	Research Gap
Population	• RCTs on relative effectiveness and adverse events of treatments by patient and tumor characteristics • Nonrandomized, high quality, large prospective cohort studies or registries that identify men at diagnosis and collect patient, tumor, and treatment-decision characteristics
Interventions	• Long-term, adequately powered, randomized trials, particularly comparative trials, on emerging technologies such as intensity-modulated radiotherapy, proton beam radiation, laparoscopic and robotic-assisted prostatectomy, and cryotherapy • A new generation of educational materials to provide balanced information for patient decisionmaking
Comparators	• Adequately powered, sufficiently long, head-to-head RCTs comparing primary treatments for localized prostate cancer • Confirmatory trials where RCTs are available
Outcomes	• Standardized reporting of key clinically relevant outcomes • Geographical differences in patient outcomes • Structure and process measures for quality of care. • Identification of factors associated with outcomes and system-wide improvement methods.
Context/other	• Approaches to adequate and timely recruitment in clinical trials • Biomarkers to provide reliable estimates about cancer aggressiveness and relative treatment effectiveness

Methods

The overall method proposed for this pilot project was to use a Technical Expert and Patient Panel (TEPP) to assist with the prioritization process. We recruited a group of individuals who had a keen interest in comparative effectiveness research, who were supportive of evidence-based decisionmaking, and who were well versed in the obstacles faced in conducting large clinical trials, especially in the case of prostate cancer. They were drawn from an array of clinical disciplines, including urology, radiation and medical oncology, family practice, and pathology.

They also included a biostatistician specializing in innovative methodologic approaches to using observational data and a consumer participant. Although affiliated with various professional societies and other stakeholder organizations, TEPP members participated as knowledgeable individuals and not as representatives of the respective organizations with which they are affiliated.

This group was asked to recommend important studies published since the publication of the Minnesota CER, agree upon prioritization criteria, revise and prioritize the research gaps listed in the CER, and develop and prioritize a list of potential research studies to address those gaps. These tasks were accomplished through an initial one-on-one telephone call between BCBSA TEC EPC staff and each TEPP member, followed by three group conference calls and email communications.

The BCBSA TEC EPC developed prioritization criteria for use by the TEPP, derived from the Agency for Healthcare Research and Quality (AHRQ) criteria used for topic selection in the Effective Health Care Program. The criteria were tailored to fit the purposes of the future research pilot and subsequently revised by TEPP members during the first conference call. The criteria "Current Importance" and "Potential for Significant Health Impact" were used to rank both research gaps and proposed studies; the criteria "Feasibility" and "Incremental Value" were also included when prioritizing the proposed research studies. The final set of criteria was distributed to TEPP members each time they were asked to prioritize research gaps or studies.

To identify recently published and ongoing studies, an update was conducted of studies cited in MEDLINE® that were published since September 2007 and of clinical trials currently underway, derived from ClinicalTrials.gov. The objective was to identify major studies that might alter or inform the research gaps identified in the Minnesota CER. This step was not intended to update the systematic review, which would require a broader search and more in-depth abstraction. Rather, the purpose was to identify important studies that addressed research gaps and should be taken into account in identifying potential research studies. A broad scope was used to identify the pool of potential studies but a narrow set of criteria were applied to them. Technical experts were also asked to name influential articles. A brief summary of the articles and trials that met search criteria was distributed to TEPP members.

Although TEPP members generally agreed that RCTs would be the best study design to address many of the research gaps, prior experience indicated the difficulty of conducting such trials in the United States for early stage disease. Furthermore, several clinical trials are currently underway; for example, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the Prostate Testing for Cancer and Treatment (ProtecT) trial; and some members advocated waiting for results from these trials while using alternative methods in the meantime. Therefore, the primary focus in generating a list of proposed research studies was on smaller, more limited RCTs or other research designs.

Stakeholders were represented indirectly through the TEPP. The members were knowledgeable about the points of view of researchers, physicians, funders, patients, and others.

As prescribed by AHRQ, conflict of interest forms were completed by all TEPP members and staff on this project. There were no conflicts that were judged to preclude participation in the project. The multidisciplinary character of the TEPP and their varied stakeholder affiliations also helped to produce a balanced process.

Results

Thirty recently published articles were chosen for inclusion, including two studies recommended by TEPP members. Together, these studies suggest that the benefit of PSA screening for preventing prostate cancer–related deaths may be small or nonexistent. They raise the question of overtreatment of patients with cancer detected through PSA screening. According to a 2009 study by Schroeder et al., 1,410 men would need to be screened and 48 additional subjects treated to prevent one prostate cancer death. The publication of these studies after the Minnesota EPC report may have shifted the TEPP members' focus from "how to treat" to "whom and when to treat."

The review of localized prostate cancer trials at ClinicalTrials.gov yielded 13 trials of potential relevance for this pilot project. The most important trials, also mentioned by several TEPP members, are the PIVOT trial in the United States, with initial results expected in about 1 year, and the ProtecT trial in the United Kingdom, with initial results expected in about 5 years. In each trial, participants were randomized to one of several treatments, including either watchful waiting or active surveillance. These trials address two of the evidence gaps selected by the TEPP. Given the time, effort, and cost required for these trials and the fact that they are already underway, TEPP members agreed that similar trials should not be initiated.

Through an iterative process, the TEPP members identified and prioritized the research gaps. They then generated and prioritized a list of potential research studies to address these gaps. The evidence gaps and specific research projects are listed in the following section. The gaps are listed in order of priority, except for Gap 4, which was not ranked. Within each gap, the proposed projects are ranked, as well.

Gap 1: Identifying Which Patients To Treat

Project 1.1. Identify predictors of disease progression

Design: Prospective registry with clinical data at diagnosis and treatment, and follow up outcome data.

Population: Patients with localized prostate cancer diagnosed in PSA era

Intervention: Active surveillance

Comparator: None (or other prostate cancer treatments)

Outcomes: 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)

Setting: Multi-institutional

Project 1.2. Standardize protocols used for patients on active surveillance

Design: Prospective randomized, controlled trials or registries focusing on frequency and timing of followup, as well as timing and indications for treatment

Population: Patients with localized prostate cancer in PSA era

Intervention: Active surveillance

Comparator: Alternative active surveillance regimens

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

Setting: Multi-institutional

Project 1.3a. Facilitate future research on potential biomarkers to identity patients whose disease is likely to be aggressive

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; and clinical data

Comparator: None

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

Setting: Prospective studies of localized prostate cancer

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

Design: RCT

Population: Patients with elevated PSA scores on screening

Intervention: Immediate biopsy

Comparator: Delayed biopsy performed based on PSA velocity. Might also vary PSA cutpoints.

Outcomes: Cancer detection, disease progression, patient preferences

Setting: Multi-institutional

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

Design: Observational or specimens from prior RCTs

Population: Patients undergoing biopsy for possible prostate cancer

Intervention: Alternative metrics for diagnosing prostate cancer, with objective criteria to standardize pathology interpretations, and testing biomarkers that may predict disease progression

Comparator: Current methods for diagnosing prostate cancer

Outcomes: Inter-rater and inter-institutional reliability, disease progression, treatment outcomes (progression-free survival [PFS], overall survival [OS])

Setting: Multi-institutional

Gap 2: Comparative Effectiveness of Different Treatment for Localized Prostate Cancer

Project 2.1. Comparative effectiveness of alternative treatments within a modality

Design: RCT

Population: Patients with recently diagnosed localized prostate cancer

Intervention: Treatments for prostate cancer

Comparator: Alternative treatments within a modality such as surgery (e.g., robotic-assisted laparoscopic prostatectomy vs. open radical prostatectomy) or radiation therapy (e.g., intensity-modulated vs. proton beam therapy)

Outcomes: Adverse events, HRQOL over 5-8 years, time to recurrence, cost-effectiveness

Setting: Multi-institutional. Include facilities and physicians with different characteristics.

Project 2.2a. Evaluate frequency of use of androgen-deprivation therapy (ADT) for low-risk prostate cancer

Design: Physician survey or analysis of combined registry and claims data. This could also be developed as an RCT of ADT vs. delayed ADT.

Population: Patients with low-risk, localized prostate cancer

Intervention: ADT

Comparator: No use of ADT

Outcomes: Frequency of ADT, outcomes of ADT

Setting: Multi-institutional. Include facilities and physicians with different characteristics.

Project 2.2b. Long-term sequelae of treatments for localized prostate cancer

Design: Longitudinal, cohort study

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

Intervention: Any treatment for localized prostate cancer

Comparator: Other treatments for prostate cancer or active surveillance

Outcomes: Adverse events such as urinary and fecal incontinence, erectile dysfunction, unrelated cancer

Setting: Multi-institutional. Include facilities and physicians with different characteristics.

Gap 3: Factors with an Impact on Treatment Decisionmaking

Project 3.1. Evaluate patient preferences and perceptions of risk in selecting prostate cancer treatment

Design: Survey pre- and post-treatment

Population: Patients with recently diagnosed localized prostate cancer

Intervention: Any treatment for localized prostate cancer and active surveillance

Comparator: Alternative treatment or active surveillance

Outcomes: Patients' preferences, perceptions of risk, and treatment choices, pre- and post-treatment

Setting: Multicenter with different types of institutions and physicians

Project 3.2. Increasing use of shared decisionmaking by physicians and patients

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, impact on treatment choices, factors that facilitate or serve as barriers to adoption of these tools

Setting: Multicenter with different types of institutions

Project 3.3. Study the psychological impact of diagnosis and treatment, especially for those under active surveillance.

Design: Survey pre- and post-treatment (length of followup 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

Gap 4: Methodologic Challenges

Project 4.1. Exploring methods to increase patient adherence with randomization scheme

Design: Surveys to help understand participants' decisionmaking; measuring the effectiveness of approaches intended to reduce unplanned crossing over to another arm

Population: Patients with newly diagnosed, low-risk prostate cancer

Intervention: To be defined

Comparator: No intervention

Outcomes: Nonadherence with randomization assignment

Setting: Multicenter with varying types of institutions and conditions

Project 4.2. **Increasing the use of statistical modeling and other advanced methods in studies on localized prostate cancer**

Design: Statistical modeling

Population: Patients with newly diagnosed, low-risk prostate cancer

Intervention: Treatment or active surveillance

Comparator: Different treatment choices

Outcomes: Signs of disease progression, treatment among the active surveillance group

Setting: Multicenter with varying types of institutions and conditions

Conclusions

The treatment of localized prostate cancer is a high priority issue due to the prevalence of disease, concern about potential overtreatment with accompanying adverse events, and the potential for severe disease and death for a small portion of patients. An overriding concern, however, is the weakness of the current state of evidence to guide individual patient decisionmaking. Because of the well recognized difficulties in maintaining robust, long-term RCTs on localized prostate cancer in the United States, the core of our approach to this pilot project was to convene an interdisciplinary TEPP. Our experience in the pilot project was that the TEPP members meshed to provide new insights into prioritizing research gaps and a diversity of approaches to the proposed research studies to address these gaps. Most notably, the TEPP reframed the most important underlying research question in the field. While most prior formulations had focused on comparing treatment strategies, the Panel concurred that the critical question is how to identify the patients with newly diagnosed, localized prostate cancer who would benefit from early treatment. Racial and ethnic disparities in treatments and outcomes were recognized as important, but again, it is difficult to address this issue without knowing more about which patients should be treated and which treatments will work best for them.

While acknowledging the RCT as the ideal study design, the TEPP recognized the need for alternative methodologies to address both questions of who should be treated and questions of the comparative effectiveness of treatments. To address the question of who should be treated, the Panel envisioned the use of prospective registries of patients under active surveillance. Linked to this would be a biospecimen repository that would permit future analyses of novel biomarkers. The TEPP also identified "meta-gaps," methodologic challenges generalizable to diseases and settings beyond localized prostate cancer. For RCTs, the Panel endorsed the need to explore methods to increase patient adherence with randomization schemes, because unplanned crossover confounds interpretation of trial results. The Panel also supported advancing the use of statistical modeling, instrumental variable analysis, and other advanced methods that might replicate some of the strengths of an RCT but use observational data, which is often more feasible to obtain than launching a de novo RCT.

We offer some lessons learned from the pilot project that would be useful to apply to ongoing efforts to develop future research needs white papers prepared in conjunction with comparative effectiveness reviews:

- Convening teleconferences was an effective way of leveraging the synergies of an interdisciplinary group and enjoyable for the participants.
- Although we used a process of rank-ordering the research study priorities, we found the qualitative discussions more informative.
- In our experience, the process of quantitative rank ordering of priorities did generally not distinguish sufficiently among options.
- We recommend an AHRQ EPC methods project that will review the literature on eliciting preferences and make recommendations for the application of such methodologies to future research needs projects conducted in conjunction with comparative effectiveness reviews.
- The pilot process was successful for prioritizing research gaps and identifying, at a high level, projects that would address those gaps. However, the scope of the pilot project was such that potential research studies could only be sketched out at a very general level.
- To achieve a greater richness in the thinking about potential research studies, we recommend generating ideas for such studies only for the highest priority evidence gap.

Objective

The objective of this project is to pilot an approach for developing future research priorities and suggesting specific projects to address evidence gaps. From the results of this and comparable pilot projects conducted by other Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPCs), AHRQ will identify generalizable strategies and lessons learned.

The topic of this pilot project, the comparative effectiveness of treatments for localized prostate cancer, was selected because of its importance. The Minnesota EPC completed a comparative effectiveness review (CER) on this topic in 2008 for AHRQ.[1] This pilot project amends the list of recommendations from that report and creates prioritized lists of research gaps and proposed research studies. Subsequently, management strategies for local prostate cancer were in the first quartile of the Institute of Medicine's 100 initial priority topics for comparative effectiveness research:

> Compare the effectiveness of management strategies for localized prostate cancer (e.g., active surveillance, radical prostatectomy [conventional, robotic, and laparoscopic], and radiotherapy [conformal, brachytherapy, proton beam, and intensity-modulated radiotherapy]) on survival, recurrence, side effects, quality of life, and costs.[2]

Background

Burden of Illness[a]

An estimated 1.8 million men living in the United States have a diagnosis of prostate cancer, with about 218,890 newly diagnosed men each year. Approximately 90 percent of men with prostate cancer have disease considered confined to the prostate gland (i.e., clinically localized disease). If left untreated, frequently men die with, rather than from, prostate cancer. Largely because of widespread prostate-specific antigen (PSA) testing, the lifetime risk of prostate cancer diagnosis in the United States has nearly doubled to 20 percent, while the risk of dying of prostate cancer has remained at approximately 3 percent. Therefore, considerable overdetection and treatment may exist. Moreover, the treatment of localized prostate cancer is associated with substantial adverse effects.

The primary goal of treatment is to target those men most likely to need intervention to prevent prostate cancer death and disability, while minimizing intervention-related complications. Common treatments include watchful waiting (active surveillance), surgery to remove the prostate gland (i.e., radical prostatectomy), radiotherapy (e.g., external-beam radiation or brachytherapy), freezing the prostate (i.e., cryotherapy), and androgen-deprivation therapy (ADT). All treatments for prostate cancer have risks of complications, although their frequency and severity may vary. Common adverse events include urinary, bowel, and sexual dysfunction. The vast majority of prostate cancers currently detected in the United States are asymptomatic, clinically localized, and found on routine PSA testing. PSA testing detects more tumors, at an earlier stage, with a smaller volume within each stage, and at an earlier period in a man's life than nonscreen-detected tumors. The clinical significance, natural history, and comparative effectiveness of treatments in PSA-detected cancers are not known but likely differ from those detected and treated in the pre-PSA era (before the late 1980s to early 1990s).

2008 Comparative Effectiveness Review

The Minnesota EPC's comparative effectiveness review (CER) on Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer[1] covered studies published between 2000 and September 2007. The key questions addressed in the report are listed below:

Key Question 1. What are the comparative risks, benefits, short- and long-term outcomes of therapies for clinically localized prostate cancer?

[a] The text of this section and the following section on "2008 Comparative Effectiveness Review" is largely drawn from the 2008 Minnesota EPC CER. The findings for each key question are reproduced verbatim, although some paragraphs were omitted in the interest of brevity. The full text is available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Key Question 2. How do specific patient characteristics, e.g., age, race/ethnicity, presence or absence of comorbid illness, preferences (e.g., tradeoff of treatment-related adverse effects vs. potential for disease progression), affect the outcomes of these therapies, overall and differentially?

Key Question 3: How do provider/hospital characteristics affect outcomes overall and differentially (e.g., geographic region and volume)?

Key Question 4: How do tumor characteristics, e.g., Gleason score, tumor volume, screen vs. clinically detected tumors, affect the outcomes of these therapies, overall and differentially?

An abbreviated version of the major findings reported in the Minnesota EPC's report follows:

Key Question 1. What are the comparative risks, benefits, and outcomes of therapies?

No one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects. All treatment options result in adverse effects (primarily urinary, bowel, and sexual), although the severity and frequency may vary between treatments. Even if differences in therapeutic effectiveness exist, differences in adverse effects, convenience, and costs are likely to be important factors in individual patient decisionmaking. Patient satisfaction with therapy is high and associated with several clinically relevant outcome measures. Data from nonrandomized trials are inadequate to reliably assess comparative effectiveness and adverse effects. Additional randomized controlled trials (RCTs) are needed….

Key Question 2. How do patient characteristics affect outcomes?

No RCTs reported head-to-head comparisons of treatment outcomes stratified by race/ethnicity, and most did not provide baseline racial characteristics. Available data were largely from case series. Few studies reported head-to-head comparisons, and there was limited adjustment for confounding factors. Modest treatment differences reported in some nonrandomized studies have not been consistently reported in well-powered studies. There was little evidence of a differential effect of treatments based on age. While differences exist in the incidence and morbidity of prostate cancer based on patient age and there are differences in the treatments offered to men at different age ranges, few studies directly compared the treatment effects of different therapies across age groups. Most RCTs did not have age exclusion criteria. The mean/median age ranged from a low of 63 years for trials of radical prostatectomy to 72 years for trials of external beam radiotherapy. Only one RCT provided subgroup analysis according to age. Results suggest that survival benefits of radical prostatectomy compared with watchful waiting may be limited to men less than 65 years of age. Practice patterns from observational studies show that radical prostatectomy is the most common treatment option in younger men with localized prostate cancer.

Key Question 3. How do provider and hospital characteristics affect outcomes?

Results from national administrative databases and surveys suggested that provider/hospital characteristics, including radical prostatectomy procedure volume, physician specialty, and geographic region, affect outcomes. (There was no information on volume and outcomes for brachytherapy, cryotherapy, or external beam radiotherapy.) Patient outcomes varied in different locations and were associated with provider and hospital volume independent of patient and disease characteristics. Screening practices can influence the characteristics of patients diagnosed and tumors detected. Screening practices and treatment choices varied by physician specialty and across regions of the United States. These did not correlate with clinician availability. Clinicians were more likely to recommend procedures they performed regardless of tumor grades and PSA levels….

Key Question 4. How do tumor characteristics affect outcomes?

Few data existed on the comparative effectiveness of treatments based on PSA levels, histologic score, and tumor volume to identify low-, intermediate-, and high-risk tumors. We [the Minnesota EPC] focused on baseline PSA levels and Gleason histologic score. The natural history of PSA-detected tumors is not known because few men remain untreated for a long period. One report assessed 20-year outcomes in the United States from a cohort of 767 men with prostate cancer detected prior to PSA testing and treated with watchful waiting. Histologic grade was associated with overall and prostate-cancer-specific survival. Men with low-grade prostate cancers had a minimal risk of dying from prostate cancer (7 percent with Gleason score 2-4 died due to prostate cancer). Men with high-grade prostate cancers had a high probability of dying from their disease within 10 years of diagnosis, regardless of their age at diagnosis (53 percent with Gleason score 8-10 died due to prostate cancer). Estimates from large ongoing screening trials suggest that PSA increases the time of detection by 5-15 years. Therefore, it is likely that men with PSA-detected tumors will have better 20-year disease-specific survival than this cohort….

Research Gaps

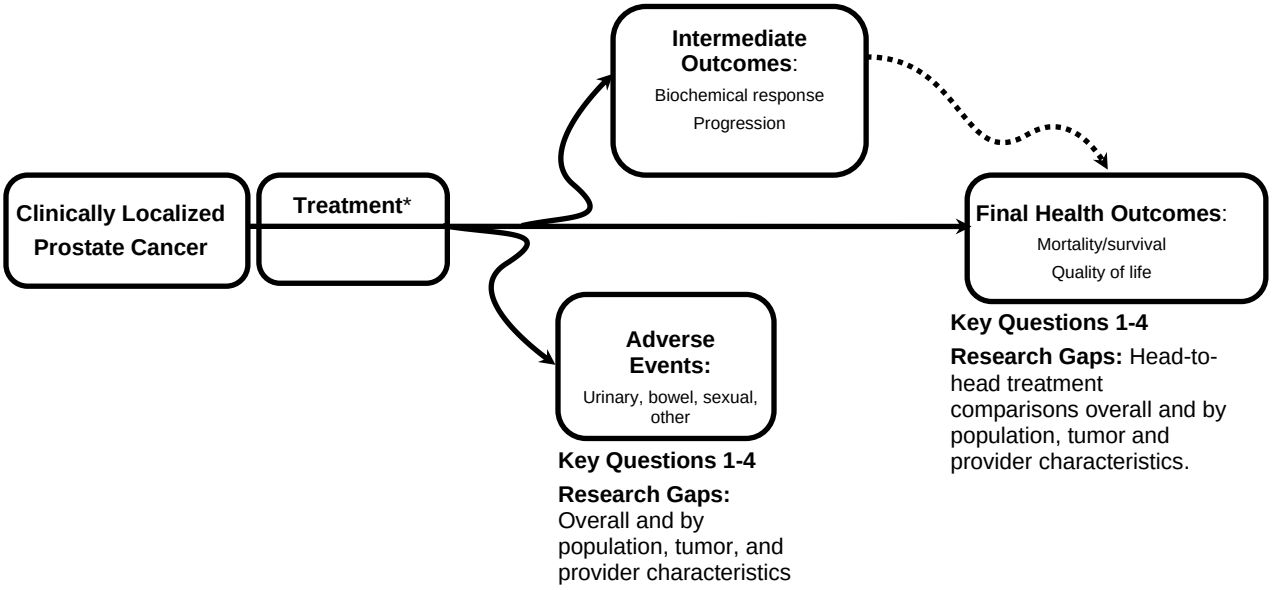
As presented in the original CER of the Minnesota EPC, the research gaps combined both the topics with insufficient evidence and the types of studies needed to address them. The CER noted the following limitations in the existing evidence for Key Question 1:

- Few randomized trials directly compared the relative effectiveness between (rather than within) major treatment categories.
- Many randomized trials are inadequately powered to provide long-term survival outcomes, with the majority reporting biochemical progression or recurrence as the main outcomes.
- Some randomized trials were old, conducted prior to prostate cancer detection with PSA testing … and used technical aspects of treatment that may not reflect current practice; therefore, their results may not be generalizable to modern practice settings.
- Wide variation existed in reporting and definitions of outcomes.
- There was little reporting of outcomes according to major patient and tumor characteristics.

- Emerging technologies have not been evaluated in randomized trials.

The analytical framework for the original CER prepared by BCBSA TEC is as follows:

Figure 1. Analytic framework for comparative effectiveness of treatments for clinically localized prostate cancer



*Includes open, laparoscopic, and robotic assisted prostatectomy, 3D conformal or intensity-modulated radiotherapy, brachytherapy, proton beam therapy, cryotherapy, high-intensity focused ultrasound, and watchful waiting or active surveillance.

The patients of interest have clinically localized prostate cancer. They undergo treatment, including the possibility of watchful waiting or delaying treatment, surgery, radiotherapy, or another approach. There are adverse events associated with these treatments, including most commonly urinary, bowel, and sexual effects. The outcomes measured may include intermediate outcomes, such as biochemical response or disease progression, or final health outcomes such as overall survival or long-term quality of life. The current research gaps identified in the CER relate to the relative lack of head-to-head comparisons of the various treatment options, their impact on both outcomes and adverse events, and the differences for various populations (e.g., age and ethnicity or disease characteristics) and types of providers.

The research gaps identified in the Minnesota EPC's CER were organized by the BCBSA TEC EPC into PICOS categories (i.e., population, intervention, comparators, outcomes, settings) as arrayed in Table 1. To summarize briefly, the evidence base amassed and evaluated by the Minnesota EPC provided insufficient evidence to address definitively any of the Key Questions regarding this important clinical issue.

Table 1. Research gaps identified in Minnesota EPC CER, as selected and categorized by the BCBSA TEC EPC

Category	Research Gap
Population	• RCTs that address relative effectiveness and adverse events of all treatments by patient characteristics (race/ethnicity, age, comorbidity) and tumor characteristics (PSA, stage, histologic grade). • Use of nonrandomized, high-quality, large prospective cohort studies or cancer registries that identify men at the time of diagnosis and collect comprehensive patient, tumor, and treatment-decision characteristics. Should report or provide data for head-to-head comparisons, adjustment for confounding factors, and use of standardized definitions.
Intervention	• Long-term, adequately powered randomized trials, particularly comparative trials, are needed on emerging technologies such as intensity-modulated radiotherapy (IMRT), proton beam radiation, laparoscopic and robotic-assisted prostatectomy, and cryotherapy • Develop new generation of educational materials to provide balanced information about the risks and benefits of treatments and assist in patient decisionmaking and incorporation of patient-centric values.
Comparator	• Adequately powered, sufficiently long, head-to-head RCTs comparing primary treatments for localized prostate cancer, especially watchful waiting, radical prostatectomy, external beam radiation therapy, brachytherapy, and androgen deprivation therapy. • Confirmatory trials where RCTs available.
Outcomes	• Standardized reporting of key clinically relevant outcomes, including overall, disease-specific, and metastatic-free survival; biochemical non-evidence of disease (bNED); adverse effects; and disease-specific quality of life/health status. • Clarify geographical differences in patient outcomes by evaluating nationally representative databases using appropriate risk adjustment. • Develop structure and process measures associated with quality of prostate cancer care. Identify factors associated with various outcomes and develop system-wide improvement methods.
Setting/other	• Investigate approaches to ensure adequate and timely recruitment in clinical trials. • Identify biomarkers to provide reliable estimates about prostate cancer aggressiveness and the relative effectiveness of treatments.

Underlying the current importance of this topic are the prevalence of disease, the concern about potential overtreatment with accompanying adverse events, and the risk of severe disease and death for a small proportion of patients with localized disease. Another contributing factor, however, is the weakness of the current state of evidence. This is due in part to the difficulties in conducting research on treatment for localized prostate cancer, which is challenging for a variety of reasons, including:

- inconsistencies in diagnosis and disease staging (for example, the same biopsy specimen may now be assigned a higher Gleason score than it would have in the past);
- the strong views among both prostate cancer patients and many treating physicians about the best course of treatment (and therefore a reluctance to participate in randomization);
- the long course of the disease, which of course benefits patients but requires long follow-up for studies;

- the fact that selection of treatment is often influenced by prostate-cancer-specific or other risk factors, which makes observational studies more difficult;
- the distinct profiles of adverse events associated with each treatment; and
- the relatively recent adoption of widespread PSA screening in the United States, relative to the average survival for those diagnosed early through PSA testing, leaving many studies of treatment effects or surveillance without sufficient follow-up to gauge the comparative effectiveness over the whole course of the disease.

Methods

Identifying Recently Published and Ongoing Studies

The literature update included both (1) studies published since September 2007, the cutoff of the literature review conducted by the Minnesota EPC; and (2) clinical trials currently underway, derived from ClinicalTrials.gov. The objective was to identify major studies that might alter or inform the list of research gaps identified in the Minnesota EPC's CER. This step was not intended to update the systematic review, which would require a broader search and more in-depth abstraction. Rather, the purpose was to identify relatively large or otherwise influential studies that might address one or more of the research gaps and, therefore, should be taken into account in identifying potential research studies. A broad scope was used to identify the pool of potential studies but a narrow set of criteria were applied to them. The TEPP was also asked to name influential articles published since the CER was released.

Search and Yield

For published studies, a MEDLINE® search was conducted using the term "prostate cancer," limited to "clinical trial." The search covered the period from the beginning of 2007 to July 2010. This search overlapped the time period used in the CER, because of the lag that sometimes occurs between publication of an article and its appearance in MEDLINE.® Of 1,395 titles screened, 212 abstracts were reviewed. Several articles were subsequently added toward the end of the pilot project, either additional papers recommended by technical experts if they otherwise met selection criteria, or articles published while the project was underway.

The pool of potential clinical trials was drawn from a search of ClinicalTrials.gov using the search term "localized prostate cancer." The search yielded 203 studies. Several of these studies were also mentioned by the TEPP.

Selection Criteria

Table 2 lists the initial study selection criteria used for both published studies and ongoing clinical trials.

Table 2. Initial inclusion criteria for published studies and ongoing clinical trials

Types of	Inclusion Criteria
Studies	• RCTs; high-quality, prospective observational studies (nonrandomized comparative studies) • Active surveillance/watchful waiting arms of otherwise excluded RCTs if patients represented a setting with broad PSA testing
Populations	• Patients diagnosed with clinically localized prostate cancer • Sample size ≥100
Interventions	Primary treatment with • Radiotherapy (external-beam and/or brachytherapy) • Radical prostatectomy (open, laparoscopic, robotic-assisted) • Active surveillance/watchful waiting • Androgen-deprivation therapy • Cryotherapy • High-intensity focused ultrasound
Outcomes	• Overall survival • Disease-specific survival/mortality • Biochemical, metastatic, progression-free survival • Adverse events • Quality of life
Multivariable analyses	Treatment interactions with • Patient characteristics, such as age, race/ethnicity, presence or absence of comorbid illness, preferences • Disease characteristics, such as Gleason score, tumor volume, screen versus clinically detected tumors • Provider/hospital characteristics, such as volume and geographic region

As the research gap list was modified by the TEPP (described below), the criteria were expanded to include studies that addressed the issue of which patients to treat and other outcomes such as satisfaction with treatment decisionmaking process. The inclusion of trials on additional interventions, e.g., pharmaceutical trials, not listed above that included an active surveillance or watchful waiting arm were excluded, to keep the list of studies manageable and focus on the key studies. More generally, articles were excluded if they did not report separately on patients with T1 and/or T2 disease. Observational studies that did not take into account potential confounders, e.g., differences in treatment groups at the beginning of the study, were also omitted. Accounting for initial differences is particularly important in treatment of localized prostate cancer, because some factors, e.g., comorbidities or age, may affect both treatment selection and outcomes.

Role and Composition of the Technical Expert and Patient Panel

The overall method proposed for this pilot project was to use a Technical Expert and Patient Panel (TEPP) to assist with the prioritization process. The intent was to elicit interdisciplinary discussion among a small group (around 9 participants) with an orientation to improving evidence in this area. This approach is primarily qualitative and builds on the BCBSA

TEC EPC's experience in leading interdisciplinary expert groups. Participation was fostered by selecting individuals with a keen interest in the issues addressed in the CER and in helping to shape future research priorities. They are national experts who are supportive of evidence-based medicine and well versed in the obstacles faced in conducting multiple, large clinical trials, especially in the context of prostate cancer. The necessary methodologic expertise included the innovative use of nonrandomized studies. This small interdisciplinary group of experts helped identify and prioritize research gaps and potential projects, taking into account which projects were feasible and potentially fundable. This pilot project can thereby help build a bridge between the synthesis of available research embodied in the CER and the conduct of future research that will target the most clinically important questions that remain to be answered.

The TEPP included practicing physicians and researchers representing an array of treatment approaches and methodologic expertise, including, for example, urology, radiation and medical oncology, family practice, biostatistics, and ethnic/population disparities. Specifically, the 11-member, multidisciplinary stakeholder Panel included two medical oncologists, a medical oncologist/hematologist, two radiation therapists, two urologists, a family practice physician, a pathologist, a biostatistician, and a consumer/patient. They came from academic medical centers, professional societies, the National Institutes of Health, and the U.S. Food and Drug Administration, but participated as individuals on the Panel, not as representatives of these organizations. Panel members were selected based on known experience, recommendations by experts, and assistance from the AHRQ Scientific Resource Center. Because of the difficulties of conducting RCTs in the field of prostate cancer, the biostatistician was selected based on his experience in using observational data in the absence of RCTs to draw causal inferences. This was not meant to exclude RCTs, but rather to widen the scope of research designs that would be considered.

This group was asked to recommend important studies published since the CER, agree upon a set of prioritization criteria, revise and prioritize the research gaps listed in the CER, and develop and prioritize a list of potential research studies to address those gaps. These tasks were accomplished through an initial one-on-one telephone call between BCBSA TEC EPC staff and each TEPP member, followed by three group conference calls as well as emails seeking feedback and prioritization. Because of difficulties in scheduling and the value of obtaining input from as many TEPP members as possible, two calls were scheduled for each of the last two conference calls. TEPP members were also asked for feedback on the pilot project itself. A process chart showing the project steps is found in Figure 2. The AHRQ Task Order Officer participated in all aspects of this pilot project. Copies of some of the interim products and means to solicit ratings or rankings can be found in Appendixes B and C.

Process for Establishing Future Research Priorities

Prioritizing Research Gaps

The BCBSA TEC EPC developed prioritization criteria for use by the TEPP derived from the AHRQ criteria used for topic selection in the Effective Health Care Program (Table 3). The criteria were tailored to fit the purposes of the future research pilot and subsequently revised by TEPP members during the first conference call. The criteria "Current Importance" and "Potential for Significant Health Impact" were used to rank both research gaps and proposed studies; the criteria "Feasibility" and "Incremental Value" were also included when prioritizing the proposed research studies. The final set of criteria is shown below and was distributed to TEPP members

each time they were asked to prioritize research gaps or studies. Interim version(s) are included in Appendix B.

Figure 2. Process chart for pilot project on future research on treatments for localized prostate cancer

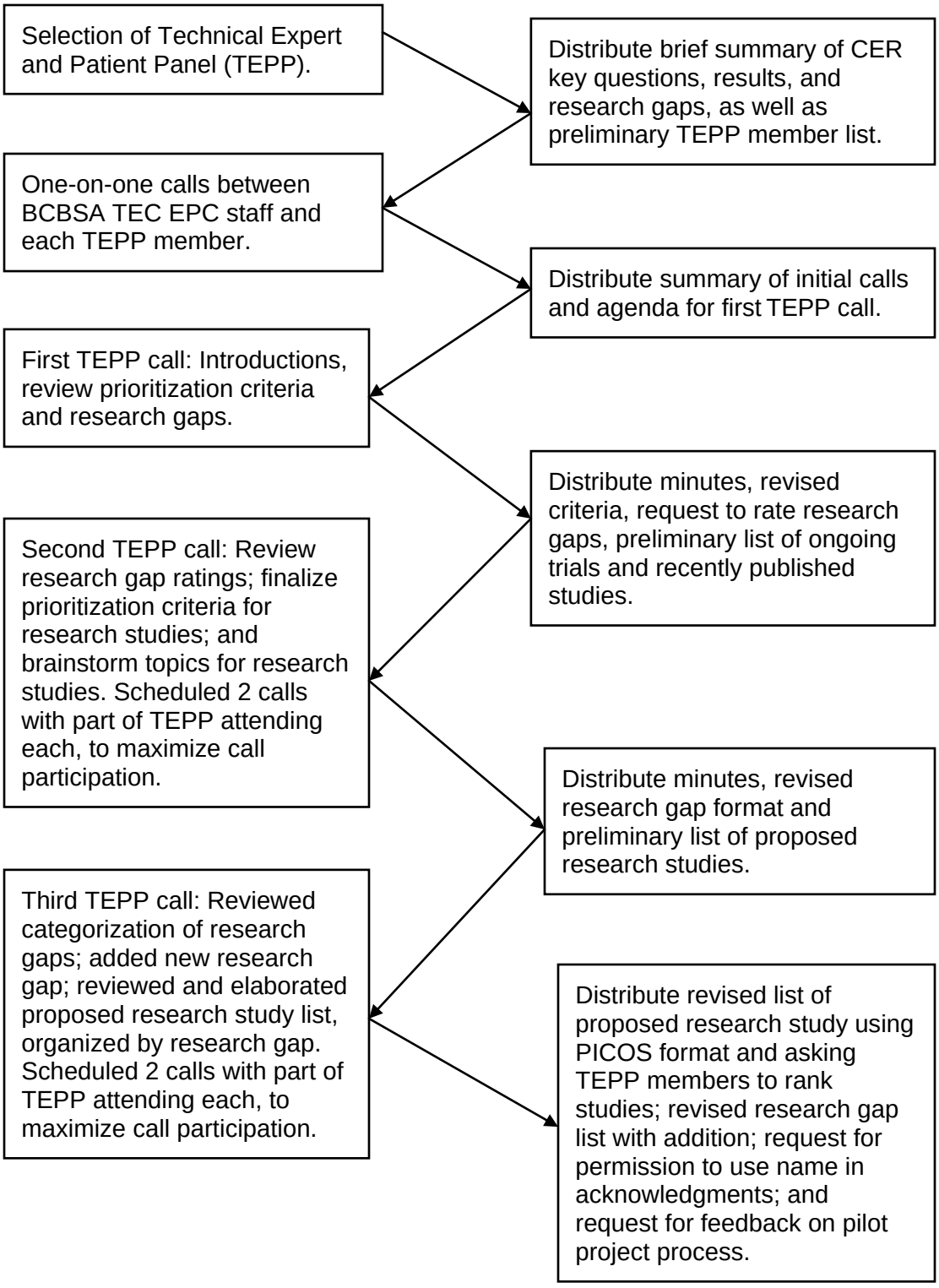


Table 3. Prioritization criteria for research gaps and proposed research studies

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 (applies to proposed research studies only)	▪ 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 (applies to proposed research studies only)	▪ Interest among researchers
	▪ Duration
	▪ Cost
	▪ Methodologic complexity (e.g., do existing methods need to be refined?)
	▪ Implementation difficulty
	▪ Patient participation
	▪ Facilitating factors
	▪ Potential funders

During the first conference call, the TEPP members also reviewed the research gaps from the initial CER and were asked to rate them via email following the call. TEPP members were asked to rate each proposed gap for each criterion—"Current Importance" and "Potential Health Impact"—on a scale from 1 to 5, with 5 being the most important. The maximum score for a research gap per member was 10. Multiple criteria and research gaps could be assigned the same number. By the second conference call, 6 of the 10 TEPP members participating in this step had responded; the biostatistician recused himself from this process because of his relative lack of expertise regarding prostate cancer. The results for each research gap were summed across both criteria for each TEPP member and then responses for all TEPP members were added together; the gaps were then rank ordered according to the gap that was rated that highest, etc. These preliminary results were distributed to the TEPP members according to the total score assigned, and these findings were discussed during the second conference call. A final list and categorization was distributed after the second conference call and approved by TEPP members.

By the end of the project, ratings had been received from 9 of the 10 TEPP members participating in this step.

Determining Appropriate and Feasible Study Design

The TEPP generated proposed research designs. The second conference call focused primarily on brainstorming ideas for projects that might address the then-final list of research gaps. BCBSA TEC EPC staff wrote up the proposals and distributed them for more in-depth discussion during the third conference call, at which time another research gap was introduced by the TEPP ("Methodologic Challenges"). After the third conference call, BCBSA TEC EPC staff rewrote the project descriptions and included all elements of the PICOS framework.

Although TEPP members generally agreed that RCTs would be the best study design to address many of the research gaps, prior experience indicated the difficulty of conducting such trials in the United States for early stage disease. During the initial one-on-one telephone calls, several major barriers to conducting RCTs were pointed out: factors relating to the medical system culture (e.g., specialists favor their own treatment, reimbursement favors treatment over surveillance), the nature of the disease (e.g., long follow-up period), and the patient (e.g., reluctance to be randomized). Furthermore, several clinical trials are currently underway (e.g., Prostate Cancer Intervention Versus Observation Trial [PIVOT; Minneapolis VA Med Ctr; PI: Tim Wilt M.D., MPH; ISRCTN007644], Prostate Testing for Cancer and Treatment [ProtecT; Oxford Radcliffe Hospital, Great Britain; PI: Freddie C. Hamdy, M.D.; ISRCTN 20141297]), and some members advocated waiting to see what these trials reported while using alternative methodologic methods in the meantime. Therefore, the primary focus in generating a list of proposed research studies was on smaller, more limited RCTs or on other research designs.

Prioritizing Proposed Studies for Each Research Gap

After the third conference call, TEPP members were asked to rank the proposed studies for each gap, ranging from 1 for the lowest priority to the number of studies under that gap for the highest, i.e., Gap 1 had 5 proposed studies, so the highest rank was 5. The rank was a global score that took all prioritization criteria into account; we did not request separate scores for each criterion. In this case, members were asked to take all prioritization criteria into account but were not asked to provide a separate rank for each. Responses were received from all TEPP members, and the responses for each study were summed and then ranked within each research gap.

Engaging Stakeholders, Researchers, Funders

Stakeholders were represented indirectly through the TEPP. The members did not formally represent specific stakeholders, but they were knowledgeable about the points of view of researchers, physicians, funders, patients, and others. Through the TEPP, these views were taken into account from the beginning of the project. Members were provided with opportunities to participate by phone and via email. In some cases, members who were not able to participate in the conference calls were individually called subsequently by BCBSA TEC EPC staff to solicit their input. Additional stakeholders will have an opportunity to provide comments when AHRQ posts this document online for publication.

Handling Conflicts of Interest

As prescribed by AHRQ, conflict of interest (COI) forms were completed by all TEPP members and staff on this project. They were reviewed initially by the project manager and delivered to AHRQ for review. There were no conflicts that were judged to preclude participation in the project. However, one potential member who initially accepted did withdraw voluntarily prior to the COI process due to a potential conflict of interest with his consulting work.

The multidisciplinary character of the TEPP and their varied stakeholder affiliations also helped to produce a balanced process. Notably, there was little discussion of specific treatment approaches or particular devices or biomarkers. Rather, the major focus of discussion was how to identify men who would benefit from treatment.

Results

Recently Published Studies and Ongoing Trials

Published Studies

Of the 212 abstracts reviewed, 30 articles were chosen for inclusion: 12 address research Gap 1; nine address Gap 2; and another nine address Gap 3 (see Appendix Table A1 for citations and brief descriptions). Two articles relevant to Gap 1 were added after final review of the table by the TEPP members; one was recommended by a TEPP member and the other was published while this report was being written.

During the initial one-on-one telephone conversations, several TEPP members also recommended two studies published in the *New England Journal of Medicine* in March 2009.[3,4] These articles examine the impact of PSA screening on prostate cancer mortality, among other outcomes, and initially might not appear to address the gaps identified in the initial Minnesota CER. However, these articles raise the issue of whether early detection of prostate cancer—and early treatment—reduces death from prostate cancer. Thus, they are relevant to Gap 1 identified by the TEPP, "Identifying Which Patients to Treat."

Schroeder et al.[3] is a very large (n=162,387) multicenter, European randomized trial designed to evaluate the effect of screening on death rates from prostate cancer, with screening conducted at approximately 4-year intervals. The median follow-up period was 9 years. More prostate cancers were detected in the screening group (8.2% vs. 4.8%). The proportion of men with cancer with a Gleason score of 7 or more was 27.8% in the screening group and 45.2% in the control group. Mortality rates began to diverge after 7 to 8 years and continued to do so. The adjusted (for interim analyses) rate ratio for death from prostate cancer in the screening group versus the control group was 0.80 (95% confidence interval [CI]: 0.65–0.95, p=0.01). To prevent one prostate-cancer death, 1,410 (95% CI: 1,142–1,721) men would need to be screened and 48 additional subjects would need to be treated. Limitations of this study include the fact that protocols differed by country, e.g., PSA cutoff value, age, use of digital rectal examination (DRE). In particular, some countries randomized patients before informed consent, so patients knew assignments before agreeing to participate (and were more compliant with screening).

Andriole et al.[4] was a large (n=76,693) multicenter trial in the United States to determine the effect of annual PSA testing and digital rectal examination (DRE) versus usual care on mortality from prostate cancer. Patients were enrolled between 1993 and 2000, and the median follow-up period was 11.5 years. There were few deaths from prostate cancer at 7 to 10 years and no significant difference between study groups (rate ratio=1.13; 95% CI: 0.75–1.70). The majority of prostate cancers were stage 2 at diagnosis with a Gleason score of 5 to 6. Compliance with screening was about 85% in the intervention group (annual PSA for 6 years; DRE for 4 years). In the control group, PSA testing increased from 40% in year 1 to 52% in year 6; and ranged from 41% to 46% for DRE. As noted in the correspondence following publication of this study, this study therefore is actually a comparison of higher versus lower levels of PSA screening, rather than an evaluation of annual PSA testing versus none.

Together, the studies by Schroeder et al.[3] and Andriole et al.[4] suggest that the benefit of PSA screening for preventing prostate-cancer related deaths may be small or nonexistent. They also raise the question of overtreatment of patients whose cancer was detected through PSA

screening, given that according to the Schroeder et al.[3] study, 1,410 men would need to be screened and 48 additional subjects would need to be treated to prevent a single prostate-cancer death. Evaluating these studies and related literature is beyond the scope of this project. However, the publication of these studies between the publications of the Minnesota EPC CER and the current project may have shifted the TEPP members' focus from how to treat to who and when to treat. TEPP members agreed that the first step is to identify whom to treat, then to decide how to treat them (i.e., comparative effectiveness of specific treatments), and finally to address racial and ethnic disparities and physician-patient decisionmaking. The latter cannot be adequately addressed without knowing the answers to the first questions.

Most of the other articles that address Gap 1, primarily retrospective studies and prospective prognostic analyses, focus on active surveillance and predictors of disease progression. Three issues evident in the active surveillance studies are that a number of men switch to active treatment in the absence of disease progression, that death from causes other than prostate cancers exceed those from prostate cancer itself, and that longer follow-up periods are needed (see, e.g., Klotz et al. 2010[5]). Several other studies examined predictors of disease progression or severity, including PSA-based measures (e.g., Radwan et al. 2007,[6] Freedland et al. 2008[7]) and MRI findings.[8] A study of men with PSA levels below 4 ng/mL at diagnosis indicated that while these men are at relatively low risk, high-grade disease is still found within this group.[9]

The studies identified relating to Gap 2 include comparative studies of alternative treatments for prostate cancer: four RCTs[10-13] and several other types of studies, including patient surveys.[14-16] However, the follow-up from any of these studies is not long enough to provide data on long-term outcomes. The studies on Gap 3 primarily address the impact of surgeon volume or other characteristics on treatment outcomes. Several studies by Vickers and colleagues suggest a definite learning curve for various types of radical prostatectomy.[17-19] Another study suggests that the specialty of the physician a patient sees after diagnosis has a strong impact on the treatment selected.[20] Additional details on all of these studies are found in Appendix Table A1.

Ongoing Trials

The review of localized prostate cancer trials at ClinicalTrials.gov yielded 13 trials of potential relevance for this pilot project. The most important trials, also mentioned by several TEPP members, are the PIVOT trial in the United States, with initial results expected in about 1 year, and the ProtecT trial in the United Kingdom, with initial results expected in about five years. In each trial, participants were randomized to one of several treatments, including either watchful waiting or active surveillance. In the ProtecT trial, enrollees were initially randomized to PSA screening and then those in whom prostate cancer was detected were randomized to treatment. These trials address Gap 1, particularly through examination of the active-surveillance arm, and Gap 2, by gauging the comparative effectiveness of surgery versus radiation therapy versus conservative management for patients with localized prostate cancer. Given the time, effort, and cost required for these trials and the fact that they are already underway, TEPP members agreed that similar trials should not be initiated. Eight other studies comparing treatments (Gap 2) are also underway, although most of them are more limited in scope (for citations and brief summaries, see Appendix Table A2). For example, they may not focus on all major treatment options or examine only a limited set of outcomes such as health-related quality of life. The three studies addressing Gap 1 focus on predictors of more aggressive disease, although in one case the population is limited to men undergoing radiation therapy. Only one

trial on treatment decisionmaking was included for Gap 3. There are additional studies on patient education but with less of a focus on joint patient-physician decisionmaking.

Prioritization of Research Gaps

As noted in the Methods section, after the first conference call TEPP members were asked to rate the proposed research gaps. Both the preliminary results based on six responses presented to the TEPP in preparation for the second conference call and the more complete results based on 9 responses are found in Appendix B. During the second conference call, members noted that the numerical sums for each research gap were relatively similar, except for the lowest ranked research gap and to a lesser degree, the highest ranked gap. While BCBSA TEC EPC staff questioned whether a different rating system should have been used, TEPP members noted that the close scores might have been due to the overlap between the different gaps. Following this discussion, BCBSA TEC EPC staff reorganized the research gaps into 3 larger categories. TEPP members endorsed this approach via email and on the last conference call. They edited some titles, moved one research gap to another category, and decided not to use the PICOS categories for this task.

The final three research gaps, in priority order, are identifying which patients to treat, the comparative effectiveness of alternative treatments for localized prostate cancer, and factors with an impact on treatment decisionmaking. During the last conference call, the TEPP members added a fourth research gap, called "Methodologic challenges," which transcends prostate cancer and applies to other important research areas as well. This late addition was not ranked.

The final, prioritized list of research gaps is shown in Table 4. The content of the gaps is largely consistent with the Minnesota CER but regrouped into fewer categories. In addition, several research gaps were added (noted in list), and the fourth gap on methodologic challenges is new.

Table 4. Prioritized list of research gaps on treatments for localized prostate cancer, 2010

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: TEPP members noted that this gap applies more broadly than prostate cancer research. It was not prioritized with the other three gaps.)** ▪ 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

Recommended Research Studies

Prioritization of Recommended Research

As described in the Methods section, during the second conference call the TEPP members began brainstorming ideas for research studies to address the proposed research gaps, then refined them, and finally prioritized them via email after the last conference call. The results of the prioritization process are shown in Table 5. The maximum potential score for a study varies with the total number of studies under each research gap. For example, there are 5 studies under Gap 1, so the maximum score for a study is 5. Summed over the 11 members responding, the maximum score for a study under Gap 1 is 55. Also, the studies address the gap generally and do not correspond to the bulleted points under each gap in Table 5.

Table 5. Potential research studies, prioritized for each research gap (n=11 of 11)

Research Gap to be Addressed (in order or priority, except for Gap 4; see note below)	**Proposed Research Study** (Detailed descriptions after table)
Gap 1: Identifying which patients to treat (Maximum possible score=55)	***Project 1.1.*** Identify predictors of disease progression (score=49)
	Project 1.2. Standardize protocols used for patients on active surveillance (score=30)
	Project 1.3a. Facilitate future research on potential biomarkers to identity patients whose disease is likely to be aggressive (score=29 [TIE])
	Project 1.3b. Evaluate whether all patients with elevated PSA scores warrant immediate biopsy (score=29 [TIE])
	Project 1.5. Investigate more accurate and reliable methods of identifying grade of disease after biopsy (score=28)
Gap 2: Comparative effectiveness of different treatments for localized prostate cancer (Maximum possible score=33)	***Project 2.1.*** Comparative effectiveness of alternative treatments within a modality such as surgery or radiation therapy (score=26)
	Project 2.2a. Evaluate frequency of use of ADT for low-risk prostate cancer (score=20 [TIE])

	Project 2.2b Long-term sequelae of treatments for localized prostate cancer (score=20 [TIE])
Gap 3: Factors with an impact on treatment decisionmaking (Maximum possible score=33)	***Project 3.1.*** Evaluate patient preferences and perceptions of risk in selecting prostate cancer treatment (score=23)
	Project 3.2. Increasing use of shared decisionmaking between physicians and patients (score=22)
	Project 3.3. Study the psychological impact of diagnosis and treatment, especially for those under active surveillance (score=21)
Gap 4: Methodologic challenges (Maximum possible score=22)	***Project 4.1.*** Exploring methods to increase patient adherence with randomization scheme (score=19)
	Project 4.2. Increasing the use of statistical modeling and other advanced methods in studies on localized prostate cancer (score=14)

NOTE: Gaps 1-3 are listed in order of priority, as established by the TEPP. Gap 4 was added on the last conference call and was not prioritized as a research gap. It applies to a large range of clinical issues, extending beyond treatments for localized prostate cancer. However, the two projects under Gap 4 were prioritized.

- The most highly ranked project to address Gap 1 is to identify predictors of disease progression. Furthermore, the score assigned to this project (49) stands out from the scores assigned to the rest of the projects under Gap 1 (28–30). These projects address the need for standardized protocols for patients on active surveillance and standardized approaches to grading disease; creating a data infrastructure that will facilitate evaluation of potentially useful biomarkers; and evaluating when biopsies should be performed in response to elevated PSA levels.
- For Gap 2, the top-ranked project addresses the comparative effectiveness of alternative treatments within a modality such as surgery or radiotherapy (Project 2.1; score=26). It is followed by a study on the use of androgen deprivation therapy among men with low risk cancer (Project 2.2a; score=20) which is tied with a study on the long-term sequelae of the treatments themselves (Project 2.2b; score=20).
- For Gap 3, the top-ranked project focuses on evaluating patient preferences and perceptions of risk in selecting treatment (Project 3.1; score=23), followed by increasing use of shared decisionmaking between patients and physicians (Project 3.2; score=22) and studying the psychological impact on patients of diagnosis and treatment (Project 3.3; score=21).
- Finally, the projects under Gap 4 on exploring methods to increase patient adherence with randomization (Project 4.1) and increasing use of statistical modeling and other advanced methods to studies on localized prostate cancer (Project 4.2) were ranked 19 and 14, respectively.

Description of Recommended Research

The specific research projects are described in more detail in the following section. They are rank ordered and the PICOS framework is used to describe each study.

Proposed Projects to Address Gap 1: Identifying Which Patients To Treat

(Maximum possible study score=55)

Project 1.1. Identify predictors of disease progression (score=49)

Context: 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 increase the likelihood of death from prostate cancer. The ability to identify those patients with aggressive disease a priori is a prerequisite to expanding the proportion of men with newly diagnosed, low-risk prostate cancer who undergo active surveillance, especially among somewhat younger otherwise healthy men.

Design: Prospective registry with clinical data at diagnosis and treatment, and follow-up outcome data. A biospecimen repository would allow analyses of novel biomarkers in the future.

Population: Patients with localized prostate cancer diagnosed in PSA era

Intervention: Active surveillance

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

Outcomes: 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)

Setting: Multi-institutional

Other: Need to collect comprehensive data on patient risk factors (those related to the disease, such as perineural invasion or inflammation, as well as comorbidities) and preferences. Might also issue Request for Proposals for ideas on how best to analyze these data.

Project 1.2. Standardize protocols used for patients on active surveillance (score=32)

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: Alternative active surveillance regimens

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

Setting: Multi-institutional

Project 1.3a. Facilitate future research on potential biomarkers to identity patients whose disease is likely to be aggressive (score=29 [TIE])

Context: 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 date with limited success, there continues to be potentially important role for biomarkers.

Design: Establish biospecimen repositories with clinical data on diagnosis, treatment, and follow-up

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 create the resources needed to test the use of novel biomarkers in the future, while providing long-term data on outcomes that would take a long time to collect. Such repositories are being established for other

studies, such as the ProtecT trial in the United Kingdom. While expensive to create and maintain, additional repositories would allow for more biomarker testing, particularly since tissue specimens are finite. In addition, given the differences in treatment regimens, populations, and possibly outcomes across studies, biospecimens from different trials might help address alternative hypotheses. The National Cancer Institute is establishing methods for each step of the process for creating and maintaining biospecimen repositories.

Project 1.3b. Evaluate whether all patients with elevated PSA scores warrant immediate biopsy (score=29 [TIE])

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 1.5. Investigate more accurate and reliable methods of identifying grade of disease after biopsy (score=28)

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 RCTs

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: Inter-rater and inter-institutional reliability, disease progression, treatment outcomes (progression-free survival [PFS], overall survival [OS])

Setting: Multi-institutional

Proposed Projects to Address Gap 2: Comparative Effectiveness of Different Treatment for Localized Prostate Cancer

(Maximum possible score=33)

Project 2.1. Comparative effectiveness of alternative treatments within a modality such as surgery or radiation therapy (score=26)

Context: 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.

Design: RCT

Population: Patients with recently diagnosed localized prostate cancer

Intervention: Treatments for prostate cancer

Comparator: Alternative treatments within a modality such as surgery (e.g., robotic-assisted laparoscopic prostatectomy vs. open radical prostatectomy) or radiation therapy (e.g., intensity-modulated radiation therapy vs. proton beam).

Outcomes: 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

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

Project 2.2a. Evaluate frequency of use of androgen-deprivation therapy (ADT) for low-risk prostate cancer (score=20 [TIE])

Context: 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. This could also be developed as a randomized, controlled trial of the use of ADT versus delayed ADT

Population: Patients with low-risk, localized prostate cancer

Intervention: ADT

Comparator: No use of ADT

Outcomes: Frequency of ADT, outcomes 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 2.2b. Long-term sequelae of treatments for localized prostate cancer (score=20 [TIE])

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). It is feasible to collect data on 10-year follow-up, for techniques used after the widespread adoption of PSA testing in the United States. Since some of these treatment effects may not emerge for 20 years, longer term follow-up will be needed as well.

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

(Maximum possible score=33)

Project 3.1. Evaluate patient preferences and perceptions of risk in selecting prostate cancer treatment (score=23)

Context: It has long been known that individual's perceptions of risk and decisions made upon them are not purely "rational," in that they 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. 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.

Design: Survey pre- and post-treatment

Population: Patients with recently diagnosed localized prostate cancer

Intervention: Any treatment for localized prostate cancer and active surveillance

Comparator: Alternative treatment or active surveillance

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

Setting: Multicenter with different types of institutions and physicians

Project 3.2. Increasing use of shared decisionmaking between physicians and patients (score=22)

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, impact on treatment choices, factors that facilitate or serve as barriers to adoption of these tools

Setting: Multicenter with different types of institutions

Project 3.3. Study the psychological impact of diagnosis and treatment, especially for those under active surveillance (score=21)

Context: 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 followup 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

Proposed Projects to Address Gap 4: Methodologic Challenges
(Maximum possible score=22)

Project 4.1. Exploring methods to increase patient adherence with randomization scheme (score=19)

Context: Trials of cancer screening in the United States have shown that some individuals in the control group undergo screening on their own (e.g., Andriole et al. 2009). If it occurs frequently enough, this unplanned crossing over of patients to a different trial arm may alter the question that can be addressed by the study. Similar patterns may occur with treatment trials, in which for example, an individual on active surveillance may 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: To be defined

Comparator: No intervention

Outcomes: Nonadherence with randomization assignment

Setting: Multicenter with varying types of institutions and conditions.

Project 4.2. Increasing the use of statistical modeling and other advanced methods in studies on localized prostate cancer (score=14)

Context: 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.[21,22] The increasing use of statistical modeling, instrumental variable analysis, and other advanced methods should be explored. For example, it is worth investigating whether some of these techniques can be applied to selecting when to treat patients with localized prostate cancer, as posed for Research Gap 1. Shepherd et al.[23] have modeled when to initiate antiretroviral treatment for individuals with HIV. The use of similar approaches to understanding when to treat localized prostate cancer might be worthwhile.

Design: Statistical modeling

Population: Patients with newly diagnosed, low-risk prostate cancer

Intervention: Treatment or active surveillance

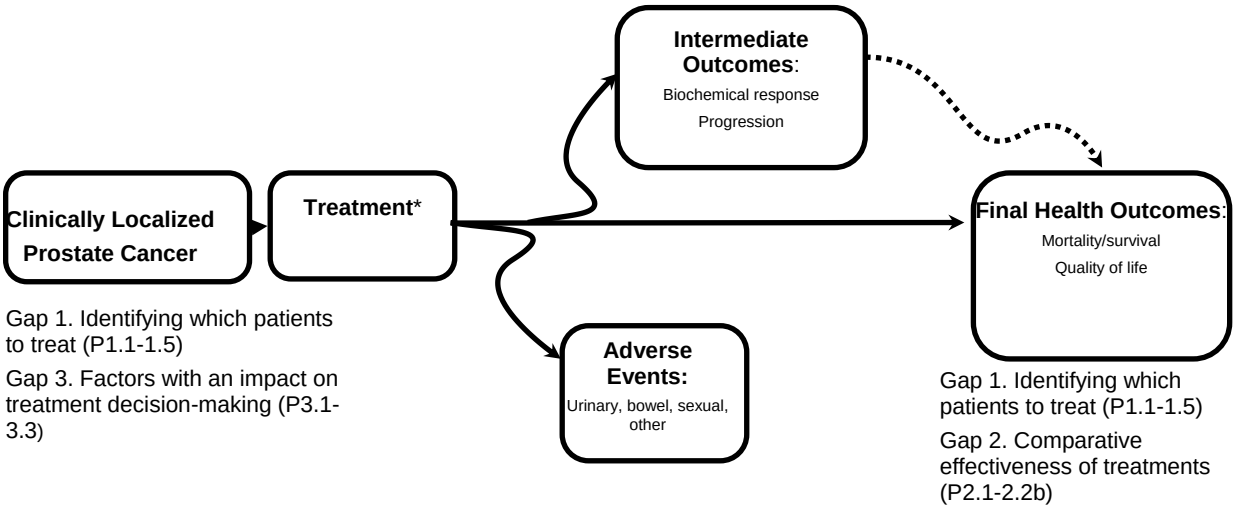
Comparator: Different treatment choices

Outcomes: Signs of disease progression, treatment among the active surveillance group.

Setting: Multicenter with varying types of institutions and conditions.

The revised analytic framework, reflecting the work of the TEPP and the proposed research studies, is shown in Figure 3. The proposed projects are indicated as P1.1 for Project 1.1, etc. As shown, projects are proposed to address each of the research gaps. Furthermore, compared to the original analytic framework, shown in Figure 1, additional research gaps and projects have been identified that focus on the treatment decision.

Figure 3. Revised analytic framework for comparative effectiveness of treatments for clinically localized prostate cancer



*Includes open, laparoscopic, and robotic assisted prostatectomy, 3D conformal or intensity-modulated radiotherapy, brachytherapy, proton beam therapy, cryotherapy, high-intensity focused ultrasound, and watchful waiting or active surveillance.
NOTE: P1.1-1.5 refers to proposed research study 1.1 to 1.5, etc.

Discussion

The treatment of localized prostate cancer is a high-priority issue due to the prevalence of disease, concern about potential overtreatment with accompanying adverse events, and the potential for severe disease and death for a small portion of patients. An overriding concern, however, is the weakness of the current state of evidence to guide individual patient decisionmaking. The difficulties of conducting research on treatments for localized prostate cancer include inconsistencies in diagnosis and disease staging; strong views among both patients and treating physicians about the best course of treatment; and the long course of the disease for most patients, making outcomes of the disease and treatment difficult to evaluate.

Because of the well-recognized difficulties in maintaining robust, long-term randomized controlled trials on localized prostate cancer in the United States, the core of our approach to this pilot project was to convene an interdisciplinary Technical Expert and Patient Panel (TEPP). We recruited a group of individuals who had a keen interest in comparative effectiveness research; who were supportive of evidence-based decisionmaking; and who were well-versed in the obstacles faced in conducting large clinical trials, especially in the case of prostate cancer. The Panelists were drawn from an array of clinical disciplines, including urology, radiation and medical oncology, family practice, pathology, and also including a biostatistician specializing in innovative approaches to using observational data and a consumer participant. Although affiliated with various professional societies and other stakeholder organizations, Panel members participated as knowledgeable individuals and not as representatives of the respective organizations with which they were affiliated. Our experience in the pilot project was that the TEPP members meshed to provide new insights into prioritizing research gaps and a diversity of approaches to the proposed research studies to address these gaps.

Most notably, the TEPP reframed the most important underlying research question in the field. While most prior formulations had focused on comparing treatment strategies, the Panel concurred that the critical question is how to identify the patients with newly diagnosed, localized prostate cancer who would benefit from early treatment. And upon reflection, this is indeed the a priori question. To assess the comparative effectiveness of treatments, the prerequisite should be to compare them in a population that is likely to have more aggressive disease and therefore benefit from early treatment. Racial and ethnic disparities in treatments and outcomes were acknowledged as important, but again, it is difficult to address this issue without knowing more about which patients should be treated and which treatments will work best for them.

In his comments on this project, one of the TEPP members summarized the challenges well:

> Many men will die “with prostate cancer” but not “from prostate cancer” and will never have any cancer related symptoms. Since all treatments have side effects—with some being quite significant—the potential for overtreatment is a real problem in this disease. Nevertheless about 32,000 men die yearly from this disease, while many others have cancer related pain. Thus, the single biggest challenge for researchers is to identify a means to distinguish lethal from nonlethal prostate cancer. Without this information we are likely to undertreat or overtreat our patients. Even within these broad categories, prostate tumors may

> have very different characteristics which may ultimately guide treatment decisions. Not all prostate tumors are like other prostate tumors, and they do not all respond to therapy in the same ways.
>
> It is unfortunate that as we attempt to "crack the code" of lethal prostate cancer we are left with biospecimens and cancer registries as our tools. The current state of the science is not quite ready for prospective randomized trials of genetic/molecular markers of potential prostate cancer lethality. However, ultimately, that is what will be needed to make a meaningful difference.

Also notable, the TEPP, while acknowledging the RCT as the ideal, recognized the need for alternative methodologies to address both questions of who should be treated and questions of the comparative effectiveness of treatments. The TEPP members held a range of views on what can be accomplished outside of clinical trials, and the final list of studies contains a mix of research designs. The TEPP envisioned the use of prospective registries of patients under active surveillance with detailed clinical data at diagnosis, treatment and follow-up. Linked to this would be a biospecimen repository that would permit future analyses of novel biomarkers. A corollary is to standardize protocols used for patients on active surveillance, a step that would yield more robust data and enable aggregation across a number of studies or sites.

The TEPP highlighted two important and large RCTs that are presently underway: the PIVOT trial in the United States, with initial results expected in about one year, and the ProtecT trial in the United Kingdom, with initial results expected in about five years. In each trial, participants were randomized to one of several treatments, including either watchful waiting or active surveillance. In the ProtecT trial, enrollees were initially randomized to PSA screening and then those in whom prostate cancer was detected were randomized to treatment. Given the time, effort, and cost required for these trials and the fact that they are already underway, TEPP members agreed that similar trials should not be initiated.

Ultimately, a major focus was put on methodologic issues, both for RCTs and observational studies. The TEPP added to the additional list of evidence gaps in localized prostate cancer a "meta-gap" on methodologic challenges, a gap generalizable to diseases and settings beyond localized prostate cancer. Noting that some RCTs have been difficult to interpret because of unplanned crossover of patients from one arm to another, the TEPP endorsed the need to explore methods to increase patient adherence with randomization schemes of RCTs. And because it is often difficult to conduct RCTs on the major questions of interest, because of their cost and complexity, the Panel also supported advancing the application of statistical modeling, instrumental variable analysis, and other advanced methods that might replicate some of the strengths of a randomized controlled trial, but use observational data.

Finally, we offer some observations on the pilot project. Our observations incorporate perspectives from both the EPC and from members of the TEPP. First, convening teleconferences was an effective way of leveraging the synergies of an interdisciplinary group, and the Panelists enjoyed participating in these discussions. As a practical matter, however, it was not always possible to schedule the entire group in a single conference call. Most of the teleconferences had to be held in two sessions, with about half of the participants on each call. This was a workable arrangement, but less desirable than convening the entire group.

Second, while we used a process of rank-ordering the research study priorities, in many respects we found the qualitative discussions more informative. It would be helpful in the future to get a deeper understanding of the methodologies available to elicit preferences, especially in small groups. On the other hand, the clustering of results might also reflect the diversity of views within the Panel. The members generally agreed on the highest priority, but beyond that, they held diverse views and no prevailing consensus emerged around other priorities.

Third, we found that it was easier to apply the process to prioritize research gaps and identify at a high level projects that would address those gaps. However, we could only sketch out the potential research studies at a very general level. Fleshing out research studies takes considerable time and effort. Within the scope of the pilot project, and likely subsequent future research needs projects, the approach to describing studies must necessarily be general. As one member noted, the best way to get good proposals to fill specific gaps may be to issue a request for proposals (RFP). Indeed, it was the EPC's expectations prior to the pilot project that we would be able to delineate proposed research studies with sufficient detail to support another organization in developing an RFP. However, we do not think that specification of the core elements pertinent to an RFP could be achieved within the scope of the pilot project.

Fourth, a limitation that was an artifact of the pilot project is that two years had elapsed between the completion of the comparative effectiveness review and the start of the future needs project. Thus, the evidence base had evolved since the original formulation of future research needs.

Conclusions

The treatment of localized prostate cancer is a high-priority issue due to the prevalence of disease, concern about potential overtreatment with accompanying adverse events, and the potential for severe disease and death for a small portion of patients. An overriding concern, however, is the weakness of the current state of evidence to guide individual patient decisionmaking. Because of the well-recognized difficulties in maintaining robust, long-term RCTs on localized prostate cancer in the United States, the core of our approach to this pilot project was to convene an interdisciplinary TEPP. Our experience in the pilot project was that the TEPP members meshed to provide new insights into prioritizing research gaps and a diversity of approaches to the proposed research studies to address these gaps. Most notably, the TEPP reframed the most important underlying research question in the field. While most prior formulations had focused on comparing treatment strategies, the Panel concurred that the critical question is how to identify the patients with newly diagnosed, localized prostate cancer who would benefit from early treatment. Racial and ethnic disparities in treatments and outcomes were recognized as important, but again, it is difficult to address this issue without knowing more about which patients should be treated and which treatments will work best for them. While acknowledging the RCT as the ideal, the TEPP recognized the need for alternative methodologies to address both questions of who should be treated and questions of the comparative effectiveness of treatments.

To address who should be treated, the Panel envisioned the use of prospective registries of patients under active surveillance. Linked to this would be a biospecimen repository that would permit future analyses of novel biomarkers. The TEPP also identified "meta-gaps," methodologic challenges generalizable to diseases and settings beyond localized prostate cancer. For RCTs, the Panel endorsed the need to explore methods to increase patient adherence with randomization schemes, because unplanned crossover confounds interpretation of trial results. The Panel also supported advancing the use of statistical modeling, instrumental variable analysis, and other advanced methods that might replicate some of the strengths of a randomized controlled trial, but use observational data, which is often more feasible to obtain than launching a de novo RCT.

We offer some lessons learned from the pilot project that would be useful to apply to ongoing efforts to develop future research needs white papers prepared in conjunction with comparative effectiveness reviews.

- Convening teleconferences was an effective way of leveraging the synergies of an interdisciplinary group and enjoyable for the participants.
- Although we used a process of rank-ordering the research study priorities, we found the qualitative discussions more informative.
- In our experience, the process of quantitative rank ordering of priorities did generally not distinguish sufficiently among options.
- We recommend an AHRQ EPC methods project that will review the literature on eliciting preferences, and make recommendations for the application of such methodologies to future research needs projects conducted in conjunction with comparative effectiveness reviews.

- The pilot process was successful for prioritizing research gaps and identifying, at a high level, projects that would address those gaps. But the scope of the pilot project was such that potential research studies could only be sketched out at a very general level.
- To achieve a greater richness in the thinking about potential research studies, we recommend generating ideas for such studies only for the highest priority evidence gap.

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Abbreviations

ADT	androgen-deprivation therapy
AHRQ	Agency for Healthcare Research and Quality
BCBSA	Blue Cross and Blue Shield Association
bNED	biochemical non-evidence of disease
CER	comparative effectiveness review
COI	conflict of interest
DRE	digital rectal examination
EPC	Evidence-based Practice Center
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IMRT	intensity-modulated radiotherapy
N	sample size
OS	overall survival
PICOS	patients, interventions, comparators, outcomes, settings
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PFS	progression-free survival
PROTECT	Prostate Testing for Cancer and Treatment
PSA	prostate-specific antigen
RCT	randomized, controlled trial
RFP	request for proposals
RP	radical prostatectomy
RT	radiotherapy
T1	tumor stage 1
T2	tumor stage 2
TEC	Technology Evaluation Center
TEPP	Technical Expert and Patient Panel

Appendix A. List of Recently Published and Ongoing Studies

Table A-1. Recently published studies

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
GAP 1: IDENTIFYING WHICH PATIENTS TO TREAT	Shappley WV, Kenfield SA, Kasperzyk et al. Prospective determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort. J Clin Oncol 2009; 27:4980-5.	To examine the consequences of deferred treatment as initial management in a contemporary prospective cohort of American men with prostate cancer.	Prospective study based on the Health Professional Follow-up Study	342 (of 3331 followed with prostate cancer) Subjects initially enrolled in 1986 FU: mean = 8.3 yrs (SD=4.6)	Deferred treatment or watchful waiting	Time to initiation of active treatment, time to metastasis or death due to prostate cancer	51% remained untreated throughout follow up (mean=7.7 yrs); remainder treated an average of 3.9 yrs after diagnosis. Factors associated with progression to treatment included younger age, higher clinical stage, higher Gleason score, and higher PSA at diagnosis. Rates of metastasis and death from prostate cancer were similar between those who chose immediate treatment and those who deferred it. Of those who deferred treatment, 63.2% were stage T1; 34.1%, T2; 2.3%, T3; 0.3%, N1/M1. About 75% had a Gleason score < 6.
	Andriole GL, Crawford D, Grubb RL III et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360:1310-9.	To determine the effect of annual PSA testing and digital rectal examination (DRE) on mortality from prostate cancer.	RCT	76,693 1993-2001 Multicenter in US FU: median = 11.5 yrs	Screening (PSA and DRE) versus usual care	Cause-specific mortality, cancer incidence, staging, and survival	Few deaths from prostate cancer at 7-10 yrs and no significant difference between study groups (rate ratio = 1.13; 95% CI: 0.75, 1.70). Majority prostate cancers were stage 2 at diagnosis with Gleason score of 5-6. Compliance with screening was about 85% in the intervention group (annual PSA for 6 years; DRE for 4 yrs). In the control group, PSA testing increased from 40% in year 1 to 52% in year 6; and ranged from 41% to 46% for DRE.

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	Schroder FH, Hugosson J, Roobol MJ et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360:1320-8.	To evaluate the effect of screening with PSA on death rates from prostate cancer.	RCT; but protocols differed by country, e.g., PSA cutoff value. In some countries, patients knew assignments before agreeing to participate and were more compliant with screening.	162,387 Multicenter Europe FU: median = 9 yrs	PSA screening (~once every 4 yrs) or not	Overall and prostate cancer mortality.	More prostate cancers were detected in the screening group (8.2% vs. 4.8%). The proportion of men with cancer with a Gleason score of 7 or more was 27.8% in the screening group and 45.2% in the control group. The adjusted (for interim analyses) rate ratio for death from prostate cancer in the screening group vs. the control group was 0.80 (95% CI:0.65, 0.95, p=0.01). Mortality rates began to diverge after 7 to 8 years and continued to do so. To prevent one prostate-cancer death, 1410 (95% CI: 1142-1721) men would need to be screened and 48 additional subjects would need to be treated.
	Lu-Yao GL, Albertsen PC, Moore DF et al. Outcomes of Localized Prostate Cancer Following Conservative Management. JAMA 2009; 302(11):1202-9.	To evaluate the outcomes of clinically localized prostate cancer managed without initial attempted curative therapy in the PSA era.	Retrospective	14,516 1992-2002 SEERS registry FU: median = 8.3 yrs	Conservative management	10-year overall survival, cancer-specific survival, and major cancer-related interventions.	Ten-year disease-specific mortality for men aged 66 to 74 for moderately differentiated disease was 60% to 74% lower than earlier studies: 6% (95% CI: 4%, 8%) in the contemporary PSA era (1992-2002) versus 15% to 23% reported in studies of earlier eras (1949-1992).
	*Shao Y-H, Albertsen PC, Roberts CB et	To describe the risk profiles and treatment patterns	Retrospective	123,934	Radical prostatectomy, brachytherapy,	Active treatment (surgery or	Men with PSA levels below 4 ng/dl made up 14% of new prostate cancer cases. 54% of them had low-risk

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	al. Less is more: Risk profiles and treatment patterns among men diagnosed as having prostate cancer and a prostate-specific antigen level below 4.0 ng/ml. Arch Intern Med 2010; 170:1256-61. Invited commentary by Hoffman RM, Zeliadt SB, The cautionary tale of PSA testing, pp. 1262-3.	of patients with prostate cancer and PSA levels below 4 ng/ml at the time of diagnosis.		2004-2006 16 SEERS registries FU: Unclear	external beam radiation therapy, conservative management	radiation therapy)	disease, and 97.3% had T1 or T2a disease. More than 75% received active treatment, comparable to rates among those with PSA levels between 4.0 and 20.0 ng/ml. In the low PSA group, treatment occurred more often among the screen-detected cancer even though these patients were less likely to have high-grade disease (OR, 0.67; 95% CI: 0.60, 0.76).
	Eggener SE, Mueller A, Berglund RK et al. A multi-institutional evaluation of active surveillance for low risk prostate cancer. J Urol 2009;	To evaluate the actuarial rates and predictors of remaining on active surveillance, the incidence of cancer progression, and the pathological findings of delayed radical	Retrospective	262 1991-2007 4 ctrs in US and Canada FU: Median (IQR) = 29 mos (15, 52); 19% of	Active surveillance, followed by radical prostatectomy for some pts.	Probability and predictors of remaining on active surveillance, incidence of cancer progression, and pathological findings of delayed radical	Patients underwent second biopsy to confirm initial findings before starting active surveillance. They were also 75 years old or younger and had a life expectancy of more than 10 years. 2- and 5-yr probabilities of remaining on active surveillance were 91% and 75%, respectively. Predictors of leaving active surveillance were having cancer on the second biopsy (HR 2.23, 95% CI: 1.23, 4.06; p=0.007) and more cancerous cores from the 2 biopsies

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	181:1635-41.	prostatectomy.		pts had > 5 yrs follow-up		prostatectomy	combined (p=0.002). Age, PSA, clinical stage, prostate volume, and number of total biopsy cores sampled were not predictors. 43 of 262 pts underwent delayed treatment, and 95% of those did not have disease progression at a median followup 23 mos after treatment. Also, predictors of delayed treatment were apparently identified by univariate Cox regression; no multivariable analysis was performed.
	*Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2009; 28:126-31.	Update and reanalysis of cohort first reported in 2002; objective is to evaluate active surveillance, with decision to intervene based on PSA kinetics and/or histologic progression.	Prospective, single arm study	450 1995-2003 FU: Median = 6.8 yrs.	Active surveillance; patients offered definitive treatment if PSA doubling time < 3 yrs, Gleason score progression to 4 + 3 or greater, or unequivocal clinical progression (palpable node).	PSA doubling time, Gleason upgrade, reclassification to higher risk, cause-specific survival, overall survival	92% were T1 – T2a; 85% had PSA $\leq$ 10 ng/ml at baseline; and 83% had Gleason score $\leq$ 6. Median age was 70.3 yrs. 71% were favorable risk by D'Amico criteria. 21.6% of patients died, with 10-year overall survival of 68% (95% CI: 62%, 74%). There was no difference in overall survival between patients still on surveillance and those treated radically. 5 men died of prostate cancer; all had been reclassified as higher risk and offered radical treatment. 135 men discontinued surveillance, with 14 due to personal preference and 8 unknown; the most common reasons were short PSA doubling time (n=65) and grade progression (n=36). The most common treatment was radiation therapy plus ADT, followed by surgery and ADT alone. The hazard ratio for non-prostate cancer to prostate cancer is 18.6.
	Hugosson J, Carlsson S,	To assess the effects of inviting	RCT but participants	19,904	PSA screening every 2 years	Prostate-cancer mortality	In the experimental group invited to undergo PSA screening, 76%

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	Aus G et al. Mortality results from the Goteburg randomised population-based prostate-cancer screening trial. Lancet 2010; published online 1 July. Comment by Neal DE, also published online 1 July.	individual to undergo PSA screening every 2 years.	randomized before invited to participate. Authors state that this allows them to gauge acceptance of screening program as well as its impact on prostate cancer mortality at a population level.	1994 Goteborg, Sweden FU: 14 years			participated at least once and 11.4% were diagnosed with prostate cancer. The cumulative incidence of prostate cancer was higher in the screened group than in the control group (12.7% vs. 8.2%; HR 1.64, 95% CI: 1.50, 1.80, p<0.0001) Median follow-up after diagnosis was 6.7 years (IQR: 3.1-9.5) in the screening group and 4.3 yrs (IQR: 2.1-7.1) in the control group. The proportion having curative treatment was similar between the two groups, but the percentage with low risk disease at diagnosis was 6.1% in the screening group vs. 2% in the control group. The cumulative risk of death from prostate cancer at 14 years was 0.5% in the screening group versus 0.9% in the control group (rate ratio: 0.56; 95% CI: 0.39-0.82; p=0.002). The rate ratio of prostate cancer death among the screening group who underwent PSA testing and the control group was 0.44 (95% CI: 0.28-0.68; p=0.0002), whereas the rate ratio of prostate cancer death among the screening group who did not undergo PSA testing and the control group was 1.05 (95% CI: 0.62-1.78; p=0.84). Overall, to prevent one cancer death, 293 (95%CI: 177-799) men needed to be screened and 12 diagnosed. NOTE: No effort was apparently made to determine whether any men in the control group underwent PSA screening; nor is it clear how common that is likely to be in the Swedish

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
							health care system. Neal pointed out that these results might differ in countries, such as the US, with a higher pre-existing level of PSA use; and as the authors and Neal state, longer followup is needed.
	Rosario DJ, Lane JA, Metcalfe C et al on behalf of ProtecT Study Group. Contribution of a single repeat PSA test to prostate cancer risk assessment: Experience from the ProtecT study. Eur Urol 2008; 53:777-84.	To determine whether a single repeat PSA test can help discriminate cancer from non-cancer-related PSA elevation among men with initial PSA of 3 to 19.9 ng/ml	Analysis of RCT data	4102 (7.6% of sample in trial) 2002-2006 Multicenter in UK FU: Not relevant	None	Presence of cancer on biopsy	Men with 20% drop in PSA on second test had lower risk of cancer (OR=0.43; 95% CI: 0.32, 0.52; p<0.001) and of high-grade cancer (OR=0.29; 95% CI: 0.19, 0.44; p<0.001). The effect of percentage reduction was greater in younger men (≤ 60 yrs). However, no level of PSA reduction confidently predicted absence of cancer (area under ROC curve for % change in PSA is 0.647 for any prostate cancer and 0.739 for high grade prostate cancer, compared to other men in sample; area under ROC for initial PSA = 0.624 and 0.708, respectively). But risk reduction of high grade cancer would decline from 4% to 0.5%, 6% to 2%, and 15% to 2% for men ≤60 yrs with initial PSA of 3.0-3.99, 4.0-5.99, and ≥6 ng/ml, respectively.
	Freedland SJ, Hotaling JM, Fitzsimons et al. PSA in the new millennium: A powerful predictor of prostate cancer	To examine the prognostic significance of preoperative PSA to predict pathological stage and biochemical progression among men undergoing	Multivariable prognostic analysis	912 2000-2006 Multicenter at VA hospitals FU: Median	Radical prostatectomy	Tumor stage, biochemical progression	Higher initial PSA levels (stratified as < 10, 10.0-19.9, or ≥ 20 ng/ml) are associated with increased odds of extracapsular extension, positive surgical margins, and seminal vesicle invasion and increased risk of biochemical progression. Among men with initial PSA < 10 ng/ml, higher initial PSA within this range is associated with positive surgical

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	prognosis and radical prostatectomy outcomes—results from the SEARCH database. Eur Urol 2008; 53:758-64. Discussion on pp. 765-6.	radical prostatectomy.		PSA follow-up = 26 mos			margins and higher risk of biochemical progression. Both analyses account for multiple clinical preoperative characteristics. Adjusting for multiple comparisons was not mentioned. Authors note that PSA doubling time may be more strongly associated than biochemical recurrence with prostate cancer death.
	Concato J, Jain D, Lis WW, Risch HA, Uchio EM, Wells CK. Molecular markers and mortality in prostate cancer. BJUI 2007; 100:1259-63.	To report on contemporary experience among men on active surveillance.	Retrospective ; descriptive and prognostic analysis	321 1991-? 1 institution in US FU: Median = 3.6 yrs	Active surveillance	Active treatment	24% received definitive treatment, with median time to treatment of 3 yrs. Two-thirds had clinical evidence of disease progression, while one-third were treated because of personal choice without signs of disease progression. Median PSA doubling time was 6.7 yrs. PSAD at diagnosis and increase in Gleason grade on repeat biopsy were significant predictors of time to treatment.
	Stattin P, Holmberg E, Johansson J-E et al on behalf of National Prostate Cancer Register (NCPR) of Sweden. Outcomes of localized prostate	To assess prostate cancer mortality and risk of death from competing causes in patients in the NPCR of Sweden follow-up study with low- or intermediate-risk prostate cancer.	Retrospective	6,849; 2,686 low risk (T1, Gleason 2-6, serum PSA <10 ng/ml) 1997-2002 National in Sweden	Surveillance (active or watchful waiting), radical prostatectomy, or radiation therapy	Death from prostate cancer, competing causes, or all causes.	Among low risk patients, the calculated 10-year prostate-cancer-specific mortality was 2.4% (95% CI: 1.2%, 4.1%) in the surveillance group (n=1,085) and 0.7% (95% CI: 0.3%, 1.4%) in the curative intent group (prostatectomy and radiotherapy; n=1,601). Among both intermediate- and low-risk patients, the 10-year risk of dying from competing causes was 19.2% (95% CI: 17.2%, 21.3%) in the surveillance group and 10.2% (95% CI: 9.0%, 11.4%) in the curative intent

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	cancer: National Prostate Cancer Register of Sweden follow-up study. J Natl Cancer Inst 2010; 102:1-9.			FU: median = 8.2 yrs			group. Although the authors tried to account for selection bias in the choice of treatment with the data available, they state the efforts "were not sufficient to compensate for the confounding by indication to treatment by treatment selection."
	Fradet V, Kurhanewicz J, Cowan JE et al. Prostate cancer managed with active surveillance: Role of anatomic MR imaging and MR spectroscopic imaging. Radiol 2010; 256:176-83.	To determine the prognostic role of MR and MR spectroscopic imaging, compared to transrectal ultrasonography, at diagnosis in disease progression among patients on active surveillance.	Retrospective ; all three diagnostic tests repeated in each patient	114 1992-2007 1 institution in US FU: Median=59 mos	Active surveillance	Changes in PSA velocity, Gleason grade, or treatment regimen	Adjusted multivariable models indicated that presence of a lesion suggestive of cancer on MR imaging had a hazard ratio of 4.0 (95% CI: 1.1, 14.9) for a Gleason score upgrade on subsequent biopsy. This was the only statistically significant finding, i.e., MRI was not indicative of other outcomes, and other imaging techniques were not significantly associated with the outcomes. Other statistics, such as sensitivity and specificity were not reported. The authors note that imaging techniques have advanced since these tests were done and that MR imaging at 1.5T is more accurate for larger than for smaller lesions.
	Radwan MJ, Yan Y, Luly JR et al. Prostate-specific antigen density predicts adverse pathology and increased risk	To determine whether PSA density is an independent predictor of adverse pathologic findings and biochemical	Prospective, prognostic analysis	1,327 1990-2003 1 institution in US	Biopsy followed by radical prostatectomy	Seminal vesicle invasion, extracapsular extension, positive surgical margins, biochemical recurrence	PSA density was measured using both ultrasound and pathology to estimate prostate volume. In a multivariable analysis also including biopsy Gleason score and clinical stage, both density measures were independent predictors of all outcomes. Pathologic PSAD is a stronger predictor than ultrasound PSAD, although pathological PSAD

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	of biochemical failure. Urol 2007; 69:1121-7.	recurrence and whether it outperforms PSA.		FU: Median = 31 mos.			can only be measured after surgery. Ultrasound PSAD had a slightly higher C index for some outcomes than PSA, including extracapsular extension (0.695 vs. 0.683) and positive surgical margins (0.640 vs. 0.613). The authors suggest the need to develop more accurate estimates of prostate volume using ultrasound.
GAP 2: COMPARATIVE EFFECTIVE-NESS OF DIFFERENT TREATMENTS FOR PROSTATE CANCER	Donnelly BJ, Saliken JC, Brasher PMA, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer 2010; 115:4695-704 and 116:323-30. Editorial by WR Lee on pp. 270-2.	To compare cryoablation to external beam radiotherapy in localized prostate cancer patients.	Randomized, unblinded, noninferiority trial, stratified by biopsy tumor classification and Gleason score.	244 12/97-2/03 1 institution in Canada FU: Median=100 months	ADT using LR-RH plus cryotherapy OR external beam RT	Disease progression, disease-specific survival, overall survival, quality of life. Failure defined as biochemical failure, radiologic evidence of disease, or initiation of further prostate cancer treatment. Repeat cryotherapy within 6 mos was not considered treatment	Observed difference in disease progression = 0.2% (95% CI: -10.8%, 11.2%). Cannot rule out inferiority, defined a priori as 10%. Cryotherapy patient reported more acute urinary dysfunction, which improved over time; the cryotherapy group reported poorer sexual function from 3 to 36 months, when the study ended. Trial closed prematurely because of diminishing patient accrual.*

* Although title refers to "localized" prostate cancer, eligible participants include those with T2 or T3 cancer and no evidence of lymph node or distant metastases. The authors explain "there was no unanimity among the trial clinicians regarding clinical staging (at least 3 opinions)...if a patient had no palpable abnormalities but had positive biopsies in the gland bilaterally, then his biopsy tumor classification was bT2C. If the biopsies revealed microscopic extraprostatic extension of seminal vesicle involvement, then the biopsy tumor classification was bT3C."

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
						failure.	
	Dahl DM, Barry MJ, McGovern FJ et al. A prospective study of symptom distress and return to baseline function after open versus laparoscopic radical prostatectomy. J Urol 2009; 182:956-65.	To conduct a more detailed examination of the functional outcomes of open and laparoscopic prostatectomy	Prospective, concurrent, single institution	206 6/03-6/04 1 institution in US FU: 1 yr	Series of questionnaires (Symptom Distress Scale, UCLA Prostate Cancer Index, Prostate Cancer Outcomes Study, and SF-36) for consecutive patients undergoing open vs. laparoscopic radical prostatectomy	Return to baseline levels for continence, erectile dysfunction, or physical function	Tx groups similar on measured variables. No statistically significant differences in return to baseline levels between the treatment groups. More complications among laparoscopic patients but number low in both Tx groups. 1 death in open prostatectomy group of MI one week post-discharge; 2nd died in accident 8 mos later. Authors conclude similar functional outcomes from both procedures.
	Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: A prospective study. World J Urol 2009; 27:607-12.	To compare the oncological and functional outcomes reported with radical retropublic prostatectomy versus brachytherapy among low risk prostate cancer patients.	RCT	200 (26 of them lost to follow-up by 5 yrs) 5/99-10/02 Italy FU mean=68.2 mos (range: 60, 102 mos	Bilateral nerve sparing radical retropublic prostatectomy vs. brachytherapy	Biochemical disease-free survival rate, pre- vs. post-scores on IPSS (International Prostate Symptom Score), IIEF (International Index of Erectile Function)-5, EORTC-QLQ-C30/PR25), rates of erectile function recovery and	Similar 5-year biochemical disease-free survival rates (91.0% vs. 91.7%). Postop urinary symptoms significantly greater and more persistent in brachytherapy group, but erectile function better. However, by 5 years no significant difference between treatment groups. Authors note need for larger studies with longer followup to confirm findings.

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
						postop urinary disorders.	
	SPCG-4: Bill-Axelson A, Holmberg L, Filen F et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: The Scandinavian Prostate Cancer Group-4 randomized trial. J Natl Cancer Inst 2008; 100:1144-54	To determine whether the absolute and relative benefits of surgical treatment would increase during longer follow up.	RCT	695 1989-1999 Scandinavia FU: 12 yrs	Radical prostatectomy vs. watchful waiting	Prostate cancer death; metastases	More prostate deaths and distant metastases in watchful waiting group. Group difference in cumulative incidence of prostate deaths and distant metastases stable after 10 years. Limitation: Not among a population where most cancer detected through PSA screening as in US.
	D'Amico AV, Chen M-H, Renshaw AA, Loffredo B, Kantoff WP. Risk of prostate cancer recurrence in men treated with radiation alone or in conjunction with combined	To determine the risk of recurrence among men with localized but unfavorable-risk prostate cancer randomized to radiotherapy or radiotherapy plus androgen deprivation therapy.	RCT	206; 1995-2001 Unclear FU: median=98.4 mos	Radiotherapy ± androgen deprivation therapy	PSA recurrence (PSA > 1.0 ng/ml and a PSA that increased by greater than 0.2 ng/ml at 2 consecutive visits after treatment) and time to PSA recurrence	Use of ADT reduced the risk of recurrence (adjusted hazard ratio=0.81; 95% CI 0.72, 0.92; p=0.001) with each additional month of ADT use. Increasing PSA level; Gleason score of 8, 9, 10; and clinical category 2 disease all statistically significantly associated with increased risk of recurrence.

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	or less than combined androgen suppression therapy. J Clin Oncol 2008; 26:2979-83.						
	Ferrer M, Suarez JF, Guedea F et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. Int J Radiation Oncology Biol Phys 2008; 72:421-32.	To compare treatment impact on HRQOL among patients with localized prostate cancer.	Longitudinal, prospective	614 FU: 2 yrs	Radical prostatectomy vs. 3D-CRT vs. brachytherapy.	Responses to SF-36, Functional Assessment of Cancer Therapy (General and Prostate-Specific), Expanded Prostate Cancer Index Composite (EPIC), American Urological Association Symptom Index.	HRQOL initially deteriorated after all treatments and then partially recovered. After accounting for clinical variables, compared to brachytherapy at 2 years radical prostatectomy patients had worse EPIC sexual summary and urinary incontinence scores; and 3DCRT patients had worse EPIC bowel, sexual, and hormonal summary scores. On the other hand, radical prostatectomy patients had significantly better EPIC urinary irritation scores than brachytherapy patients.
	Freedland SJ, Sun L, Kane CJ et al. Obesity and oncological outcomes after	To indirectly test the hypothesis that PSA-based screening is biased against obese men due to	Retrospective database study	3,389 1988-2008 Multicenter	Radical prostatectomy for men with PSA-detected cancers (cT1c) or with	Disease grade, positive surgical margins, biochemical progression	Body mass index (BMI) was associated with high-grade disease and positive surgical margins regardless of clinical stage. When stratified by stage, higher obesity related to greater cohorts among men

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	radical prostatectomy: Impact of prostate-specific antigen-based prostate cancer screening: Results from the Shared Equal Access Regional Cancer Hospital and Duke Prostate Cancer Databases. BJUI 2088; 102:969-74.	hemodilution of PSA and therefore results in delayed diagnosis and poor outcome beyond the biological link between obesity and aggressive prostate cancer.		Follow-up: Median = 4.5 or 4.8 yrs, depending on database	abnormal digital rectal examinations (cT2/T3)		with cT1c disease but not with cT2/T3 disease. Among men with T1c disease, the association between BMI and biochemical progression was limited to men treated in 2000 or later but not before that. All these results are statistically significant.
	Sanda MG, Dunn RL, Michalski J et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008; 358:1250-61.	To identify determinants of HRQOL after primary treatment of prostate cancer and to measure their effects on satisfaction with treatment among patients and their partners	Survey	1,201 pts and 625 partners 2003-2006 Multicenter FU: Before treatment and 2, 6, 12, 24 mos after	Prostatectomy, brachytherapy, or external beam radiation therapy	Patient reported measures from the Expanded Prostate Cancer Index Composite (EPIC-26 or EPIC-Partners) and Service Satisfaction Scale for Cancer Care (SCA or SCA-P)	HRQOL results varied with treatment. ADT lowered QOL in a number of domains for radiotherapy patients (brachytherapy or external beam). Treatment-related symptoms were exacerbated by obesity, large prostate size, high PSA, and older age. Black patients reported lower satisfaction with treatment outcomes overall. Changes in HRQOL were significantly associated with degree of outcome satisfaction among patients and their partners.
	Buron C, Le Vu B, Cosset J-M	To prospectively compare HRQOL,	Survey	435	Brachytherapy versus radical	Patient outcomes	Using multivariable analysis to account for potential confounders (including

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	et al. Brachytherapy versus prostatectomy in localized prostate cancer: Results of a French multicenter prospective medico-economic study. Int J Radiation Oncology Biol Phys 2007; 67:812-22.	patient-reported treatment-related symptoms, and costs of brachytherapy versus radical prostatectomy		2001-2002 Multicenter in France FU: Before treatment and 2, 6, 12, 18, 24 mos after	prostatectomy (14% laparoscopic, 86% retropubic)	reported from the EORTC QLQ-C30 and P25	use of ADT but not surgical approach) and adjusting for multiple comparisons, changes from baseline were examined for each treatment group. Just after treatment, the global HRQOL change favored brachytherapy (13.5 points; p<0.0001); 2 months after treatment, there was no statistically significant difference between treatment groups in global score change (-4 points; p=0.2720); by 6 months and up to 24 mos, the global score change slightly favored radical prostatectomy (-7.5 points; p ranges from 0.0164 to 0.0379 over the time period). Urinary incontinence was more frequent for radical prostatectomy than brachytherapy over all time periods. Other urinary problems, fecal incontinence, and rectal bleeding were more common with brachytherapy. Results for sexual effects did not take into account use of ADT, which were to be published in a later paper.
GAP 3: FACTORS WITH IMPACT ON DECISION-MAKING	Jang TL, Bekelman JE, Liu Y et al. Physician visits prior to treatment for clinically localized prostate cancer. Arch Intern Med 2010; 170:440-449.	To evaluate how visits to specialists and PCPs by men with localized prostate cancer are related to treatment choice.	Registry and claims data analyses	85,088 1994-2002; areas covered by SEER program FU: ~9 mos post-diagnosis	Specialty of physicians visited after diagnosis	Primary therapy received (radical prostatectomy, androgen deprivation, radiotherapy, expectant management)	Strong association between type of specialist seen and primary therapy chosen. About one-fifth of patients see a PCP between diagnosis and treatment, and they were more likely to have expectant management.

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	(1) Vickers AJ, Bianco FJ, Serio AM et al. The surgical learning curve for prostate cancer control after radical prostatectomy. J Natl Cancer Inst 2007; 99:1171-7. (2) Bianco FJ, Vickers AJ, Cronin AM et al. Variations among experienced surgeons in cancer control after open radical prostatectomy. J Urol 2010; 183:977-83.	To determine the learning curve for performing radical prostatectomy.	Retrospective	(1) 7,765 pts, 72 surgeons; (2) 7,725 pts, 54 surgeons 1987-2003; Multicenter US FU: Median = 3.9 yrs	Radical prostatectomy	Biochemical recurrence	(1) Learning curve is steep and does not plateau until 250 cases. After accounting for potential confounding variables, predicted probabilities of recurrence at 5 years were 17.9% (95% CI: 12.1%, 25.6%) for surgeons with 10 prior operations; 10.7% (95% CI: 7.1%, 15.9%) for surgeons with 250 prior operations (difference = 7.2%; 95% CI: 4.6%, 10.1%; p<0.001). The results were robust to sensitivity analysis, including restricting analysis to patients treated between 2000 and 2003. (2) Heterogeneity in outcomes persists even among high volume surgeons (40 or more cases). The adjusted, 5-year biochemical recurrence rate was less than 10% among 7 experienced surgeons, while it was more than 25% among another 5 experienced surgeons.
	Vickers AJ, Savage CJ, Hruza M et al. The surgical learning curve for laparoscopic radical prostatectomy: A retrospective cohort study. Lancet Oncol	To determine the learning curve for performing laparoscopic radical prostatectomy.	Retrospective	4,702 1/1998-6/2007; multinational FU: Median = 1.7 yrs	Laparoscopic radical prostatectomy	Biochemical recurrence	Slow learning curve for surgeons until after 250 such surgeries performed. 5-yr risk of biochemical recurrence is 17% for surgeons completing 10 laparoscopic prostatectomy; 16% after 250 surgeries; and 9% after 750 surgeries (adjusted for case mix). Recurrence is greater for surgeons who previously performed open radical prostatectomies. Learning curve is different shape for open radical prostatectomy, with sharp

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	2009; 10:475-80. Editorial by Nelson JB, pp. 437-9.						improvement earlier on. Follow-up is short. Editorial notes the need to investigate means to hasten learning process for surgeons inexperienced in this technique and suggests regionalization of care so that fewer patients are treated with less experienced surgeons.
	Spencer BA, Miller DC, Litwin MS et al. Variations in quality of care for men with early-stage prostate cancer. J Clin Oncol 2008; 26:3735-42.	To measure the quality of prostate cancer care nationally using the American College of Surgeons cancer registry	Cross-sectional based on hospital chart review and RAND quality of care criteria	2,775 cases, extrapolated to 55,160 cases using SUDAAN 2001-2006; National (US)	Radical prostatectomy or external beam radiation therapy	Compliance with quality of care criteria	Overall compliance > 70% for structural and pretherapy disease indicators but lower for documentation of pretreatment functioning (46.4-78.4%), surgical pathology (37.1-86.3%), radiation technique (62.6-88.3%) and followup (55%). Regional variations detected. Higher compliance at teaching/research hospitals and comprehensive cancer centers than at community cancer centers. No racial differences detected.
	Sommers BD, Beard CJ, D'Amico AV, Kaplan I, Richie JP, Zeckhauser RJ. Predictors of patient preferences and treatment choices for localized prostate cancer. Cancer 2008; 113:2058-67.	To examine determinants of patients' preferences for health states related to prostate cancer and whether those preferences or other factors predict treatment choice	Survey using time-tradeoff approach and multivariable predictive analyses	167; 2004-2007; 4 academic medical practices in Boston Follow-up: None	Radical prostatectomy, external beam radiotherapy, brachytherapy, hormonal therapy, watchful waiting, undecided	QALYs associated with erectile dysfunction, urinary incontinence, bowel problems, and metastatic prostate cancer; and predictors of treatment choice at time of survey	QALYs were highest for urinary incontinence (0.906), followed by erectile dysfunction (0.923), bowel/rectal discomfort (0.859), and metastatic prostate cancer (0.651). In other words, patients were more willing to accept shorter survival in turn for avoiding metastatic cancer than for avoiding urinary incontinence. The only predictor of all conditions was age, with older men more willing than younger men to exchange shorter survival for the lack of those conditions. The strongest predictor of treatment choice was the specialty of the physician (radiation oncology or urology) seen at

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
							the time of enrollment in the study.
	Macefield RC, Lane JA, Metcalfe C et al. Do the risk factors of age, family history of prostate cancer or a higher prostate specific antigen level raise anxiety at prostate biopsy? Eur J Cancer 2009; 45:2569-73.	To examine impact of age, family history of prostate cancer, or PSA on patients' anxiety at biopsy.	Survey using Hospital Anxiety and Depression Scale; part of ProtecT trial	4,198 Multicenter in UK FU: Mean time between initial PSA test and biopsy = 54.8 days.	Biopsy	Anxiety score of 8 or more	Older men were less anxious at biopsy than younger men, but younger men had a greater decrease in anxiety between PSA and biopsy. Neither family history of prostate cancer nor significantly elevated PSA level was associated with a higher anxiety level at biopsy or a greater change in anxiety between PSA test and biopsy. However, the number of patients with a positive family history was small.
	Aronowitz JN, Crook JM, Michalski JM et al. Inter-institutional variation in implant activity for permanent prostate brachytherapy. Brachytherapy 2008; 7:297-300.	To determine whether there is interinstitutional consensus regarding the parameters of an ideal implant.	Retrospective, comparative study among institutions	3 institutions, 136 implants Not reported; Multicenter in Canada and US FU: Not relevant	Brachytherapy	Utilization of seeds and implanted activity.	Despite agreement on implant philosophy, target volume, and dosimetric constraints, there were statistically significant differences in the number of seeds and total implant activity. The variation was greater for small glands.
	Hack TF, Pickles T, Bultz BD, Ruether JD, Degner LF. Impact of providing	To systematically examine the efficacy of providing men with prostate cancer with an	RCT	425 pts and 15 radiation oncologists 2001;	Standard care, consultation audiotaped but audiotape not given to pt; audiotape given	Perceived degree of information provision, audiotape satisfaction and	Of the patients receiving the audiotape, 65.4% listened to the whole tape and 57.4% had someone else listen to at least part of it. Patients who received it reported having been given significantly more disease and

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	audiotapes of primary treatment consultations to men with prostate cancer: A multi-site, randomized, controlled trial. Psycho-Oncol 2007; 15:543-52.	audiotape of their primary treatment consultation.		4 centers in Canada FU: 12 wks	to pt; or pt offered audiotape. Pts also surveyed using Control Preferences Scale, the Patient Perception Scale; Audiotape use and satisfaction questionnaire; Informed Communication Scale, Profile of Mood States (POMS), and Functional Assessment of Cancer Therapy (FACT-P).	use, communication satisfaction with oncologist, mood state, and cancer-specific quality of life	treatment information in general and more information about treatment alternatives and side effects. Audiotape benefit was not significantly associated with patient satisfaction with communication, mood state or quality of life 12 weeks after consultation, or being given the choice of receiving the audiotape. Patients who listened to the audiotape rated the intervention highly.
	Davison BJ, Goldenberg SL, Wiens KP, Gleave ME. Comparing a generic and individualized information decision support intervention for men newly diagnosed with localized prostate	To compare a generic and individualized approach to providing decisional support to men newly diagnosed with localized prostate cancer.	RCT and surveys	324; Not reported; 1 institution in Canada FU: 6 wks	View general videotape on early stage prostate cancer with or without additional part of computer program individualized based on medical information from physician's referral.	Measures of decision control, satisfaction, and decision conflict at baseline and after treatment decision made	Group with individualized information more satisfied with type, amount, and method of providing information, and role played in treatment decisionmaking with their physician. No difference between groups with regard satisfaction with treatment choice after decision made. Both groups also played more active role in treatment decisionmaking than initially preferred.

Table A-1. Recently published studies (continued)

Research Gap	Study	Study objective	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Summary results
	cancer. Cancer Nursing 2007; 30:E7-E15.						

*Articles added after last review by Technical Expert Panel.

Table A-2. Ongoing trials

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
GAP 1: IDENTIFYING WHICH PATIENTS TO TREAT	Pre-Operative Gleason Score and PSA and Clinical Stage in Predicting the Risk of Failure in Patients Undergoing Radiation Therapy for Localized Prostate Cancer; UCSF; PI: Mack Roach, MD; NCT00769223	Studying the Gleason score, PSA level, and cancer stage in predicting outcome in patients who have undergone radiation therapy for localized prostate cancer.	Multivariable prognostic analysis	3500 2/93-2/13; treated with RT at SF General Hospital or VAMC-SF 1987-2006	RT ± hormonal Tx	Evaluate the value of the pre-operative Gleason score, prostate-specific antigen level, and clinical stage in predicting the risk of failure and death in patients who have undergone radiotherapy for localized prostate cancer	Recruiting
	Active Surveillance in Prostate Cancer: A Prospective Cohort Study; PI: Jeri Kim, MD; MD Anderson Cancer Ctr; NCT00490763	Find out if men who have a type of prostate cancer that has been classified as “low risk” can safely not be treated for the disease	Prospective cohort study	650 2/06-2/20; MD Anderson FU: 5 yrs	Active surveillance	Disease progression rate	Recruiting

Table A-2. Ongoing trials (continued)

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
	Multi-Institutional Inter-SPORE Prostate Biomarker Study; Memorial Sloan-Kettering Cancer Ctr; PI: James Eastham, MD; NCT00574899	To identify and evaluate prostate biomarkers that will provide exact information regarding the likelihood of a recurrence (prediction) of prostate cancer.	Observational: case-control	700; 5/07-5/10; Multicenter US	Collect DNA samples from men with localized prostate cancer scheduled for radical prostatectomy or RT	Collect and contribute biologic specimens to Inter-SPORE Prostate Biomarker Study for men with clinical localized prostate cancer scheduled to get standard of care therapy for localized prostate cancer, either radical prostatectomy or RT therapy; to participate in the IPBS by conducting a prospective analysis of the prognostic utility of serum hK2 in predicting biochemical recurrence after definitive local therapy for prostate cancer	Recruiting
	START trial, described under GAP 2						
	See control arm of PIVOT trial						
GAP 2: COMPARATIVE EFFECTIVE-NESS OF DIFFERENT TREATMENTS FOR PROSTATE CANCER	Regional Cryoablation for Localized Adenocarcinoma of the Prostate; MD Anderson Cancer Ctr/Endocare, Inc, Gen-Probe Inc, Firmamed, Envisioneering Medical Technologies; PI:	To learn if using cryotherapy to treat only the part of the prostate that contains cancer is an effective treatment for prostate cancer	Safety/efficacy study	100; 4/09-4/11; Texas FU: 3 yrs	Cryotherapy	Patient Response (Result of biopsy at 6 months after therapy)	Recruiting (not clear whether all patients have localized disease)

Table A-2. Ongoing trials (continued)

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
	John F. Ward, MD; NCT00877682						
	Phase III Trial of Neutron + Photon Radiation Versus Photon + Hypofractionated Intensity Modulated Radiation Therapy in Localized Prostate Cancer; Barbara Ann Karmanos Cancer Inst; PI: Jeffrey D. Forman, MD, FACR; NCT00258466	Studying different types of radiation therapy to compare how well they work in treating patients with stage I, stage II, or stage III prostate cancer.	RCT	300; 5/05-11/06 (primary outcome measure); Michigan FU: 5 yrs+	Neutron radiotherapy over 15-45 minutes 5 days a week for 2 weeks followed by photon radiotherapy over 15-45 minutes 5 days a week for 5 weeks vs. photon radiotherapy over 15-45 minutes 5 days a week for 5 weeks followed by hypo-fractionated photon irradiation over 15-45 minutes 5 days a week for 2 weeks.	Occurrence of chronic grade 2 or higher toxicity as measured by RTOG/EORTC late morbidity scoring scheme at 1, 4, 8, and 12 months after treatment, then every 6 months for 5 years, then annually; Disease free survival at 1, 4, 8, and 12 months after treatment, then every 6 months for 5 years, then annually.	Study completed; follow-up continuing. Includes T1, T2, and T3 (latter not included in this project)
	Prostate Cancer: Multicentric Study Comparing Carcinological and Functional Results of Surgery; Université Paris XII; PI: Claude Abbou, PU-PH;	To show that radical prostatectomy by laparoscopic way could obtain carcinological results not lower than those with radical retropubic	Phase III, non-randomized	1440 12/07-7/12 France FU: 3 yrs	Radical retropubic prostatectomy versus radical laparoscopic prostatectomy	For each type of surgery, carcinological (percentage of positive surgical margins, percentage of capsular crossing); functional (urinary continence, sexuality, quality of life) at 2 years; pre and post operational morbidity at 36 mos; economic	Recruiting

Table A-2. Ongoing trials (continued)

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
	NCT00502723	surgery.				(hospitalization)	
	Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer: CHHIP; Institute of Cancer Research, UK: PI: David P. Dearnaley, MD, FRCP, FRCR; NCT00392535	Studying the side effects of three schedules of intensity-modulated radiation therapy and compares how well they work in treating patients with localized prostate cancer	RCT	2,163 10/02-9/12 Multicenter UK FU: 15 yrs	Conventional versus hypo-fractionated high dose IMRT	Acute and late radiation-induced side effects, freedom from recurrence, development of metastases, recommencement of hormonal therapy for disease recurrence, DSS, OS, QOL, health econ, models of normal tissue and tumor control	Recruiting (says clinical stage T1b-T3a, N0, M0, but locally confined disease)
	Pilot Evaluation of High Dose-Rate Brachytherapy ± Image-Guided Intensity Modulated Hypofractionated External Radiotherapy for Localized Prostate Cancer; Mayo Clinic; PI: Thomas Pisansky, M.D.	To study side effects and efficacy of treating patients with internal brachytherapy with or without image-guided IMRT	Phase II	142; 8/08-12/10 1 institution in US FU: 5 yrs	High Dose-Rate Brachytherapy ± Image-Guided Intensity Modulated Hypofractionate d External Radiotherapy	Tolerability using CTCAE (Common Terminology Criteria for Adverse Events) v. 3.0, dose-adverse event parameters for organs at risk, quality of life, patient preferences. biochemical and clinical failure, other treatments (e.g., ADT)	Recruiting
	Prostate Cancer Intervention Versus Observation Trial (PIVOT), Minneapolis VA Med Ctr; PI: Tim Wilt M.D., M.P.H.; ISRCTN007644	To determine whether radical prostatectomy or expectant management is more effective in reducing mortality and extending life.	RCT	731; 06/04-01/10; US	Radical Prostatectomy Versus Palliative Expectant Management	Prostate specific cancer mortality, quality of life, occurrence or recurrence of symptoms and need for cancer treatment	Recruitment and followup completed; data now being cleaned; expect results ~mid-2011. NOTE: Palliative expectant management in PIVOT trial is less aggressive surveillance and

Table A-2. Ongoing trials (continued)

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
							treatment than active surveillance in PROTECT trial. CITATION: Wilt TJ, Brawer MK, Barry MJ, et al. The Prostate cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. Contemp Clin Trials. 2009 Jan;30(1):81-7. Also, other articles in 1990s.
	Prostate testing for cancer and Treatment (ProtecT); Oxford Radcliffe Hospital, Great Britain; PI: Freddie C. Hamdy, MD; ISRCTN 20141297	To compare alternative treatments	RCT	2,050 06/01-12/13 Multicenter UK FU: 10+ yrs	Active Monitoring, Radical Prostatectomy, or Radiation Therapy	Survival time as assessed after the first information appointment at 5 years,10 years, and then every 5 years thereafter; disease progression, treatment complications, quality of life, etc.	Recruiting

Table A-2. Ongoing trials (continued)

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
	Health-Related Quality Of Life In Patients With Low Risk, Localized Prostate Cancer Randomized To Radical Prostatectomy Or Brachytherapy; Beth Israel Deaconess Medical Center, NY; Martin Sanda, MD	Evaluate quality of life in patients undergoing radical prostatectomy or brachytherapy for stage II prostate cancer.	Part of ACOSOG-Z0070 RCT	500; 09/02-08/09; Multicenter US FU: 10 yrs	Radical Prostatectomy versus Brachytherapy	HRQOL at baseline; 2 and 6 months; 1, 2, 4, 7, 10 years and interaction with treatment modality or disease progression	First stage of data collection complete; results not published.
	A Phase III Study of Active Surveillance Therapy Against Radical Treatment in Patients Diagnosed With Favourable Risk Prostate Cancer [START]; NCIC Clinical Trials Group (CALGB, ECOG, SWOG); PI: Laurence H. Klotz, MD et al; NCT00499174	Studying observation to see how well it works compared with radical treatment as an initial intervention in patients with favorable prognosis prostate cancer.	RCT stratified by treatment center, ECOG performance status, disease stage, baseline PSA, and age.	2,130; 6/07-4/23; Multicenter US	Active surveillance (move to radical treatment if biochemical, clinical, and/or grade progression) versus radical treatment (radical prostatectomy or radiotherapy per pt/physician preferences)	Disease-specific and overall survival, QOL, distant disease free survival, use of ADP, PSA relapse/progression after radical treatment; proportion active surveillance who receive radical treatment; prognostic significance PSA doubling-time prior to diagnosis, prognostic significance molecular markers	Recruiting
	Health-Related Quality Of Life In Patients With Low Risk, Localized Prostate Cancer Randomized To Radical	Evaluate quality of life in patients undergoing radical prostatectomy or brachytherapy for stage II prostate cancer.	Part of ACOSOG-Z0070 RCT	500; 09/02-08/09; multicenter	Radical Prostatectomy versus Brachytherapy	HRQOL at baseline; 2 and 6 months; 1, 2, 4, 7, 10 years and interaction with treatment modality or disease progression	First stage of data collection complete; results not published.

Table A-2. Ongoing trials (continued)

Research Gap	Study	Study objective (group by this)	Research design	Sample size; Years; Location; Follow-up	Treatment(s)	Outcomes	Status
	Prostatectomy Or Brachytherapy; Beth Israel Deaconess Medical Center, NY; Martin Sanda, MD			US FU: 10 yrs			
GAP 3: FACTORS WITH IMPACT ON DECISION-MAKING	Treatment Decision-Making in Early Stage Prostate Cancer; Georgetown Univ; PI: KL Taylor; NCT00196781	To test the effectiveness of a recently developed computer-based program to improve patient knowledge about prostate cancer treatments; also designed to help men clarify their values using a computer-based 'decision aid.'	RCT	168; 9/02-12/05 FU: 12 mos	Computer-based patient education aid ± decision aid.	Treatment satisfaction, quality of life, prostate cancer knowledge, shared decisionmaking	Trial completed; no publications to date. Long period since completion of study, with no apparent publications.

Appendix B. Prioritization Tools

This appendix contains a series of materials created by BCBS EPC and used by the TEPP in identifying prioritization criteria; ranking research gaps, with preliminary results; and requesting ranking of the draft list of proposed research studies. Items II-VI stem from the TEPP conference calls. In each case, the final results are presented in the report.

I. Prioritization Criteria, 1st Draft, May 14, 2009 (distributed to TEPP before first conference call)

Draft Prioritization Criteria for

BCBSA TEC Pilot Project on Identifying Research Needs on *Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer* (Minnesota EPC, February 2008)

When approved, the following criteria will be used to prioritize (1) research gaps originally identified in Minnesota EPC's comparative effectiveness review and modified by members of the pilot project Technical Expert Panel and (2) potential studies recommended by the TEPP members to fill those gaps.

Category	Applies to	Criterion
Importance	Research gaps and potential studies	▪ Addresses issue with important uncertainty for decisionmakers.
		▪ Incorporates both clinical benefits and potential clinical harms.
		▪ Represents important variation in clinical care or controversy in what constitutes appropriate clinical care.
		▪ Addresses high costs due to common use, high unit costs, or high associated costs to consumers, patients, health-care systems, or payers.
Potential value	Research gaps and potential studies	▪ Potential for significant health impact: o To improve health outcomes. o To reduce significant variation in clinical practices known to be related to quality of care. o To reduce unnecessary burden on those with health-care problems.
		▪ Potential for significant economic impact: o To reduce unnecessary or excessive costs.
		▪ Potential for change: o The proposed topic exists within a clinical, consumer, or policymaking context that is amenable to evidence-based change.
		▪ Potential risk from inaction: o Unintended harms from lack of evidence for decisionmaking.
		▪ Addresses inequities, vulnerable populations (including issues for patient subgroups).

Feasibility	Potential studies	*Factors to be considered:*
		▪ Interest among researchers.
		▪ Is not redundant with published or ongoing research.
		▪ Duration.
		▪ Cost.
		▪ Methodological complexity (e.g., do existing methods need to be refined?).
		▪ Complexity of implementation.
		▪ Facilitating factors.
		▪ Identification of potential funders.

II. Prioritization criteria, 2nd Draft, May 19, 2009 (distributed to TEPP after first conference call)

Draft Prioritization Criteria for BCBSA TEC Pilot Project on Identifying Research Needs on *Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer* (Minnesota EPC, February 2008)

Prioritization Criteria for Research Gaps

Category	Criterion
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.
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 (e.g., by age).

Prioritization Criteria for Research Studies/Designs to Address Research Gaps

Category	Criterion
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.
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 (e.g., by age).
Incremental value	• Adds useful new information to existing portfolio of research on topic OR
	• Validates existing research when body of evidence is scant.
Feasibility	*Factors to be considered:*
	▪ Interest among researchers.
	▪ Duration.
	▪ Cost.
	▪ Methodological complexity (e.g., do existing methods need to be refined?).
	▪ Implementation difficulty.
	▪ Facilitating factors.
	▪ Potential funders.

III. Tool Used To Solicit TEPP Members' Research Gap Ratings via Email (May 19, 2010) (distributed to TEPP after first conference call, with item II above)

Prioritizing Draft Research Gaps

BCBSA TEC Pilot Project on Identifying Research Needs on *Comparative Effectiveness of Therapies for Clinically Localized Prostate Cancer*

INSTRUCTIONS: Using the criteria for rating research gaps (see separate document), please rate each research gap listed below in terms of Current Importance and Potential for Significant Health Impact. Please rate (not rank) the gaps from 1 to 5, using the following scoring system:

1=Less Important/Low Impact to 5=More Important/High Impact

Please return via email by **Wednesday, May 26, 2010**. Thank you.

Research Gap by PICOS Category	***Priority Rating:*** **Current Importance**	***Priority Rating:*** **Potential for Significant Health Impact**
Population		
• Identifying which patients to treat (e.g., those most likely to have aggressive cancer) and when		
• Understanding the natural history of the disease among men with screen-detected cancer		
Intervention		
• Having better evidence on advanced technologies such as IMRT, proton beam radiation, laparoscopic and robotic assisted prostatectomy, high-intensity focused ultrasound, cryotherapy		
• Identifying biomarkers to provide reliable estimates about prostate cancer aggressiveness and the relative effectiveness of treatments		
Comparison		
• Having better comparative evidence on alternative treatment strategies, such as surgery vs. radiotherapy vs. active surveillance		
• Making better treatment decisions that incorporate physician and patient preferences		
Outcomes		
• Investigating racial and other disparities		
• Obtaining better evidence on outcomes of treatment for patient subgroups (e.g., age, comorbidities, disease characteristics, racial/ethnic groups)		
Setting		
• Investigating treatment patterns by physician characteristics (e.g., specialty, years in practice, volume)		
• Investigating treatment patterns by institution (e.g., tertiary vs. community hospital)		

IV. Results from Research Gap Rating Tool

TEPP Priority Ratings for 8 Research Gaps

Research Gap	Priority Rating Category	Partial Total (6/8/10*) (n=6)	Partial Rank	Final Total (n=9)	Final Rank
Population 1: Identifying which patients to treat (e.g., those most likely to have aggressive cancer) and when.	Current Importance	30		44	
	Potential for significant health impact	29		44	
	Total	**59**	**1**	**88**	**1**
Population 2: Understanding the natural history of the disease among men with screen-detected cancer	Current Importance	26		38	
	Potential for significant health impact	28		41	
	Total	**54**	**2 (tie)**	**79**	**2**
Intervention 1: Having better evidence on advanced technologies such as IMRT, proton beam radiation, laparoscopic and robotic assisted prostatectomy, high-intensity focused ultrasound, cryotherapy	Current Importance	23		32	
	Potential for significant health impact	27		37	
	Total	**50**	**5**	**69**	**6**
Intervention 2: Identifying biomarkers to provide reliable estimates about prostate cancer aggressiveness and the relative effectiveness of treatments	Current Importance	23		33	
	Potential for significant health impact	24		37	
	Total	**47**	**6 (tie)**	**70**	**5**
Comparison 1: Having better comparative evidence on alternative treatment strategies, such as surgery vs. radiotherapy vs. active surveillance	Current Importance	27		37	
	Potential for significant health impact	27		38	

Research Gap	Priority Rating Category	Partial Total (6/8/10*) (n=6)	Partial Rank	Final Total (n=9)	Final Rank
	Total	**54**	**2 (tie)**	**75**	**3**
Comparison 2: Making better treatment decisions that incorporate physician and patient preferences	Current Importance	23		32	
	Potential for significant health impact	24		34	
	Total	**47**	**6 (tie)**	**66**	**7**
Outcomes: Obtaining better evidence on outcomes of treatment for patient subgroups (e.g., age, comorbidities, disease characteristics, racial/ethnic groups, including disparities)	Current Importance	25		32	
	Potential for significant health impact	27		37	
	Total	**52**	**4**	**72**	**4**
Setting: Investigating treatment patterns by physician characteristics (e.g., specialty, years in practice, volume) or institutional characteristics (e.g., tertiary vs. community hospital)	Current Importance	17		24	
	Potential for significant health impact	15		22	
	Total	**32**	**8**	**46**	**8**

Biostatistician recused himself because of lack of clinical expertise; one other member did not respond.

*Received before second conference call.

V. Second List of Prioritized Research Gaps (July 9, 2010) (distributed to TEPP before second conference call)

Gap 1: Identifying which patients to treat

> ***Subgap 1a:*** Identifying which patients to treat (e.g., those most likely to have aggressive cancer) and when

Subgap 1b: Understanding of the natural history of localized prostate cancer in the PSA era.

Subgap 1c: 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

Subgap 2a: Comparing alternative treatment strategies such as surgery vs. radiotherapy vs. androgen deprivation therapy.

Subgap 2b: 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.

Subgap 2c: Comparing alternative strategies within a given modality, e.g., laparoscopic vs. open prostatectomy or intensity-modulated radiotherapy vs. brachytherapy. (Added by TEPP)

Subgap 2d: 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

Subgap 3a: Incorporating physician and patient preferences into treatment decisions.

Subgap 3b: Investigating treatment patterns by physician characteristics (e.g., specialty, years in practice, volume) or institutional characteristics (e.g., tertiary vs. community hospital).

Subgap 3c: Understanding patient psychology in dealing with uncertainty regarding screening, diagnosis, and treatment, especially for active surveillance choice. (Added by TEPP)

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.

Appendix C. Interim List of Potential Research Studies

This appendix contains the first draft of the list of proposed research studies (July 9, 2010). This list was composed by BCBSA TEC EPC staff based on discussions during the second TEPP conference call. It was distributed to the TEPP for comment and review before the third conference call.

Projects to Address Gap 1: Identifying which patients to treat

Project 1.1. Multi-institutional, observational study/registry to identify predictors of disease progression. Collect all relevant data on patients selecting active surveillance (AS), including tissue, serum, and urine; other risk factors (e.g., perineural invasion, inflammation); reasons for selecting AS; comorbidities; quality of life (QOL); etc. Although survival would take many years to gauge, potential intermediate outcomes include bone metastases and PSA failure. An "Oncotype Dx" type study could then be performed. Might also issue RFP asking for ideas on how analyze such data.

Project 1.2. More generally, establishing banks of tumor, serum, and urine that can be used in future studies of biomarkers. (As a reminder one member mentioned that a large bank has been created as part of PROTECT trial).

Project 1.3. Triage study of response to suspicious PSA results on screening, similar to studies done for cervical cancer: biopsy now, delay biopsy, etc. Could also address variations in the ways in which PSA is interpreted, e.g., cutpoints.

Project 1.4. Identify grade of disease after biopsy, using more biomarkers.

Project 1.5. Use modeling to determine when to begin treatment, similar to research done on HIV-positive patients.

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

Project 2.1. Multicenter RCTs of alternative treatments within a modality, with focus on adverse events and QOL within a relatively short time frame, e.g., 5 years. Could address the value added by more expensive technologies. Also, need to 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 in men with low risk prostate cancer, given serious side effects, including cardiac disease. When and for whom do the benefits outweigh the adverse events?

Project 2.3. Study the psychological impact of diagnosis and treatment, especially for those under active surveillance.

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

Project 3.1. Evaluate patient preferences and perceptions of risk in weighing adverse effects of treatment vs. chance for benefit.