Evidence Report/Technology Assessment

Number 209

Multigene Panels in Prostate Cancer Risk Assessment

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Number 209

Multigene Panels in Prostate Cancer Risk Assessment

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments. To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. Comments may be sent by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Multigene Panels in Prostate Cancer Risk Assessment

Structured Abstract

Objectives: The aim of this review is to identify, synthesize, and appraise the literature on the analytic validity, clinical validity, and clinical utility of commercially available single nucleotide polymorphism (SNP) panel tests for assessing the risk of prostate cancer.

Data Sources: MEDLINE®, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and Embase, from the beginning of each database to October 2011. Search strategies used combinations of controlled vocabulary (medical subject headings, keywords) and text words. Grey literature was identified.

Review Methods: Three Key Questions (KQs) encompassing broad aspects of the analytic validity, clinical validity, and clinical utility of SNP-based panels were developed with the input of a Technical Expert Panel assembled by the Evidence-based Practice Center and approved by the Agency for Healthcare Research and Quality. Standard systematic review methodology was applied, with eligibility criteria developed separately for each KQ.

Results: From 1,998 unique citations, 14 were retained for data abstraction and quality assessment following title and abstract screening and full text screening. All focused on clinical validity (KQ2), and evaluated 15 individual panels with two to 35 SNPs. All had poor discriminative ability for predicting risk of prostate cancer and/or distinguishing between aggressive and asymptomatic/latent disease. The risk of bias of the studies was determined to be moderate. None of the panels had been evaluated in routine clinical settings.

Conclusions: The evidence on currently available SNP panels does not permit meaningful assessment of analytic validity. The limited evidence on clinical validity is insufficient to conclude that the panels assessed would perform adequately as screening or risk stratification tests. No evidence is available on the clinical utility of current panels.

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Executive Summary

Background

Prostate cancer is the fifth most common malignancy in the world, [1] with a large variation in incidence rates. In 2010, it was estimated that almost a quarter of a million new cases were diagnosed in North America, and more than 36,000 men died from the disease.[2,3] These numbers are likely to increase with the aging of the population.[4] In data from the Surveillance, Epidemiology, and End Results Program, more men were diagnosed with prostate cancer at a younger age and earlier stage in 2004–2005 than in the mid- to late 1990s, and disparity between ethnic groups in cancer stage at diagnosis decreased.[5]

Apart from age, ethnic group, and family history, the risk factors associated with prostate cancer are unclear, [6] making primary prevention difficult.

Striking differences in incidence have been observed for different ethnic groups and populations. A high incidence has been observed in populations of African descent in several countries.[7] First-degree relatives of men with prostate cancer have a two- to threefold increased risk for developing the disease,[6,8,9] and its estimated heritability is high.[10] Some patterns of familial aggregation have been observed that are consistent with an autosomal dominant mode of inheritance of a susceptibility gene, but this accounts for no more than 15 percent of cases.[11,12] Prostate cancer is currently considered to be a complex, multifactorial disease with the vast majority of familial clustering attributed to the interaction of multiple shared moderate to low penetrance susceptibility genes and shared environmental factors within these families. Many epidemiological studies have suggested a wide range of other risk factors for prostate cancer, but these have not been confirmed in controlled trials.

The natural history of prostate cancer is highly variable.[13] In a large proportion of men, the disease is indolent, and it is difficult to predict which tumors will be aggressive. African-American men have a poorer prognosis than other groups, independent of comorbidity or access to health services.[7] The value of aggressive management for localized prostate cancer is also debated, and only a small proportion of men with early stage prostate cancer die from the disease within 10 to 15 years of diagnosis.

Prostate-specific antigen (PSA) was approved by the U.S. Food and Drug Administration in 1986 for monitoring progression in patients with prostate cancer, and later approved for the detection of the disease in symptomatic men (but not for screening asymptomatic men).[14] A meta-analysis of seven randomized controlled trials of screening using PSA testing alone, or in combination with digital rectal examination, suggested no evidence of benefit in reducing mortality,[15,16] and some evidence of harms from overdiagnosis.[16] Amidst substantial debate,[17-23] the argument has been made for developing more accurate screening tests, including possible genetic markers.

Single nucleotide polymorphisms (SNPs) are minute inherited variations in the DNA sequence. SNPs occur about once in every 800 base pairs[24] and are the most common type of genetic variation in humans. Since 2001, there have been about 1,000 published studies reporting associations between prostate cancer, SNPs, and other genetic variants. To date, genome-wide association (GWA) studies have identified replicated associations between prostate cancer and almost 40 specific SNPs.[25-34] The magnitude of the odds ratios (ORs) in these studies was in the range of 1.1 to 2.1, that is, of low penetrance. It is generally accepted that information on single low-penetrance alleles has no value in screening,[35-38] but a small to moderate number of

common, low-penetrance variants, in combination, may account for a high proportion of a disease[36,39,40] and may be useful in predicting the risk for disease.[41] The aim of this review is to assess the evidence on the possible value of SNP panels in the detection of and prediction of risk for prostate cancer, and their value in predicting disease prognosis in affected men.

Scope and Purpose of the Systematic Review

This report addresses the evidence on the validity and utility of using SNP panels in the detection, diagnosis, and clinical management of prostate cancer. It is intended to encompass all relevant areas of test evaluation as proposed by the ACCE framework (see Table A).

Table A. Elements and key components of evaluation framework for SNP-based panels in prostate cancer risk assessment[42]

Element	Definition	Components
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (e.g., genomic variations) that it is intended to measure	Analytical sensitivity Analytical specificity Reliability (e.g., repeatability of test results) Assay robustness (e.g., resistance to small changes in pre-analytic or analytic variables)[43]
Clinical validity	A measurement of the accuracy with which a test or tool identifies or predicts a clinical condition	Clinical sensitivity Clinical specificity Positive predictive value Negative predictive value
Clinical utility	Degree to which benefits are provided by positive and negative test results	Availability and impact of effective interventions Health risks and benefits Economic assessment
Ethical, legal, and social implications	Issues affecting use of SNP-based panels that might negatively impact individuals, families, and society	Stigmatization Discrimination Psychological harms Risks to privacy and confidentiality

Note: Reprinted from Amer Jour Prev Med 24(2), Yoon PW, Scheuner MT, and Khoury MJ., Research Priorities for Evaluating Family History in the Prevention of Common Chronic Diseases. Pp 128-35, 2003, with permission from Elsevier.

The specific Key Questions (KQs) are:

1. What is the analytic validity of currently available SNP-based panels designed for prostate cancer risk assessment? (KQ1)
2. What is the clinical validity of currently available SNP-based panels designed for prostate cancer risk assessment? (KQ2)
3. What is the clinical utility of currently available SNP-based panels for prostate cancer risk assessment, in terms of the process of care, health outcomes, harms, and economic considerations? (KQ3)

These questions represent the links in the chain between using an SNP-based panel to assess a person's genotype and producing benefit in terms of reduction in mortality: do currently available SNP panels actually assess genotype accurately, and, if so, do they predict or stratify a person's risk accurately? Does such risk prediction or stratification lead to altered clinical decisionmaking and/or change in personal behavior sufficient to alter important disease outcomes? Are there any direct harms of a SNP-based approach? How do SNP-based strategies (alone or in combination with PSA) compare with current practice?

This review's focus is firmly on the potential value of applying SNP-based genotype panels in clinical practice as a supplement to, or substitute for, current PSA-based strategies.

Methods

Standard systematic review methodology was employed. MEDLINE®, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and Embase databases were searched from their inception to October 2011 inclusive.

The commercial availability of a test panel was defined as a clinical test offered (or soon to be offered) by a certified laboratory, or licensed or certified kit reagent test panels sold for use by clinical service laboratories within continental North America.

The Web sites of relevant specialty societies and organizations were searched, as well as the reference lists of eligible studies.

On behalf of the authors, the Scientific Resource Center directly contacted 40 companies known to provide either test services or diagnostic reagents potentially relevant to the KQs, in an effort to elicit unpublished sources of information.

Eligibility criteria included English language studies evaluating SNP analysis of human populations, or samples derived from human populations. The SNP analysis had to be across more than one gene, commercially available (or close to this), and at least one of the gene variants included in the panel must have been validated in a GWA study. Study designs varied by question.

Quality assessment was performed using The Newcastle Ottawa Scale (NOS)[44] supplemented by selected items for the QUADAS tool.[45]

Results

Our comprehensive search yielded 1,998 unique citations. In total, 1,303 (65 percent) were excluded from further review following the initial level of title and abstract screening. The remaining 695 citations were screened at full text and from these a total of 14 articles[46-59] were eligible. All were considered primarily relevant to KQ2, but they also provided data that permitted extrapolation to address KQ1.

KQ1. What is the analytic validity of currently available SNP-based panels designed for prostate cancer risk assessment?

1. ***What is the accuracy of assay results for individual SNPs in current panels?***

No direct assessment of the analytic validity of any SNP-based panels was identified in the literature search. Companies known to offer testing for the risk of prostate cancer based on SNP panels were approached in May of 2011, as were companies known to offer genetic testing more generally. As of September 1, 2011, no response had been received. From the articles that were identified as providing information relevant to the assessment of the clinical validity of SNP panels, no data on the analytic validity of individual SNPs that were components of the panels were presented.

2. ***What is the analytical validity of current panels whose purpose is, or includes, predicting risk of prostate cancer?***

Reports concerning 15 test panels were considered eligible for KQ2, and data were available, with overlaps from different sources, for most of these. Reported accuracy rates ranged up to >99.9 percent; SNP call rates were usually reported in the range of 98 to 99 percent (with a low of 90 percent), and reported concordance on retesting was usually greater than 99 percent. However, the methodologies described as the basis for determining analytical validity were not uniform across all analytes for some panels; in multiple cases, the SNP call rate of a given test

panel was reported on the basis of data from two or more different chip platforms or analytical techniques. (For the purpose of this report, call rate was defined as the proportion of samples for which genotypes are called for a converted marker).

3. ***What are the sources of variation in accuracy or analytical validity across different test platforms?***

No evidence to address this question was identified.

KQ2. What is the clinical validity of currently available SNP-based panels designed for prostate cancer risk assessment?

Fourteen articles, describing 15 distinct SNP-based panels, were identified as eligible for KQ2. The properties of a 5-SNP panel were investigated in six articles, four of which also considered family history. The other 14 panels included between 2 and 35 SNPs, but each was investigated in a single study only; several of these considered family history and age in the risk prediction model. All but two evaluations were case-control (association) studies, and were heterogeneous in terms of the composition of each panel (specific SNPs and the number included), the inclusion of other risk factor data, the populations in which they were evaluated, and the metrics used to judge the performance of the panel as a "test." One evaluation was a cross-sectional study, and one was a cohort study of survival in men with prostate cancer. None of the studies were performed in routine clinical settings.

1. ***How well do available SNP-based genotyping panels predict the risk of prostate cancer in terms of:***

a. stratifying future risk and/or screening for current disease?

Across six studies, the range of observed diagnostic ORs for the 5-SNP panel was 2.4 to 4.5. Receiver-operator characteristic curves were computed in two of these studies, with the reported figures for area under the curve (AUC) ranging from 58 to 73 percent, depending on the study and inclusion of other variables. AUCs across all panels ranged between 58 and 74 percent. In general, proposed tests with an AUC of 75 percent or less are unlikely to be clinically useful.[60,61] Moreover, within individual studies, the incremental gain in AUC observed when the predictive model including the SNP data was compared against the best alternative non-SNPs model (i.e., the absolute improvement in AUC) ranged from +0.025 to +0.04.

b. distinguishing between clinically important and latent/asymptomatic prostate cancer?

Data pertaining to this question were available for the 5-SNP panel.,[48,62] the 14-SNP panel,[51] the 11-SNP panel,[50] and the 35-SNP panel.[58] Regardless of the operational definition of "clinically important" prostate cancer, none of the evaluations suggested that any of these panels performed well in distinguishing between more and less aggressive disease.

2. ***How well do available SNP-based genotyping panels predict prognosis in individuals with a clinical diagnosis of prostate cancer?***

Prediction of prostate cancer mortality in affected men was evaluated for the 5-SNP panel, with and without inclusion of family history, [47] the 6-SNP panel, [55] and the 16-SNP panel.[59] Followup periods ranged from 3.7 to 10 years. There was no association between risk alleles and prostate cancer mortality for any of the panels, [47,55,59] and no increase in the AUC of a model based on age, PSA, Gleason score, and tumor stage when SNPs panel data were added.[47]

No data were identified to address the questions of risk reclassification or predicted performance in simulation analyses.

3. ***What other factors (e.g., race/ethnicity, gene-gene interaction, gene-environment interaction) affect the predictive value of available panels and/or the interpretation of their results?***

No data were found which directly addressed this question. For one of the panels,[54] we noted the development of separate tests for SNPs in steroid hormone pathway genes for non-Hispanic Whites and Hispanic Whites. Also, the deCODE ProstateCancer test includes different subsets of variants for assessing risk in men of European, African American, and East Asian descent.[63]

KQ3. What is the clinical utility of currently available SNP-based panels for prostate cancer risk assessment, in terms of the process of care, health outcomes, harms, and economic considerations?

No eligible studies addressing any component of clinical utility were identified.

Quality Assessment of Individual Studies

We considered that all the included studies had at least a moderate risk of bias.

Rating the Body of Evidence

We considered the domains of risk of bias, consistency of findings, directness, and precision. As indicated above, all included studies were considered to have at least a moderate risk of bias. We could not assess consistency of results for panels assessed in single studies only. For one panel (Focus 5), evaluated in multiple studies, consistency could not be assessed quantitatively. For directness, all included studies were conducted in a research context, and none of the panels were applied in settings that might be considered close to routine clinical practice. In particular, there was no meaningful comparison of any SNP panel against a routine clinical alternative "test."

Finally, the assessment of precision requires a clear idea of clinically meaningful differences between different levels of sensitivity, specificity, AUC, and other accuracy metrics. This area of evaluation is underdeveloped in the clinical literature, and we were unable to offer a valid assessment of this domain.

We were unable to assess the extent of publication bias in this review. We contacted a comprehensive list of companies we considered most likely to be developing SNP panels for commercial application, and received no responses.

Overall, it is unlikely that any of the biases identified would be sufficient to alter the interpretation of the findings from (at best) inadequacy of evidence to clearly positive supporting evidence for any of the SNPs panels reviewed.

Discussion

We identified a number of evaluations of SNP panels that varied in their composition. We could not draw robust conclusions regarding their analytic validity. These studies showed statistically significant associations between combinations of SNPs and risk of prostate cancer. However, when assessed using test evaluation designs, the risk models based on SNP panels improved the AUC only marginally compared with non–SNP-based tests in distinguishing cases from noncases, clinically meaningful from latent or asymptomatic cancer, or in stratifying the prognosis of confirmed cases. These evaluations were not conducted in routine clinical settings. No evidence was identified to address the question of clinical utility.

Future research should focus on evaluating clinical validity more extensively and robustly in participants more representative of general clinical populations, and on comparing SNP-based panels directly with the existing standard of care. There would be value in applying decision analysis methods. In the development of new panels, there is also a need to characterize further the regions in which genetic markers have so far been identified and validated, as well as to identify and validate further genetic markers to enable a greater proportion of the genetic variation to be considered in stratifying risk. More emphasis needs to be placed on distinguishing between aggressive and nonaggressive disease, and investigators should consider the possibility for subgroup analyses at the planning stage of studies.

Conclusion

The potential value of using SNP-based panels in prostate cancer risk assessment includes risk stratification, screening for undiagnosed disease, and assessing prognosis. We identified 15 SNP panels that we considered fulfilled the definition of "close to commercially available." They were widely variable in their makeup, containing 2-35 different SNPs, many combined with other risk factor data in predictive algorithms.

With regard to stratifying future risk and/or screening for current disease, a 5-SNP panel was evaluated in six articles. The other 14 panels were investigated in single studies only. AUCs across all panels ranged between 58 and 74 percent. Thus, all of the panels had AUCs below 75 percent, the threshold below which tests are in general considered unlikely to be clinically useful. Any increase in AUC compared with models not incorporating the SNP combinations was small. In the few studies that investigated the distinction between clinically important and latent/asymptomatic prostate cancer or prognosis, no associations were observed with risk scores derived from the SNP panels. Thus, currently available or documented SNP panels proposed for prediction of risk for prostate cancer have poor discriminative ability.

No evidence was found which addressed the important questions of clinical utility. However, even if the review had identified more compelling evidence to support clinical utility, this would not in itself provide any direct evidence of the value of SNP-based test panels in reducing morbidity and mortality. Any benefit from improvements in prostate cancer risk prediction, screening, and prognostic stratification will depend to a large extent on clearer evidence that surveillance, diagnostic, and treatment strategies in themselves lead to reductions in morbidity and mortality.

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Introduction

Prostate Cancer

Worldwide, more than 900,000 cases of prostate cancer were diagnosed in 2008, making its incidence second only to lung cancer in men.[1] Incidence rates vary approximately 25-fold worldwide, with the highest rates being observed in North America, Australia and New Zealand, and Western and Northern Europe. It is believed that a large part of this variation reflects differences in the use of prostate specific antigen (PSA) screening.[1] Excluding skin cancer, prostate cancer is the most common cancer in American men. In 2010, it was estimated that almost a quarter of a million new cases of prostate cancer were diagnosed in North America, and more than 36,000 men died from the disease.[2,3] The risk for prostate cancer increases with age; the median age of diagnosis in the United States during 2004–2008 was 67 years.[4] With the aging population, prostate cancer will present a significant burden to health care services. In data from the Surveillance, Epidemiology, and End Results Program, more men were diagnosed with prostate cancer at a younger age and earlier stage in 2004–2005 than in the mid- to late 1990s, and the disparity between ethnic groups in cancer stage at diagnosis decreased.[5]

Risk Factors

Apart from age, ethnic group, and family history, the risk factors associated with prostate cancer are unclear,[6] which makes primary prevention difficult.

Ethnic Group

Striking differences in incidence have been observed for different ethnic groups and populations. A high incidence has been observed in populations of African descent in several countries,[7] including Brazil, the Caribbean, and France.[8] In parts of sub-Saharan Africa, the incidence of prostate cancer in black populations lies in the range of 14 to 25 per 100,000 per year, compared with 40 to 70 per 100,000 per year in white populations in these areas, although it is noted that the black population does not have access to diagnostic and screening facilities that are available to the white population in these areas.[9] These observations are complicated by differences in the use of PSA screening and/or access to care, which may result in differential ascertainment. Migrant studies suggest that prostate cancer incidence increases when men move from a lower to a higher incidence population. Many epidemiological studies have suggested a wide range of risk factors for prostate cancer, but controlled trials have either not been conducted, or have shown negative results.

Hereditary Factors

First-degree relatives of men with prostate cancer have a two- to threefold increased risk for developing the disease.[6,10,11] In addition, the risk of relatives developing prostate cancer increases with an increase in the number of affected individuals in the family and with a decrease in the age at diagnosis of the index prostate cancer case.[12] High concordance rates have been observed in monozygotic twins. In a combined analysis of data from three Scandinavian countries, the estimated heritability for prostate cancer was the highest of all the types of cancer investigated.[13]

A subset of familial prostate cancer cases show patterns of familial aggregation consistent with an autosomal dominant mode of inheritance of a susceptibility gene, but this accounts for no

more than 15 percent of prostate cancer.[14,15] Prostate cancer is currently considered to be a complex, multifactorial disease with the vast majority of familial clustering attributed to the interaction of multiple shared moderate to low penetrance susceptibility genes as well as shared environmental factors within these families.

Other Risk Factors

Compared with other common types of cancer, the risk factors associated with prostate cancer are unclear.[6] Many epidemiological studies have suggested a wide range of risk factors for prostate cancer, but controlled trials have either not been conducted, or have shown negative results.

An analysis of individual patient data from 12 studies of the association between insulin-like growth factors (IGFs) and IGF binding proteins and prostate cancer suggests that higher levels of serum IGF1 are associated with a higher risk for prostate cancer.[16] Several studies have investigated the possible association between diabetes mellitus and the risk for prostate cancer. Meta-analyses indicate an inverse relationship.[17,18]

Observational studies have suggested that diet may be important in the etiology of prostate cancer, but these have not translated into effective preventive interventions. An analysis of the Alpha-Tocopherol Beta-Carotene Intervention Trial of heavy smokers in Finland showed a 40 percent decrease in incidence and mortality in prostate cancer in men taking alpha-tocopherol compared with those taking placebo.[19] Analysis of further randomized controlled trials (RCTs) that included prostate cancer as a secondary end-point have also indicated a possible protective effect of alpha-tocopherol.[20] However, in a large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of prostate or total cancer,[21] and in another long-term trial, it was concluded that dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.[22] While observational studies have suggested a protective role for selenium, this was not confirmed in a large RCT.[23] Inverse associations with consumption of tomatoes/lycopene[24,25] and soy products[26,27] have been reported. Positive associations with the consumption of dairy products and calcium have been reported.[24,28,29] The evidence of association with alcohol,[24,30] coffee,[31] dietary fiber,[32] fish consumption,[33] and beta-carotene supplementation[34] has been interpreted as null.

Other risk factors that have been considered include androgens,[35] anthropometric measures,[24,36] physical activity,[6] sexual behavior,[37] sexually transmitted infection,[35,38,39] vasectomy,[40,41] occupation as flight personnel,[42,43] agricultural pesticide applications,[44] use of nonsteroidal anti-inflammatory drugs,[45] statin use,[46,47] smoking,[25,48] use of smokeless tobacco,[49] sun exposure,[50] and serum 25-hydroxyvitamin D level.[51,52]

Natural History

The natural history of prostate cancer is highly variable.[53] In studies of autopsy series, histologically proven prostate cancer was found in approximately 30 to 40 percent of men over 50 years of age who died of other causes.[54-60] This is three to four times higher than the lifetime risk of prostate cancer diagnosis in American men (approximately 11 percent),[53] which suggests that the disease is indolent in a large proportion of affected men. However, it is difficult to predict the aggressiveness of the disease in individual men. The most commonly used scheme to grade prostate cancer is the Tumor, Nodes, Metastases (TNM) scheme, which evaluates the size and histological features of the tumor, the extent of involved lymph nodes, and the presence of

metastasis. This information is used to classify the tumor into one of four categories: Stage I–small, localized focus within prostate, typically found when prostatic tissue is removed for other reasons such as benign prostatic hyperplasia; Stage II–more of the prostate is involved and a lump can be palpated (by digital rectal examination [DRE]) within the gland; Stage III–the tumor has broken through the prostatic capsule and the lump can be palpated on the surface of the gland; Stage IV–the tumor has invaded nearby structures, or has spread to lymph nodes or other organs.

The Gleason score is based on histopathological assessment of the glandular architecture of prostate tissue samples, usually obtained by transurethral ultrasound (TRUS) guided biopsy.[61] The assessment involves determination of: the most prevalent pattern of growth and differentiation; and, the most aggressive pattern, each of which is assigned a score (range 1 to 5), which is then summed to give the overall Gleason score. The Gleason scoring system was modified,[62] which resulted in a shift of the most commonly found score from six to seven.[61] This has implications for the comparison of subgroup analyses by Gleason scores over time.

Several studies have sought to provide an estimate of the long-term risk of death from prostate cancer in men whose disease was clinically localized at diagnosis and who were managed solely by observation (watchful waiting), with or without androgen withdrawal therapy.[53,63-72] Most of these studies were carried out before the advent of PSA testing, which is thought to have increased the detection of clinically indolent disease and extended lead time.[73-78] Only a small proportion of men with prostate cancer diagnosed at an early clinical stage (Gleason scores ≤4) die from prostate cancer within 10 to 15 years of diagnosis. Men with poorly differentiated tumors frequently die within 5 to 10 years of diagnosis.[66,69] The greatest variation in outcome is for men with moderately differentiated tumors (Gleason scores 5 to 7).[53,66,69] The natural history over longer periods of observation is uncertain. A study in Sweden,[69] observed an increase in prostate cancer mortality among a relatively small number of men who were alive more than 15 years after diagnosis of localized prostate cancer, but this was not observed in a larger study in Connecticut, United States.[66] Numerous differences between these cohorts could account for this inconsistency.[79] A modeling study in the United States projected that 20 to 33 percent of men have preclinical onset (i.e., asymptomatic, but diagnosed as a result of a routine PSA test) of whom, 38 to 50 percent would be clinically diagnosed, and 12 to 25 percent would die of the disease in the absence of screening and primary treatment.[80]

Treatment in Men With Clinically Localized Prostate Cancer

The value of aggressive management for localized prostate cancer is also debated, and only a small proportion of men with early stage prostate cancer die from the disease within 10 to 15 years of diagnosis. In the United States, African-American men have a poorer prognosis, which does not appear to be fully explained by comorbidity, PSA screening, or access to free health care, although the variation in the measurement of these factors complicates the interpretation.[7]

Two RCTs have compared the efficacy of radical prostatectomy and watchful waiting in men with clinically localized prostate cancer, almost all of which were detected by methods other than PSA testing. A small trial showed no differences in survival between these two management strategies.[81] A larger trial by the Scandinavian Prostate Cancer Study Group showed a small reduction in the risk of progression or death from prostate cancer in the men treated with radical prostatectomy, but also noted the potential harms that resulted from surgery.[70,71] Two further RCTs are ongoing, one in the UK[82,83] and one in the United States.[84]

PSA Screening

PSA was discovered in the 1960s and 1970s,[85] and the work identifying it as a serum marker for adenocarcinoma of the prostate was published in 1987.[86] It was first approved by the U.S. Food and Drug Administration (FDA) in 1986 for monitoring progression in patients with prostate cancer, and later approved for the detection of the disease in symptomatic men (but not for screening asymptomatic men).[87] Since 1986, it is estimated that more than a million additional men in the United States have been diagnosed and treated for prostate cancer because of PSA screening than would otherwise have been the case, the most dramatic increase observed being for those under the age of 50.[88] The increase in incidence following the introduction of PSA screening has never returned to prescreening levels, and has been accompanied by an increase in the relative fraction of early stage cancers, but not a decrease in the rate of regional or metastatic disease.[89]

Seven randomized trials (12 publications) of screening using PSA testing alone, or in combination with DRE, have been reported, in the United States,[90,91] Canada,[92-94] and Europe,[95-101] with conflicting results.

Meta-analysis of these trials indicates that prostate cancer screening did not result in a statistically significant decrease in all-cause or prostate cancer-specific mortality,[102,103] and that overdiagnosis resulted in harms that are frequent, often persist, and are at least moderate in severity.[103] The individual trials and meta-analyses have generated substantial debate, with many commentaries arguing for the development of more accurate markers to use in screening or a risk stratification approach.[104-112] Investigation of genetic variants associated with prostate cancer has been considered a promising route to the identification of such markers.

Single Nucleotide Polymorphisms

Single nucleotide Polymorphisms (SNPs) are minute variations in the DNA sequence that are passed on from parents to children. They are the most common type of genetic variation in humans. Formally, an allele, that is, a variation in DNA sequence, is defined to be "polymorphic" if it occurs in at least 1 percent of a population.[113] Therefore, although overall humans are very similar at the DNA sequence level, because the genome is large there is substantial latitude for individual genetic variation. SNPs occur about once in every 800 base pairs.[114] The Human Genome Project and advances in related technologies have fostered the investigation of the relationship between genetic variation and many health outcomes, including prostate cancer.

Since 2001, about 1,000 publications have reported associations between prostate cancer and SNPs and other genetic variants. The vast majority of the studies have related to candidate genes, in which the genes and variants, usually SNPs, have been specifically selected for investigation based on biological and physiological information regarding the involvement of gene products in early developmental pathways, biochemical and cellular process of progression, and/or clinical manifestations (a "candidate gene" approach). For prostate cancer, the most intensively investigated associations have related to genes in the following pathways: adhesion molecules (*CDH1*[115]); androgen metabolism (*AR*,[116,117] *ESR2*,[118] *SRDA2*[119,120]); angiogenesis (*VEGF*[121]) angiotensin conversion (*ACE*[122,123]); base-excision repair (*XRCC1*[124,125]); inflammation and immune response (*IL8*, *IL10*,[126-128] *MSR1*,[129] *PTGS2*,[130] *TNF*[131]); inhibition of cell growth (*FGFR4*,[132,133] *TGFB1*,[134] *TGFBR1*[135]); insulin-like growth factor metabolism (*IGF1*,[136]

IGFBP3[137]); one carbon metabolism (*MTHFR*,[138] diverse genes[139]); oxidative response (*MnSOD*,[140] *hOGG1*[141]); substrate metabolism (*CYP1A1*,[142] *CYP3A4*,[143] *CYP17*,[144,145] *GSTM1*, *GSTT1*, *GSTP1*,[146] *NAT1* and *NAT2*,[124] *UGT2B17*[145]); vitamin D metabolism (*VDR*[147]); and, common variants of genes for which rare mutations are associated with increased cancer risk (*ELAC/HPC2*,[148] *RNASEL*,[149,150] *TP53*,[151,152] *MDM2*[153]). In general, the results of candidate gene studies have been inconclusive, for reasons discussed in many commentaries.[154,155] However, when associations have been confirmed, they have been modest, with odds ratios (ORs) in the range of 1.1 to 2.2.[156] Thus, the proportion of individuals carrying any one of these variants that also developed the health outcome under investigation is low (i.e., these variants are of low penetrance).

The HapMap Project, completed in 2005, has shown that SNPs are often correlated with their neighboring SNPs, which has provided a methodology for investigating the associations between genetic variation and health outcomes on a genome-wide scale.[114] In genome-wide association (GWA) studies, a dense array of genetic markers that capture a substantial proportion of common variation in genome sequence, are typed in a set of DNA samples and tested for association with the trait of interest without specific prior hypotheses.[157] In most investigations of this type, the ability to validate findings in independent samples is built in to the study.[157] As of 31 January 2012, GWA studies have identified replicated associations between prostate cancer and more than 50 specific SNPs (Table 1),[158-164,164-171] all of which appear to be of low penetrance at best.

It is generally accepted that screening based on single low penetrance alleles is of little value,[172-175] and may in fact be harmful when psychosocial factors are considered. In contrast, it has been suggested that combinations of a small to moderate number of common, low penetrance variants may account for a high proportion of disease in a population[173,176,177] and may be useful in predicting risk for disease.[178] For example, for a common disease with a 5 percent lifetime risk, for which three hypothetical gene variants at different loci and one environmental exposure are modest risk factors (risk ratios 1.5 to 3.0), the positive predictive value of information for subjects with a variant allele at two to three loci could be 50 to 100 percent in the presence of a modifiable exposure.[173] Thus, there has been mounting interest in the possibility that panels comprising combinations of germline genetic variants (SNPs) might be of value in screening for common chronic diseases,[179,180] including prostate cancer. The aim of this review is to assess the evidence as to the possible value of SNP panels in the detection of, and prediction of risk for, prostate cancer.

Table 1. Replicated associations between prostate cancer and SNPs in GWA studies

Chromosomal Region	rs Number	Intergenic or Intronic[61]	Reported Gene	Reference
2p11.2	10187424	Intergenic	*GGCX , VAMP8, VAMP5, RNF181*	Kote-Jarai, et al., 2011[170]
2p15	721048	Intronic	*EHBP1*	Gudmundsson, et al., 2008[162]
2p15	6545977	Intergenic		Eeles, et al., 2009[168]
2p21	651164	Intronic	*LOC1002891682*	Eeles, et al., 2009[168]
2p24.1	13385191	Intronic	*C2orf43*	Takata, et al., 2010[166]
2q31.1	12621278	Intronic	*ITGA6*	Eeles, et al., 2009[168]
2q37.3	2292884	Intergenic	*MLPH*	Schumacher, et al., 2011[169]
2q37.3	7584330	Intergenic		Kote-Jarai, et al., 2011[170]
3p11.2	7629490	Intergenic		Schumacher, et al., 2011[169]
3p12.1	2660753	Intergenic		Eeles, et al., 2008[163]
3p12.1	17181170	Intergenic		Eeles, et al., 2009[168]
3p12.1	9284813	Intergenic		Takata, et al., 2010[166]
3q21.3	10934853	Intronic		Gudmundsson, et al., 2009[165]
3q23	6763931	Intronic	*ZBTB38*	Kote-Jarai, et al., 2011[170]
3q26.2	10936632	Intergenic	*SKIL, CLDN11*	Kote-Jarai, et al., 2011[170]
4q22.3	17021918 and 12500426	Intronic	*PDLIM5*	Eeles, et al., 2009[168]
4q24	7679673	Intergenic	*TET2*	Eeles, et al., 2009[168]
5p12	2121875	Intronic	*FGF10*	Kote-Jarai, et al., 2011[170]
5p15.33	12653946	Intergenic		Takata, et al., 2010[166]
5p15.33	2242652	Intronic	*TERT*	Kote-Jarai, et al., 2011[170]
6p21.1	1983891	Intronic	*FOXP4*	Takata, et al., 2010[166]
6p21.33	130067	Missense	*CCHCR1*	Kote-Jarai, et al., 2011[170]
6q22.1	339331	Intergenic	*GPRC6A, RFX6*	Takata, et al., 2010[166]
6q25.3	651164	Intergenic	*SLC22A1*	Schumacher, et al., 2011[169]
6q25.3	9364554	Intronic	*SLC22A3*	Eeles, et al., 2008[163]
7p15.2	10486567	Intronic	*JAZF1*	Thomas, et al., 2008[161]
7q21.3	6465657	Intronic	*LMTK2*	Eeles, et al., 2008,[163] 2009[168]
8p21.2	1512268	Intergenic	*NKX3.1*	Eeles, et al., 2009;[168] Takata, et al., 2010[166]
8q24.21	1447295	Intergenic		Yeager, et al., 2007;[158] Gudmundsson, et al., 2007a;[159] Gudmundsson, et al., 2009[165]
8q24.21	6983267	Intergenic		Yeager, et al., 2007;[158] Thomas, et al., 2008;[161] Eeles, et al., 2008[163]
8q24.21	1690179	Intergenic		Gudmundsson, et al., 2007a;[159] Gudmundsson, et al., 2009[165]
8q24.21	Hap C	Intergenic		Gudmundsson, et al., 2007a[159]
8q24.21	4242382	Intergenic		Thomas, et al., 2008;[161] Eeles, et al., 2008;[163] Eeles, et al., 2009[168]
8q24.21		Intergenic		Schumacher, et al., 2011[169]
8q24.21	1016343	Intergenic		Eeles, et al., 2008;[163] Schumacher, et al., 2011[169]
8q24.21	16902094	Intergenic		Gudmundsson, et al., 2009[165]
8q24.21	445114	Intergenic		Gudmundsson, et al., 2009;[165] Schumacher, et al., 2011[169]

Table 1. Replicated associations between prostate cancer and SNPs in GWA studies (continued)

Chromosomal Region	rs Number	Intergenic or Intronic[61]	Reported Gene	Reference
8q24.21	1456315	Intergenic		Takata, et al., 2010[166]
8q24.21	6983267	Intergenic		Schumacher, et al., 2011[169]
8q24.21	7837688	Intergenic		Takata, et al., 2010[166]
8q24.21	13252298	Intergenic		Schumacher, et al., 2011[169]
10q11.23	10993994	Intronic	*MSMB*	Thomas, et al., 2008;[161] Eeles, et al., 2008;[163] Schumacher, et al., 2011[169]
10q26.12	11199874	Intergenic		Nam, et al., 2012[171]
10q26.13	4962416	Intronic	*CTBP2*	Thomas, et al., 2008[161]
11p15.5	7127900	Intronic	*ASCL2*	Eeles, et al., 2009[168]
11q13.3	10896449	Intergenic		Thomas, et al., 2008[161]
11q13.3	7931342	Intergenic		Eeles, et al., 2008[163]
11q13.3	7130881	Intergenic		Eeles, et al., 2009;[168] Schumacher, et al., 2011[169]
11q13.3	11228565	Intergenic		Gudmundsson, et al., 2009[165]
12q13.12	10875943	Intergenic	*PRPH*	Kote-Jarai, et al., 2011[170]
12q13.3	902774	Intergenic	*KRT8, EIF4B, TENC1*	Schumacher, et al., 2011[169]
13q22.1	9600079	Intergenic		Takata, et al., 2010[166]
15q21.1	4775302	Intergenic		Nam, et al., 2012[171]
17q12	4430796	Intronic	*TCF2*	Gudmundsson, et al., 2007b;[160] Thomas, et al., 2008;[161] Gudmundsson, et al., 2009[165]
17q12	7501939	Intronic	*HNF1B*	Eeles, et al., 2008,[163] 2009;[168] Takata, et al., 2010;[166] Schumacher, et al., 2011[169]
17q21.33	7210100	Intronic	*ZNF652*	Haiman, et al., 2011[167]
17q24.3	1859962	Intergenic		Gudmundsson, et al., 2007b;[160] Eeles, et al., 2008,[163] 2009;[168] Schumacher, et al., 2011[169]
19q13.2	8102476	Intergenic		Gudmundsson, et al., 2009[165]
19q13.33	2735839	Intronic	*KLK3*	Eeles, et al., 2008[163]
22q13.1	9623117	Intronic	*TCNC613*	Sun, et al., 2009[164]
22q13.2	742134	Intronic	*BIK*	Schumacher, et al., 2011[169]
22q13.2	4242384	Intronic	*RPS25P10*	Eeles, et al., 2009[168]
22q13.2	5759167	Intergenic		Eeles, et al., 2009[168]
Xp11.22	5945572, 5945619	Intronic	*NUDT11*	Gudmundsson, et al., 2008;[162] Eeles, et al., 2008,[163] 2009[168]
Xq12	5919432	Intergenic	*AR*	Kote-Jarai, et al., 2011[170]

Scope and Purpose of This Review

The Centers for Disease Control and Prevention (CDC), through the office of Public Health Genomics, and the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project, requested a review of the evidence on the use of SNP-based genotyping panels to assess risk of prostate cancer. The overall goal of EGAPP is to facilitate the use of evidence-based decisionmaking that will assist health care providers, consumers, policymakers, and payers in distinguishing genetic tests that are safe and useful, and guiding their appropriate application in clinical practice. Within the "ACCE framework" (see Table 2), the EGAPP working group has

developed approaches to evaluating, synthesizing, and grading evidence.[181] This synthesis will be used by EGAPP to develop evidence-based recommendations on the application of SNP-based panels to prostate cancer. The overarching goal of the use of such panels is to facilitate early detection of, and enhance the ability to target men at increased risk for prostate cancer, as well as to assist in targeting invasive interventions at those men with diagnosed prostate cancer who are most likely to have an unfavorable prognosis.

An initial set of questions was proposed by the EGAPP to guide the development of the evidence report, focusing on all aspects of the use of these panels. The intent of the original questions was to encompass all areas of evaluation, including analytic and clinical validity of panels and associated algorithms for prostate cancer risk assessment, their clinical utility in bringing about change in clinical decisionmaking, and their potential for harm.

Table 2. Elements and key components of evaluation framework for SNP-based panels in prostate cancer risk assessment[182]

Element	Definition	Components
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (e.g., genomic variations) that it is intended to measure	Analytical sensitivity Analytical specificity Reliability (e.g., repeatability of test results) Assay robustness (e.g., resistance to small changes in preanalytic or analytic variables)[183]
Clinical validity	A measurement of the accuracy with which a test or tool identifies or predicts a clinical condition	Clinical sensitivity Clinical specificity Positive predictive value Negative predictive value
Clinical utility	Degree to which benefits are provided by positive and negative test results	Availability and impact of effective interventions Health risks and benefits Economic assessment
Ethical, legal, and social implications	Issues affecting use of SNP-based panels that might negatively impact individuals, families, and society	Stigmatization Discrimination Psychological harms Risks to privacy and confidentiality

Note: Reprinted from Amer Jour Prev Med 24(2), Yoon PW, Scheuner MT, and Khoury MJ., Research Priorities for Evaluating Family History in the Prevention of Common Chronic Diseases. Pages 128-35, 2003, with permission from Elsevier.

Objectives of This Review

The primary objectives of the review were to identify, synthesize, and appraise the literature on the use of SNP-based panels in men who may be at risk of prostate cancer, encompassing all relevant areas of test evaluation as proposed by the ACCE framework. Anticipating a limited evidence base for some of the key questions, an objective of this review was also to characterize the knowledge gaps and provide targeted recommendations for future research.

Key Questions of This Review

The original key questions articulated in the Task Order were revised and rearticulated for the purposes of clarity. Thus, the three Key Questions (KQs) encompassing broad aspects of the analytic validity, clinical validity, and clinical utility of SNP-based panels were developed with the input of a Technical Expert Panel (TEP) whose membership was nominated by the Evidence-based Practice Center and approved by the Agency for Healthcare Research and Quality (AHRQ).

Note: for the purposes of the review, the term 'SNP-based panels' is used to indicate any risk assessment system designed to assess risk of prostate cancer, which incorporates one or more defined SNPs alone or in combination with other indicators.

KQ1. What is the analytic validity of currently available SNP-based panels designed for prostate cancer risk assessment?

1. What is the accuracy of assay results for individual SNPs in current panels?
2. What is the analytic validity of current panels whose purpose is, or includes, predicting risk of prostate cancer?
3. What are the sources of variation in accuracy or analytical validity across different panels?

KQ2. What is the clinical validity of currently available SNP-based panels designed for prostate cancer risk assessment?

1. How well do available SNP-based genotyping platforms predict the risk of prostate cancer in terms of
    a. stratifying future risk and/or screening for current disease?
    b. distinguishing between clinically important and latent/asymptomatic prostate cancer?
    c. How well do available SNP-based genotyping panels predict prognosis in individuals with a clinical diagnosis of prostate cancer?
2. What other factors (e.g., race/ethnicity, gene-gene interaction, gene-environment interaction) affect the predictive value of available panels and/or the interpretation of their results?

KQ3. What is the clinical utility of currently available SNP-based panels for prostate cancer risk assessment, in terms of the process of care, health outcomes, harms, and economic considerations?

Process of care

1. Does the use of panels alter processes of care and behavior, in terms of
    a. screening or management decisions, and the appropriateness of these decisions, by patients and/or providers
    b. alteration in health-related behaviors of patients (e.g., adherence to recommended screening interventions and/or other lifestyle changes)?

Health outcomes

2. Does the use of panels lead to changes in health outcomes, in terms of
    a. all-cause mortality
    b. cancer-specific mortality
    c. morbidity, and do any such changes vary by race or ethnicity?

Harms

3. Does the use of panels lead to harms in terms of
    a. psychological harms

b. other negative individual impacts (e.g., discrimination), and do any such harms vary by race or ethnicity?

Economics

4. What is known about the costs, cost-effectiveness, and/or cost-utility of using SNP-based panels for prostate cancer risk assessment, compared to current practice?

Methods

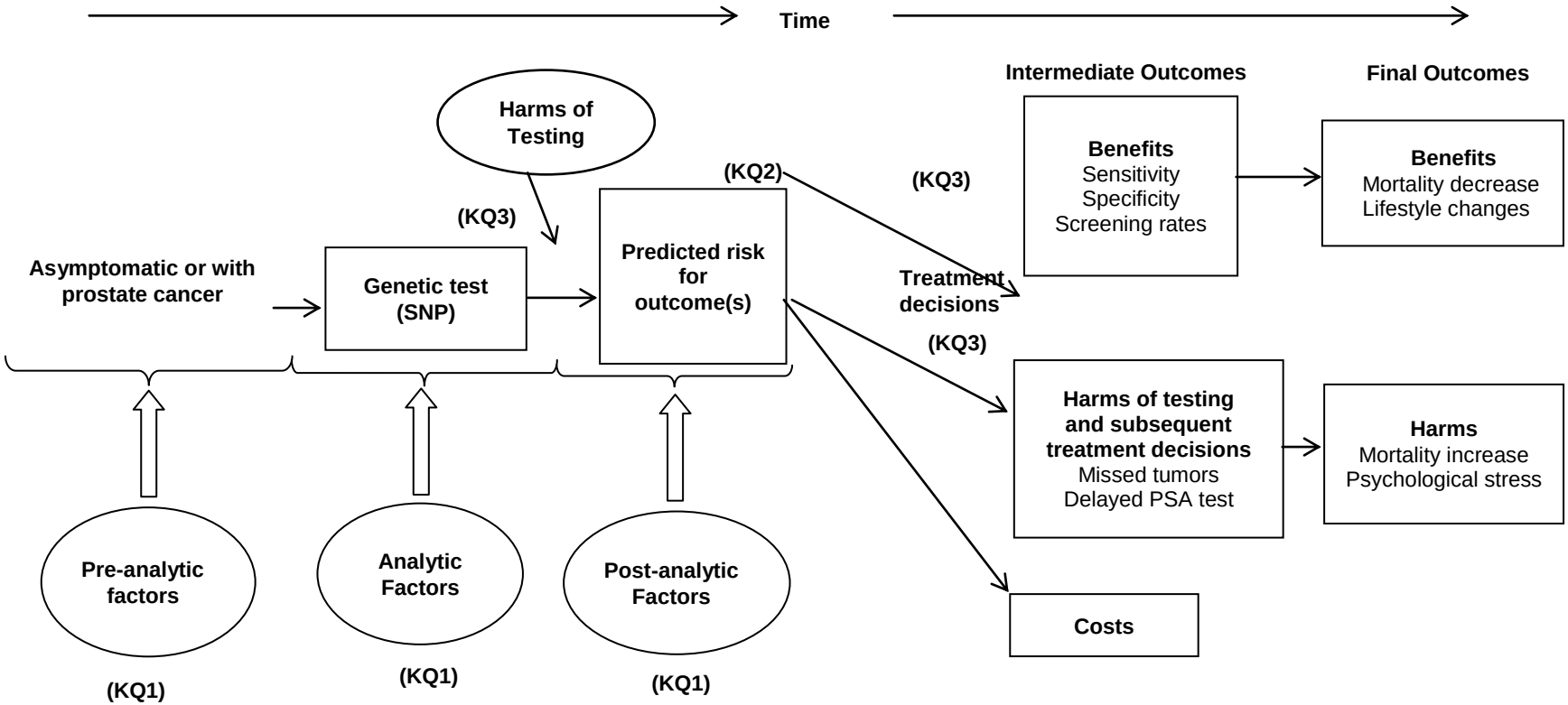
Topic Development

The McMaster University Evidence-based Practice Center (MU-EPC) engaged with representatives of Evaluation of Genomic Applications in Practice and Prevention (EGAPP) to seek clarification on the intended uses for the evidence report and for future recommendations. Subsequently, a Technical Expert Panel (TEP) was assembled, whose membership was nominated by the Evidence-based Practice Center and approved by the Agency for Healthcare Research and Quality (AHRQ). The TEP advised MU-EPC on aspects of the Key Questions (KQs), which were then revised to reflect the intent of the report from the perspective of AHRQ and EGAPP.

Analytic Framework

Figure 1 depicts the KQs within the context of the study selection criteria described in the following section. In general, the figure illustrates how the use of single nucleotide polymorphisms (SNP) test panels may result in different types of intermediate and final outcomes, including adverse events.

Figure 1. Use of multigene panels involving SNPs for prostate cancer risk assessment



Search Strategy

Studies were limited to those published in English, from the beginning of each database to October 2011. The following databases were searched: MEDLINE®, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and EMBASE. Strategies used combinations of controlled vocabulary (medical subject headings, keywords) and text words (see Appendix A).

Review was limited to commercially available SNP panels. The commercial availability of a test panel was defined as a clinical test offered (or soon to be offered) by a certified laboratory, or licensed or certified kit reagent test panels sold for use by clinical service laboratories within continental North America. To identify potential test panels for review, the following sources of information were used: PubMed, the Genetests Web site (now www.ncbi.nlm.nih.gov/sites/GeneTests/), grey literature, and letters to companies. Grey literature was identified through searching the Web sites of relevant specialty societies and organizations, Health Technology Assessment agencies (Hayes Inc. Health Technology Assessment), guideline collections, regulatory information (i.e., United States Federal Drug Agency, Health Canada, Authorized Medicines for European Community), clinical trial registries (i.e., clinical.trials.gov, Current Controlled Clinical Trials, Clinical Study Results, World Health Organization (WHO) Clinical Trials), grants and federally funded research (i.e., National Institute of Health (NIH), HSRPROJ), abstracts and conference proceedings (i.e., Conference Papers Index, Scopus), and the New York Academy of Medicine's Grey Literature Index. On behalf of the authors, the Scientific Resource Center directly contacted 40 companies known to provide either test services or diagnostic reagents potentially relevant to the key questions, in an effort to elicit unpublished sources of information.

Review of reference lists of included studies was undertaken. Any potentially relevant citations were cross-checked with our citation database. Any references not found were retrieved and screened at full text. Study authors were contacted to request details of relevant unpublished data.

Study Selection

Studies without a quantitative component were excluded (e.g., editorials, commentaries, notes, and qualitative studies). No restrictions were placed on study setting, minimum sample size, or duration of followup.

Intervention

For all KQs, the eligible intervention was a commercially available (or soon to be available) test panel with at least two SNPs, at least one of which must have been validated in a genome-wide association (GWA) study. The criterion of having been validated in a GWA study was imposed because many associations with candidate genes have not been found to be replicated.[154,155] We operationalized this criterion by checking the list of included SNPs against the list presented in Table 1, which was developed by reviewing the original articles indexed in the National Human Genome Research Institute GWA catalogue.[184] Validation required observation of association in one or more independent data sets with a significance level of $p<10\text{-}5$. Studies of single gene tests, and/or panels which were not commercially available, were excluded. A test panel was defined by the list of SNPs (or other genetic sequence analytes) included in the assay. The included SNPs could be either informative (i.e., provide test results

utilized in the interpretation of the result), or be controls used to assist in determining the accuracy and conclusiveness of the test result.

Table 3 summarizes the eligibility criteria by KQ.

Table 3. Eligibility criteria

	Eligibility	Population/ Participants	Study Designs	Comparators	Outcome
KQ1: Analytic validity	Inclusion	Biological samples derived from human populations	Split sample comparative studies External proficiency assessment Genotyping applied to standard reference materials	With reference method (validity) Between same method applied more than once (repeatability)	Analytical sensitivity Analytical specificity Reliability (e.g., repeatability of test results) Assay robustness (e.g., resistance to small changes in preanalytic or analytic variables)
	Exclusion		Gene discovery studies	N/A	
KQ2: Clinical validity	Inclusion	Males only	Clinical test evaluations Controlled/uncontrolled trials Cohort studies Case-control studies	N/A	Prostate cancer Dx, stage/type, aggressiveness, mortality Overall mortality Survival Clinically actionable measures of disease recurrence
	Exclusion		Case reports Gene discovery studies (e.g., GWA studies[1])	N/A	
KQ3: Clinical utility *Process*	Inclusion		Randomized/ nonrandomized controlled trials Uncontrolled trials Interrupted time series analyses Cohort studies Case-control studies Clinical test evaluations	None Current risk assessment, screening, prognostic practices or tests (PSA, digital rectal examination, etc.) individually or in combination	Physician recommendations (e.g., PSA testing, digital rectal examination, biopsy, therapeutic intervention) Adherence with physician recommendations Health related behavior
	Exclusion		Case reports	N/A	
KQ3: Clinical utility *Health outcomes*	Inclusion		Randomized/non-randomized controlled trials Uncontrolled trials Interrupted time series analyses Cohort studies Case-control studies Clinical test evaluations	None Current risk assessment, screening, prognostic practices or tests (PSA, digital rectal examination, etc.) individually or in combination	Prostate cancer incidence Prostate cancer mortality All cause mortality Morbidity
	Exclusion		Case reports	N/A	

Table 3. Eligibility criteria (continued)

	Eligibility	Population/ Participants	Study Designs	Comparators	Outcome
KQ3: Clinical utility *Harms*	Inclusion		Randomized/non-randomized controlled trials Uncontrolled trials Interrupted time series analyses Cohort studies Case-control studies Clinical test evaluations	None Current risk assessment, screening, prognostic practices or tests (PSA, digital rectal examination, etc.) individually or in combination	Prostate cancer incidence Prostate cancer mortality All cause mortality Morbidity Psychological impact Insurance coverage Access to care
	Exclusion		Case reports Simulation studies	N/A	
KQ3: Clinical utility *Economics*	Inclusion		Cost analyses Cost effectiveness analyses Cost utility analyses Cost benefit analyses	None Current risk assessment, screening, prognostic practices or tests (PSA, digital rectal examination, etc.) individually or in combination (dependent on design)	Prostate cancer incidence Prostate cancer mortality All cause mortality Morbidity Utility Service use
	Exclusion		Studies without an economic component	N/A	

Abbreviations: Dx = diagnosis; GWA = Genome wide association study; N/A = not applicable; PSA = prostate-specific antigen

Data Abstraction

Relevant fields of information were abstracted from individual studies by trained data abstractors using standardized forms and a reference guide. Prior to performing the data abstraction, a calibration exercise was conducted using a random sample of two included studies. Key study elements were reviewed by a second person (study investigator) with respect to outcomes, seminal population characteristics, and characteristics of the intervention. Disagreements were resolved by consensus.

Data were abstracted on study characteristics, SNP panels, metrics specific to each KQ, and other relevant data. Abstracted data included study characteristics (author and publication year, study objective, study design, setting, location, dates of data collection, and source of study funding) as well as details of the study participants (eligibility, sources and methods of selection, and number assessed for eligibility). Information was also abstracted about SNPs (number genotyped, type of laboratory, genotyping method and if done blind to participant status, call rate, concordance rate for duplicate samples, other quality control checks, Hardy Weinberg equilibrium information, rs (reference SNP) number and chromosomal region by model, method for handling SNPs in analysis, and other variables included in SNP panel). Analysis data was abstracted that included: method of constructing SNP panel, method for validating SNP panel, missing data, measures used to evaluate SNP panel (e.g., odds ratios (ORs) by risk score, area under the receiver operator characteristics curve (AUC), ΔAUC, maximum test accuracy, and cross-validation consistency). Data for results was abstracted as follows: number of participants included in analysis, mean age and standard deviation by group, ethnicity, first-degree family history of prostate cancer, prostate-specific antigen (PSA), Gleason score, pathologic stage (Tumor, Nodes, Metastases [TNM]), aggressive disease (definition and proportion of cases with

aggressive disease), risk score, AUC, ΔAUC, other measure, subgroup analysis, results of validation if relevant (see Appendix B).

Assessment of Analytical Validity of Individual Studies

Information indicative of the rigor of assessment of analytical validity in individual studies was also abstracted and considered. Examples of sources of technical variation included:

1. *Pre-analytic phase:* sample collection and handling, storage of sample, transport time, patient characteristics (age, race, ancestry, family health, etc.), patient preparation, other patient related attributes;
2. *Analytic phase:* type of assay platform used and its reliability, specific analytes evaluated in the panel (specification of alleles, genes, or biochemical analytes), genotyping methods used, inclusion of relevant alleles), the type of software used to analyze and call SNPs (determination of positive or negative conclusion) of the test, and post-hoc review to ensure the result is correct (looking and reviewing the batch) was considered; and,
3. *Post-analytic phase:* type of quality controls utilized, difficulty of interpretation, method of test interpretation and application, reporting protocols, post-test interpretation, contents of the report, and counseling information provided to the patient.

Assessment of Methodological Quality of Individual Studies

The methodological quality was interpreted to include primarily elements of risk of bias (systematic error) related to the design and conduct of the study.

Assessment of Studies Relating to Analytic Validity

As there were no studies that solely provided data on analytical validity, quality assessment was not performed.

Assessment of Studies Relating to Clinical Validity

We selected the Newcastle-Ottawa Scale (NOS)[185] to assess risk of bias for observational studies (case-control and cohort). The study design elements evaluated with this tool include: selection of the study population, appropriate means for measuring exposures (case-control studies) and outcomes (cohort studies), and comparability of groups (controlling for confounding). We also selected some items from the QUADAS[186] to evaluate the risk prediction aspect of the included studies.

Applicability

Applicability was assessed by considering the key attributes of the population, intervention, comparator, and outcome in the context of a wider spectrum of patients in primary care settings that would likely benefit from these interventions in “real-world” conditions.

Rating the Body of Evidence

The overall strength of the body of the evidence was assessed using the AHRQ Strength of Evidence (SOE) approach.[187] There are several factors that influenced the overall strength of the evidence:

1. Study limitations (predominately risk of bias criteria);
2. Type of study design (experimental versus observational);

3. Consistency of results (degree to which study results for an outcome are similar; i.e. variability is easily explained, range of results is narrow);
4. Directness of the evidence (assesses whether interventions can be linked directly to the health outcomes); and,
5. Precision (degree of certainty surrounding an effect estimate for a specific outcome).

Publication Bias

Although the search strategy was comprehensive there is always the potential for publication bias. To help address publication bias, the Scientific Resource Centre (SRC) was asked to contact companies in an attempt to locate unpublished trials. No information was received from any of the companies.

Data Synthesis

A qualitative descriptive approach was used to summarize study characteristics and outcomes. Multiple publications for the same study were grouped together and treated as a single study, with the most current data reported for the presentation of summary results. Standardized summary tables explaining important study and target population characteristics, as well as study results, were created. Quantitative synthesis and subgroup analyses were not performed because of lack of comparability of the studies.

For KQ1, the analysis focused on assembling evidence that the SNP panels measured what they were intended to measure (i.e., their performance as assays). The metrics of primary interest were sensitivity, specificity, positive and negative predictive values, diagnostic OR, and the type of risk prediction (quantitative or qualitative) provided by the test, with the gold standard represented by some other form of genotyping. Because of the anticipated scarcity of relevant studies, we also scrutinized the reports for findings related to laboratory quality assurance (e.g., reliability (repeated sample testing), within and between laboratory precision, the time interval for testing, the proportion of specimens providing a conclusive result, failure rates for usable results, proportion of inconclusive results resolved, and more general evidence of external or internal quality control programs).

For KQ2, the focus of the analysis was on how well the SNP panels appeared to perform in classifying individuals in terms of the outcomes of interest (prostate cancer occurrence, detection, mortality, or stage/aggressiveness of cancer). The primary metrics were clinical sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratios, and AUC, and/or c-statistic.

For KQ3, the analysis assembled and evaluated the findings relating to the processes of care, health outcomes, harms, and economic aspects of using the SNP-based panels in practice. The range of relevant metrics was dependent on primary study design and the outcomes reported. For the economic analyses, direct and indirect cost estimates of the use of SNP-based panels were reviewed, and all cost-effectiveness and cost utility metrics were included.

Peer Review Process

Experts in the field were asked to act as peer reviewers for the draft report. They represented stakeholder groups including physicians, researchers and other professional representatives with knowledge of the topic. Additional peer reviewers included the Task Order Officer (TOO), associate editors, and members of the AHRQ internal editorial staff. The peer reviewer

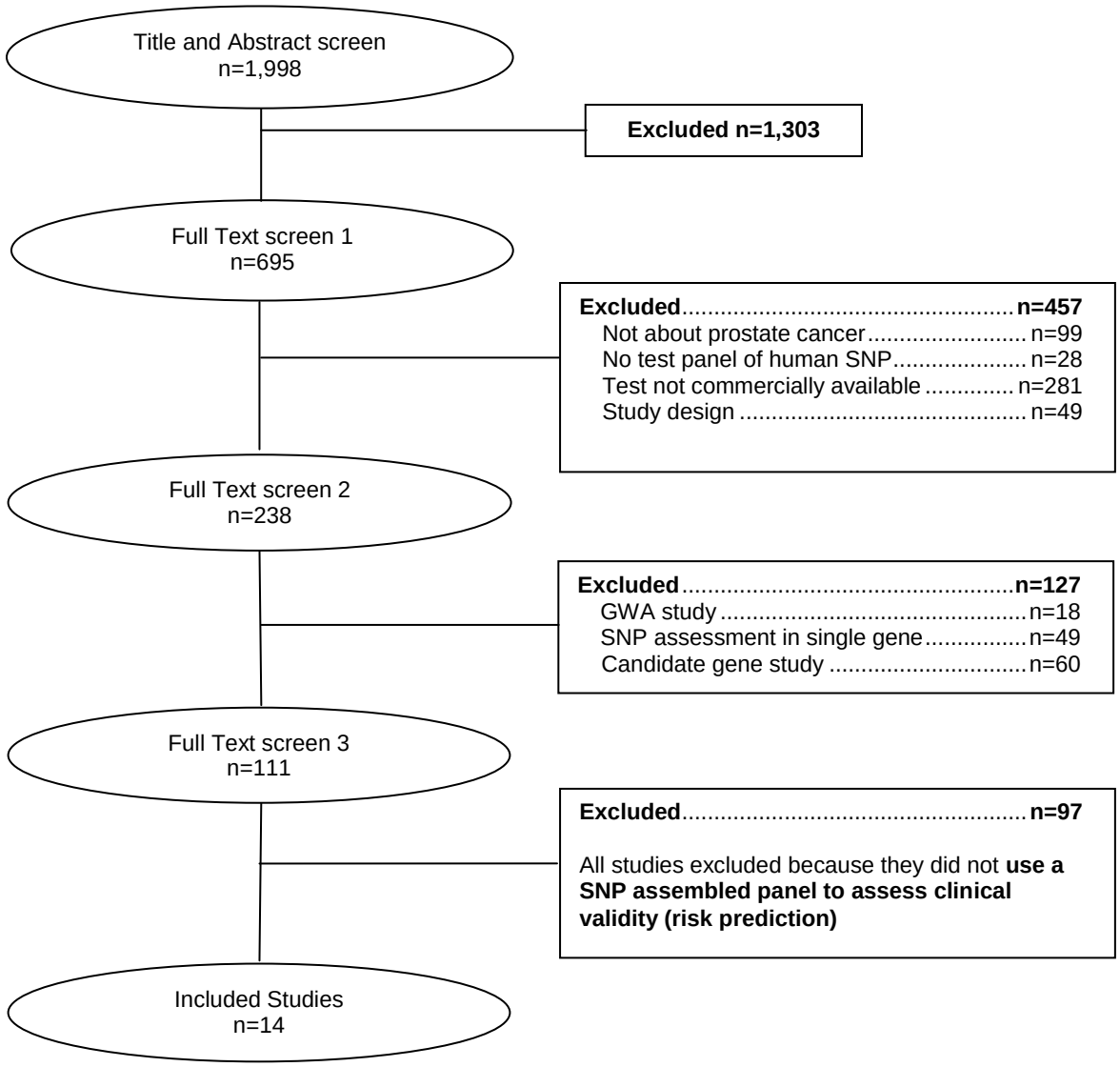
comments on the draft report were considered by the EPC in preparation of the final report. The responses to the peer reviewers were documented and will be published three months after the publication of the final evidence report.

Results

The literature search yielded 1,998 unique citations. In total, 1,303 (65 percent) were excluded from further review following the initial level of title and abstract screening. Because of the complexity of the content area, and challenges in defining the 'clinical relevance' of the reported evaluations, full text screening was conducted in three phases. The first phase was conducted by EPC staff and focused on the most straightforward assessment of the overall study against eligibility criteria; the second phase was conducted by investigators and focused on establishing the eligibility of the specific SNPs within the panel reported; the third phase was also conducted by the investigators and focused on deciding whether the SNP panel could be considered 'available' and whether the evaluation context could be considered, at least to some extent, clinically relevant. Therefore, out of the 695 citations promoted to full text screening, 457 were excluded at the first phase, 127 were excluded at the second phase, and 97 at the third phase. This left 14 articles [188-201] retained for the review, which proceeded to data abstraction and quality assessment. All 14 focused on the assessment of clinical validity (KQ2). Figure 2 depicts the flow of studies through the screening process, and reasons for study exclusion. The remainder of this chapter describes the evidence for the key questions (KQs) and a quality assessment of the studies.

One challenge that became evident during the assembly of source material for review was a lack of published data describing the technical protocols and analytical accuracies achieved for specific SNPs, and in particular, their analytical validation. There was also a paucity of information describing the laboratory protocols used to demonstrate the analytical validation of SNP panels used for clinical service testing. The reviewers sought but did not receive additional unpublished details about the analytical and clinical validation of proprietary commercial panels from the providers of these services. Therefore, from the articles eligible for KQ2 (clinical validity), we abstracted any information that was relevant to KQ1 (analytic validity).

Figure 2. Flow diagram depicting the flow of studies through the screening process



Characteristics of the Studies

All but two of the studies were of case-control design with the number of cases ranging from 203 to 2,899 and the number of controls from 560 to 1,781 (Tables 8 through 10). One study was a cross-sectional study of 5,241 men who had undergone prostate biopsy,[200] and one was an investigation of survival in 2,875 men diagnosed with prostate cancer.[201] The studies were carried out in Canada,[195] Sweden,[188,192,198,200,201] the United States,[189,191,194,196,197,199] (clarified in an email from W. Catalona, M.D. (WCatalona@nmff.org) in February 2012) and in both Sweden and the United States.[190,193]

There was complete overlap in the participants included from five of the six studies that included Sweden: a risk model was initially developed for a panel of 5 SNPs,[188] extended to 11 SNPs[192] in data from the same participants, then 14 SNPs,[193] and then 28 SNPs;[198] the study of prostate cancer survival used a 16-SNP panel.[201] For the initial 5-SNP model, validation was

undertaken in King County (Washington, United States),[189] and a combined estimate of the cumulative effect of the five risk variants was made, which incorporated these data and the Swedish data.[190] For the 14-SNP model, data from the United States were used for confirmation;[193] the U.S. data in this study was based on the same participants (in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Trial)[90] as in one of the U.S. studies used to validate the 5-SNP model.[190] There was also overlap between the studies in the United States, first of participants recruited at the Johns Hopkins Hospital, Baltimore 1999-2006,[190,194] second in participants recruited in King County, Washington 1993-2002 to 2002-2005,[189,197] and third in participants recruited in Chicago 2002-2008[191] and 1997-2009.[199]

Nine of the studies were concerned solely with the development of models for the prediction of risk for prostate cancer,[188,192,194,196-201] two solely with model validation,[189,190] and three with both development of new models and validation of previously-developed models.[191,193,195] All five of the studies that carried out model validation used data independent of those in which the models had been developed. However, in two of the studies, the teams of investigators validating the models included some who were also involved in the model development.[190,193]

Most of the studies related to participants of European origin. In all but one[200] of the studies of Swedish participants,[188,190,192,193,198,201] the ethnicity was not explicitly specified. All but one of the studies of United States' participants were limited to men of European origin.[189-191,193,194,197,199] The exception to this presented a stratified analysis for non-Hispanic European (54 percent of controls), Hispanic (33 percent), and African-American origin (13 percent).[196] The study including Canadian subjects also related to ethnically diverse participants: European origin (81 percent of controls), Asian (8 percent), black (7 percent), and other (4 percent); some analyses were adjusted for ethnicity and some were restricted to participants of European origin.[195]

In one study, estimates were presented separately for cases from families in which two additional first-degree relatives had been diagnosed with prostate cancer and for cases that were recruited irrespective of family history.[194]

Eight studies presented information on the proportion of cases and controls with a family history of prostate cancer. In five, this was specified as relating to first-degree relatives – in three different analyses of the same Swedish participants, the proportion of cases with a family history was 19 percent and controls 9.4 percent,[188,192,198] in a study in King County, WA, the proportions were 21.6 percent and 11.1 percent, respectively,[189] and in the study in which cases were recruited in Chicago, IL, and St. Louis, MO, the proportions were 36.4 percent and 14.9 percent.[199] In one study, family history referred to first- and second-degree relatives, and the proportion of cases for which such a history was reported was 11.6 percent and of controls 6.1 percent.[193] In the other two studies, the degree of relationships included in "family history" were not defined: in the Canadian study, the proportion for cases was 16.4 percent and for controls was 12.1 percent,[195] while in the Stockholm study, the proportions were 29.0 percent and 21.9 percent respectively.[200]

Ten articles were based on newly incident cases, one that related to the Canadian study (cases detected following referral for prostate-specific antigen (PSA) ≥4.0ng/mL or abnormal digital rectal examination without previous history of prostate cancer),[195] six to data on the same participants from Sweden,[188,190,192,193,198,201] one to the Stockholm study,[200] and two to partially overlapping studies from the United States.[189,197]

Two publications (one of which also reported on participants from Sweden) reported analyses on prevalent cases from overlapping studies in the United States.[190,194] One study in the

United States was based on a mixture of newly incident and prevalent cases.[196] In another two, it was unclear whether the cases were newly incident or prevalent – it was stated only that the cases were recruited after radical prostatectomy.[191,199]

The mean age of cases ranged from 56.8 years[193] to 70.5 years.[197] There was no obvious pattern according to inclusion of newly incident or prevalent cases.

As might be expected given trends in PSA testing, there appeared to be a pattern that the average PSA level at diagnosis of cases was lower for more recent study periods. The proportion of cases with a PSA level of ≤4ng/ml varied between under 8 percent in Canada 1999-2007[195] and Sweden 2001-2003,[188,192,198] to 13.6 percent in Washington State (United States) 1993-1996 and 2002-2005,[202] and 22 percent in Chicago 2002-2008.[191]

Where reported (n=9), the proportion of cases with a Gleason score of ≤6 at diagnosis ranged from 51 percent (Physicians' Health Study) 1982-2008[197] to 81 percent (Chicago and St. Louis 1997-2009).[199] Only one study[190] explicitly referred to having used the revised scoring as described by Epstein, et al.,[62] for the Johns Hopkins Hospital component of the study. The stage at diagnosis was reported for the Swedish cases,[188,192,198,200,201] in the study comprising three sets of cases and controls in the United States,[197] and the Chicago study;[191] over two-thirds of the cases were stage T2 or less at diagnosis. All of the cases in the Chicago-St. Louis study were stage T1c at diagnosis.[199]

In some of the studies, cases and controls clearly derived from the same study base. Thus, in the Canadian study, controls were selected from the same group of men referred to the prostate cancer centers of the University of Toronto who had either a PSA value ≥4.0ng/ml or an abnormal digital rectal examination (DRE), and who had no biopsy evidence of prostate cancer.[195] In five of the studies including Swedish cases, the controls were population-based and selected from the Swedish population registry.[188,190,192,193,198] In the Stockholm study, participants had undergone at least one prostate biopsy.[200] The cases from the PLCO Trial were compared with controls participating in the trial.[193,203] Cases arising in the Physicians' Health Study[197] and cases from the San Antonio cohort[196] were compared with controls selected from the same cohorts. Cases with prostate cancer in King County, Washington were compared with men without a self-reported history of prostate cancer who were resident in the county and identified by random digit dialing (participation rate 44.5 to 51.6 percent).[189,197] Cases from the Johns Hopkins Hospital series, all of whom had undergone radical prostatectomy, were compared with men undergoing surgery for prostate cancer at the Johns Hopkins Hospital and in the greater Baltimore metropolitan area who had normal DRE, PSA <4.0ng/ml, and were aged >55 years.[190,194] Cases for the Northwestern Memorial Hospital series, all of whom had undergone radical prostatectomy, were compared with 777 healthy male volunteer controls; from these, 247 may have been selected for the Icelandic genealogical database or from other genome-wide association (GWA) studies at deCODE, while the remaining participants were from a prostate cancer screening program done in April 2007 (it is not stated where this occurred).[191,204] In the Chicago-St. Louis study,[199] 203 stage T1c cases (who had undergone radical prostatectomy, had a PSA <4.0ng/ml and a nonsuspicious DRE) were compared with 611 controls who had a PSA <4.0ng/ml, normal DRE, and no prior history of prostate biopsy that are stated to have been selected from a GWA study that included participants from the University of Chicago and Northwestern,[205] per an email from W. Catalona. M.D.(WCatalona@nmff.org) on February 2, 2012.

Source of Funding and Conflict of Interest

All of the studies were publicly funded. In addition, two studies received support from deCODE Genetics.[191,199] All but five studies[189,190,194,198,199] included conflict of interest statements. Of the nine studies in which there was such a statement, two referred to the filing of a patent application[188,192] and two indicated specific nonpublic funding received by one of the authors.[191,197]

Overview of the SNP-Based Genotype Panels

There were 15 panels identified from the included studies (Tables 11 and 12). The number of SNPs included in the panels ranged from two to 35. Almost all of the individual SNPs had been discovered and replicated as being associated with prostate cancer in GWA studies.

Apart from overlap for the five SNPs included in the Focus 5 test panel, there were considerable differences between the panels assessed (Table 12).

The first test panel included five SNPs as described in the article of Zheng, et al.,[188] and is the basis of the Focus 5 predictive test for prostate cancer. A patent application has been filed by Xu, et al.,[206] "Methods and compositions for correlating genetic markers with prostate cancer risk." The test has been marketed by Proactive Genomics.[207] Four other articles assessed this test in independent data.[189-191,195]

The second test, again initially proposed by Zheng, et al.,[188] included family history with the five SNPs included in the first test, and two of the articles that assessed the first test panel also assessed this test.[189,190] In two of these studies, family history was defined to include first degree relatives.[188,189]

The other 13 tests were reported in 11 articles[191-201] (Table 11). Four of these included family history, two in first-degree relatives,[192,198] one in first- and second-degree relatives,[193] and one in relatives of unspecified degree.[200]

deCODE markets the deCODE ProstateCancer test, which tests for 27 genetic variants associated with prostate cancer in men of European descent (including the five SNPs included in the Focus 5 test), a subset of 9 variants for African-American men, and a subset of 12 variants for men of East Asian descent (Table 13); the specific variants in the subsets are not specified in the Web site (www.decodhealth.com/prostate-cancer).[208] If the deCODE ProstateCancer is sought separately, it has to be obtained through a licensed health professional. The test can also be ordered as part of the deCODEme Complete Scan, which analyzes genetic risk factors for 47 traits and conditions ($1,100 USD as of 19 June 2011) or the deCODEme Cancer Scan, which analyzes genetic risk factors for seven types of cancer ($500 USD).[209] A patent application was filed by Gudmundsson, et al., in May, 2010.[210]

KQ1. What is the analytic validity of available SNP-based panels designed for prostate cancer risk assessment?

1. What is the accuracy of assay results for individual SNPs in current test panels?

No data addressing this question were identified in the literature search. Companies known to offer testing for the risk for prostate cancer based on SNP panels were approached in May 2011, as were companies known to offer genetic testing more generally. As of September 1, 2011, no response had been received. From the articles that were identified as providing information

relevant to the assessment of the clinical validity of SNP panels (KQ2), no data were presented on the analytic validity of individual SNPs from which the panels were composed.

2. ***What is the analytic validity of current test platforms whose purpose is, or includes, predicting risk of prostate cancer?***

5-SNP panel. The 5-SNP panel that is the basis of the Focus 5 test, and the test that incorporates family history of prostate cancer, was genotyped using the Mass ARRAY QGE iPLEX system (Sequenom) in the report in which these models were developed.[188] The same method was applied in samples from the Johns Hopkins Hospital[190] and Canada.[195] Some of the analytic validity information relevant to the initial study in Swedish samples[188] are reported in other articles which relate to the same platform, including the initial five SNPs as well as additional SNPs.[192,193,201] A call rate of 98.3 percent was reported,[192,193,201] with a concordance rate for duplicate SNPs of >99 percent, and the genotypes for each SNP conformed to Hardy-Weinberg equilibrium (HWE) in controls.[188,192,193] (For the purpose of this report, call rate was defined as the proportion of samples for which genotypes are called for a converted marker). It was not reported whether genotyping was done blind to case-control status.

The 5-SNP panel was genotyped with one modification (substitution of rs6983561 for rs16901979; it was stated that there was perfect correlation between these two SNPs in HapMap CEPH individuals), in a study using the Applied Biosytems (ABI) SNPlex Genotyping System.[189] There was perfect agreement for the five SNPs between 140 blind duplicate samples distributed across all genotyping batches. Genotyping was done blind to case-control status. All genotype frequencies observed in controls were consistent with HWE.

One of the sets of samples used to assess the 5-SNP panel was the PLCO trial.[190] Four of the SNPs had already been genotyped as part of a GWA.[159] The genotyping had been undertaken by means of Sentrix HumanHap300 and Sentrix HumanHap240 platforms (Illumina).[158,161] The fifth SNP (rs16901979 in 8q24) was imputed from the adjacent genotyped SNPs at 8q24.[190]

9-SNP panel. In the study of Helfand, et al.,[191] it is stated that genotyping was done by deCODE and reference is given to previous papers describing genotyping methods, quality control, and genotyping accuracy (5 companion papers).[159,160,162,165,205] The methods include the Illumina Infinium Human Hap300 SNP chip, for which it is stated that samples with a call rate of <98 percent were excluded from analysis.[159,160,162,165] In addition, the Centaurus (Nanogen) platform was used[159,160,162,165,205] and the concordance rate of SNPs genotyped by both the Illumina and Centaurus methods was stated to be >99.5 percent.[159,160] It is also stated that all genetic variants were in HWE.[191]

17-SNP panel. In the Chicago-St. Louis study,[199] as for the 9-SNP panel, it is stated that genotyping was also done by deCODE and reference is given to the same companion papers describing genotyping methods, quality control, and genotyping accuracy.[159,160,162,165,205] It is also stated that all 17 genetic variants were in HWE in controls.[199]

11-SNP panel. This panel was genotyped using the Mass ARRAY QGE iPLEX system (Sequenom).[192] A call rate of 98.3 percent was also reported, with an average concordance rate for duplicate SNPs of 99.8 percent, and the genotypes for each SNP conformed to HWE in controls.[192] It was not reported whether genotyping was done blind to case-control status.

14-SNP panel. In the Swedish samples in this study, this panel was genotyped using the Mass ARRAY QGE iPLEX system (Sequenom).[193] A call rate of 98.3 percent and a concordance rate between duplicate samples included in each-96-well plate of 99.8 percent was reported. For the samples from the PLCO Trial included in this study, it is stated that 13 SNPs had been genotyped already as part of a companion paper,[161] and one (rs16901979 in 8q24) was imputed. In the PLCO samples, genotyping was undertaken by means of Sentrix® HumanHap300 and Sentrix HumanHap240 platforms (Illumina).[158,161] It is stated that tests for HWE in control participants in each of the two sets of samples were made, but results are not presented. It was not reported whether genotyping was done blind to case-control status.

16-SNP panel. This panel was genotyped using the Mass ARRAY QGE iPLEX system (Sequenom).[201] A call rate of 98.3 percent was reported, with an average concordance rate for duplicate SNPs of 99.8 percent. As the study examined survival in prostate cancer cases, conformity of the genotypes to HWE was only assessed in the cases; each SNP was stated to be in equilibrium.[201]

28-SNP panel. No specific information was presented in the article where this panel was reported.[198]

Three SNPs in 8q24. The three SNPs included in this test were part of 12 SNPs at 8q24 that were genotyped using the Mass ARRAY QGE iPLEX system (Sequenom), with a call rate of >98 percent and an average concordance rate between duplicate samples included in each-96-well plate of >99 percent.[194] Genotype proportions were consistent with HWE in controls.

4-SNP test: KLK2, HPC1, TNF, ETV1 and 8q24, 17q24, TNF, ETV1. The Sequenom iPLEX technology was applied in the genotyping of the Canadian study used to develop these tests. The call rate was >90 percent for 25 SNPs; six of these were not in HWE and were excluded from further analysis.[195] The call rate of SNPs significantly associated with prostate cancer was >95 percent.

Test for three SNPs in steroid hormone pathway genes. The three-SNP test in non-Hispanic whites was developed on the basis of the genotyping of 120 SNPs in the steroid hormone pathway by different methods.[196] One hundred and four of the SNPs were genotyped using the GoldenGate assay (Illumina), four by TaqMan, and the remainder by methods described in four publications.[109,211-213] It is stated that >80 percent of SNPs were successfully genotyped in >90 percent of the samples. Three SNPs failed (rs632148 within *SRD5A2*; rs280663 in *HSD97B3*; rs10877012 in *CYP27B1*) and one was not polymorphic (rs9332900 in *SRD5A2*). Three of the remaining SNPs were not in HWE in non-Hispanic whites and were excluded from the analysis of this ethnic group.

Test for two SNPs in steroid hormone pathway genes. The two-SNP test in Hispanic whites was developed on the basis of the genotyping of 120 SNPs in the steroid hormone pathway by different methods.[196] One hundred and four of the SNPs were genotyped using the GoldenGate assay (Illumina), four by TaqMan, and the remainder by methods described in four publications.[109,211-213] It is stated that >80 percent of SNPs were successfully genotyped in >90 percent of the samples. Three SNPs failed (rs632148 within *SRD5A2*; rs280663 in *HSD97B3*; rs10877012 in *CYP27B1*) and one was not polymorphic (rs9332900 in *SRD5A2*). Two of the remaining SNPs were not in HWE in Hispanic whites and were excluded from the analysis of this ethnic group.

6-SNP panel. This panel was developed to predict risk for prostate cancer in two sets of samples, and to predict risk for prostate cancer mortality in three, on the basis of genotyping six 8q24 and two 17q variants.[197] The Sequenom iPLEX technology was used to genotype samples from the Physicians' Health Study and the Gelb Center; there was >99 percent concordance for six SNPs that were assessed on a subset (n=1,370) of specimens twice.[197] The Applied Biosytems (ABI) SNPlex Genotyping System was used to genotype the samples from King County, Washington. None of the eight SNPs violated HWE in either set (Physicians' Health Study or King County, Washington) of controls. The call rate for the eight SNPs genotyped was >94 percent.

35-SNP panel. This panel was developed by genotyping 36 SNPs validated in previous studies using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry based on allele-specific primer extension using the Sequenom iPLEX technology.[200] Genotyping rs2660753 (at 3p12) failed completely. For the remaining 35 SNPs, a 98.6 percent average call rate was reported. Hardy-Weinberg equilibrium was assessed in controls, no departure from HWE was observed (per an email from H. Grönberg, M.D., Ph.D. (Henrik.Gronberg@ki.se) on February 2, 2012). The genotyping was performed at a core mutation analysis facility in Huddinge and was fully blinded to the case-control status (clarified in emails from H. Grönberg, M.D., Ph.D. (Henrik.Gronberg@ki.se), and M. Aly, M.D. (markus.aly@ki.se) on February 2, 2012).

deCODE ProstateCancer test. The company's Web site states that the deCODE ProstateCancer test is performed by Illumina I-Select Bead Chip method – and based on proprietary Illumina technology using DNA amplification hybridization and fluorescent detection.[208] Greater than 99.9 percent accuracy is claimed.

3. ***What are the sources of variation in accuracy or analytical validity across different test panels?***

No evidence to address this question was identified.

KQ2. What is the clinical validity of available SNP-based panels designed for prostate cancer risk assessment?

1. ***How well do available SNP-based genotyping platforms predict the risk of prostate cancer in terms of***

    a. ***stratifying future risk and/or screening for current disease?***

5-SNP panel (Focus 5) with and without inclusion of family history. Zheng, et al.,[188] developed a model for the cumulative effect of five SNPs, selected as the most significant of 16 SNPs genotyped in five chromosomal regions (three at 8q24, and two at 17q). The number of genotypes associated with prostate cancer was counted for each subject and showed a significant trend of association, with the odds ratio (OR) for four or more genotypes compared with none being 4.47 (95% CI, 2.93 to 6.80, adjusted for age, geographic region, and family history). When family history was included in the risk score for each subject, the OR for five or more factors (genotype or family history) was 9.96 (95% CI, 3.62 to 24.72, adjusted for age and geographic region). Receiver operating curves were calculated. The area under the curve (AUC) for a model including age and geographic region was 57.7 percent (95% CI, 56.0 to 59.3), for a model adding family history to these factors was 60.8 percent (95% CI, 59.1 to 62.4), and for a model further adding in the number of genotypes associated with prostate cancer was 63.3 percent (95% CI, 61.7 to 65.0). These data were also presented in a later paper focusing on the development of a 28-SNP panel.[198] In the later analysis, the sensitivities and specificities of a risk score combining the five SNPs and family history in first-degree relatives were presented for cutoffs of onefold, twofold, and threefold the median risk score (Table 4). As would be expected, sensitivity decreased and specificity increased with increasing cutoffs of absolute risk. The positive predictive value of the five SNPs (family history excluded) was 34 percent.

Table 4. Sensitivity and specificity for absolute risk of prostate cancer for risk score based on 5-SNP and family history (FHx) in first-degree relatives in Swedish study[198]

	5-SNP + FHx	
Cutoff	Sensitivity	Specificity
Onefold median	0.53	0.61
Twofold median	0.16	0.93
Threefold median	0.05	0.98

The model was tested in independent data from men of European origin in King County, Washington,[189] in data from the Johns Hopkins Hospital and the PLCO Cancer Screening Trial,[190] in a Canadian study,[195] and in a study in which cases underwent radical prostatectomy in a hospital in Chicago.[191] The pattern of association with risk score was attenuated compared with the original study of Swedish data,[188] with the OR for four or more genotypes compared with the reference category of no risk genotypes being 3.36 (95% CI, 1.90 to 6.08, adjusted for age and family history) in King County, 2.42 (95% CI, 1.4 to 4.1) in the Canadian study, 2.84 (1.30 to 6.21) in Johns Hopkins Hospital, 3.09 (95% CI, 1.62 to 5.90) in the PLCO Trial, and 3.19 (95% CI, 1.85 to 5.50, adjusted for age) in Chicago. In the Canadian study, the AUC for a baseline model that included age, family history of prostate cancer, ethnicity, urinary symptoms, PSA, free: total PSA ratio, and DRE was 72 percent (95% CI, 70 to 74), and with the addition of five SNPs, 73 percent (95% CI, 71 to 75).[195] In these studies, the proportion of controls with four or more risk genotypes ranged between 1.6 percent[190] and 3.4 percent,[191] while the population with five or more risk factors (one of which could be family history of prostate cancer) was 0.3 percent or less.[188-190]

When family history was included in the risk score, the ORs for five or more risk factors compared with none was 4.92 (95% CI, 1.58 to 18.53, adjusted for age) for King County,[189] and 20.68 (95% CI, 2.61 to 163.85) for the PLCO trial.[190] In the King County data, the AUC for a model including age, serum PSA level, and history of prostate cancer in a first-degree relative was 63 percent, which increased to 66 percent when the five SNPs were added (difference 3 percent, 95% CI, -12 to +6); this difference was not statistically significant.[189]

9-SNP panel. Helfand, et al.[191] extended the 5-SNP model, adding four variants at 2p15, 10q11, 11q13, and Xp11. The OR associated with having six or more of the nine risk genotypes was 5.75 (95% CI, 2.50 to 13.24), and the proportion of controls in the category of highest risk was 2.5 percent. For the model with five genetic variants, the crude AUC was 58 percent, and with adjustment for age, 65 percent. With inclusion of the four additional variants, the AUCs were 61 percent and 66 percent, respectively.

17-SNP panel. In the Chicago-St. Louis study (Helfand et al.),[199] the 9-SNP model was modified by changing one variant at 2p15, and adding one variant at 3q21.3, 11q13, 17q12, 19q13.2, and two at 5p15 and 8q24. The study differed from the others in that it was limited to men with a PSA level <4.0ng/ml and with normal DRE, and cases were limited to clinical stage T1c. Compared with men who had four or fewer variants, the OR for men with 11 or more variants was 10.6 (95% CI, 2.7 to 42.0), and the proportion of controls in this highest risk category was 2.5 percent. When history in first-degree relatives was added to the risk score, compared to men with zero to five variants/family history, the OR for men with 11 or more variants was 11.2 (95% CI, 4.3 to 29.2), and the proportion of controls in this highest risk category was 3.2 percent. The AUC for the model including all the carrier numbers of the 17 SNPs was 0.66; this was not significantly different from an AUC of 0.62 for age alone. The AUC of a model containing the 17 SNPs and family history was 0.71, which was statistically significantly higher than the model based on age alone.

11-SNP panel. Zheng, et al.,[192] examined the effect of including 14 additional SNPs in the same Swedish study participants as in the original 5-SNP model.[188] On the basis of an SNP by SNP analysis, 12 remained associated with prostate cancer risk after adjustment for age, family history, geographic region, and the other SNPs. However, one of these SNPs was not included in further analysis because it was originally discovered in this study population and "has not been extensively confirmed in other study populations."[192] Thus, further evaluation focused on counts of risk alleles for 11 SNPs and family history. The AUC for a model involving age only was 58 percent (95% CI, 56 to 59), for age and family history was 61 percent (95% CI, 59 to 62), and for age, family history, and all eleven SNPs was 65 percent (95% CI, 63 to 66). Stratified analysis of data on sensitivity and specificity by number of risk factors did not show differences by disease aggressiveness or age at diagnosis. These data were also presented in a later paper focusing on the development of a 28-SNP panel.[198] In the later analysis, the sensitivities and specificities of a risk score combining the 11 SNPs and family history in first-degree relatives were presented for cutoffs of onefold, twofold, and threefold the median risk score (Table 5). As would be expected, sensitivity decreased and specificity increased with increasing cutoffs of absolute risk. The positive predictive value of the 11 SNPs (family history excluded) was 37 percent.

Table 5. Sensitivity and specificity for absolute risk of prostate cancer for risk score based on 11-SNP and family history (FHx) in first-degree relatives in Swedish study[198]

	11-SNP + FHx	
Cutoff	Sensitivity	Specificity
Onefold median	0.54	0.62
Twofold median	0.18	0.92
Threefold median	0.07	0.98

14-SNP panel. The Swedish data were also investigated in development of a prediction model of absolute risk for prostate cancer using 14 SNPs and family history, and using data for the PLCO trial for confirmation.[193] The number of risk alleles could range from zero to 27 (because one of the risk alleles was on the X chromosome), with the mode being 11 for controls. In the Swedish data, the OR for prostate cancer in men who had ≥14 risk alleles and positive family history (which occurred in 1 percent of control men) compared with men with 11 risk alleles and no family history of prostate cancer was 4.92 (95% CI, 3.64 to 6.64). The corresponding OR for the PLCO trial data was 3.88 (95% CI, 2.83 to 5.33). In the Swedish data, the risk did not differ between aggressive and nonaggressive disease. With regard to absolute risk in Sweden, a 55 year old man with ≥14 risk alleles and a positive family history was estimated to have a 52 percent risk of being diagnosed with prostate cancer in the next 20 years, compared to a risk of 8 percent for men with seven or fewer risk alleles and no family history. The corresponding estimates for the men in the United States were 41 percent and 6 percent, respectively.

28-SNP panel. The Swedish data were also used in the development of a 28-SNP panel.[198] The AUC for the panel was 0.62, compared with 0.61 for the 11-SNP panel, and 0.60 for the 5-SNP panel; these differences were statistically significant. The sensitivities and specificities of a risk score combining the 28 SNPs and family history in first-degree relatives were presented for cutoffs of onefold, twofold, and threefold the median risk score (Table 6). As would be expected, sensitivity decreased and specificity increased with increasing cutoffs of absolute risk. The positive predictive value (PPV) of the 28-SNPs (family history excluded) was 37 percent. When the SNPs and family history were sorted on the basis of their contribution to genetic variance, from highest to lowest, at each cutoff of onefold, twofold, and threefold population median risk, the PPV increased only slightly with increasing numbers of SNPs.

Table 6. Sensitivity and specificity for absolute risk of prostate cancer for risk score based on 28-SNP and family history (FHx) in first-degree relatives in Swedish study[198]

	28-SNP + FHx	
Cutoff	Sensitivity	Specificity
Onefold median	0.55	0.62
Twofold median	0.23	0.91
Threefold median	0.11	0.97

Three SNPs in 8q24. One study in the Johns Hopkins Hospital investigated multiple variants of 8q24 in men with prostate cancer who had at least two additional first-degree relatives with prostate cancer, men who did not fall into this category, and controls.[194] To assess the combined effects of variants in three regions of 8q24, one variant from each region was selected. Compared to men with no risk genotype, the OR of prostate cancer for men with 2+ affected first-degree relatives for two or more risk genotypes was 2.94 (95% CI, 1.68 to 5.15), and for prostate cancer without such a family history was 2.23 (95% CI, 1.52 to 3.28).

4-SNP test: KLK2, HPC1, TNF, ETV1. In a Canadian study,[195] in addition to examining the 5-SNP model of Zheng, et al.,[188] a model comprising four SNPs, one each in *KLK2, HPCI, TNF,* and *ETV1*was evaluated. The OR associated with presence of all four variants compared with none was 2.53 (95% CI, 1.6 to 4.1). The proportion of controls that had variants of all four SNPs was 3.2 percent. The AUC for the baseline model that included age, family history of prostate cancer, ethnicity, urinary symptoms, PSA, free: total PSA ratio, and DRE was 72 percent (95% CI, 70 to 74), and with the addition of the four SNPs was 73 percent (95% CI, 71 to 74).

4-SNP test: 8q24, 17q24, TNF, ETV1. In the same Canadian study,[195] a model comprising four SNPs, one each from 8q24, 17q24.3, *TNF*, and *ETV1*, was evaluated. The OR associated with presence of all four variants compared with none was 6.07 (95% CI, 2.0 to 18.5). The proportion of controls that had variants of all four SNPs was 0.3 percent. The AUC for the baseline model that did not include SNPs (see above) was 72 percent, and with the four SNPs included was 74 percent (95% CI, 72 to 76). Using two thirds of the data, the investigators developed a nomogram that incorporated these SNPs, age, family history of prostate cancer, ethnicity, urinary voiding symptom, PSA level, free: total PSA ratio, and DRE in predicting all prostate cancer, and predicting prostate cancer with a Gleason score of 7 or more. Predicted and actual probabilities were compared in the remaining one third of the data, and the incremental drop in AUC for each predictor variable when removed from the nomogram model was assessed. The incremental drop was greater (1.4 percent) for the SNP combination than PSA (0.1 percent), family history of prostate cancer (0.3 percent), urinary voiding symptom (0.1 percent), and DRE (1.0 percent), but not age (2.2 percent) or free: total PSA ratio (6.6 percent).

Test for three SNPs in steroid hormone pathway genes. Beuten, et al.,[196] examined SNPs in the steroid hormone pathway. They presented information on the cumulative effect of three risk variants, (one in *HSD3B2*, two in *CYP19*) in non-Hispanic whites. There was a trend with an increasing number of risk genotypes. The OR for three risk genotypes compared with none was 2.87 (95% CI, 1.64 to 5.02, adjusted for age), with 3.6 percent of controls in the category of highest risk.

Test for two SNPs in steroid hormone pathway genes. In the investigation of SNPs in the steroid hormone pathway described in the preceding subsection, Beuten, et al.,[196] presented information on the cumulative effect of two risk variants (one in *CYP19*, different from those in non-Hispanic whites, one in *CYP24A11*) in Hispanic whites. Again, there was a trend with an increasing number of risk genotypes. The OR for two risk genotypes compared with none was 4.58 (95% CI, 2.19 to 9.61, adjusted for age), with 5.6 percent of controls in this category of risk.

6-SNP test. Penney, et al.,[197] evaluated eight SNPs, six in 8q24 and two in 17q, in data from the Physicians' Health Study (PHS) and from King County, Washington. Four of the 8q24 and the two 17q SNPs were significantly associated with prostate cancer in the two data sets, and the association with a risk score obtained by adding up the alleles was evaluated. The risk of prostate cancer increased by 19 percent for each additional risk allele in the PHS, and 23 percent in King County.

35-SNP panel. Aly, et al.,[200] focused their analyses relating to clinical validity of a 35-SNP panel on men with a PSA level ≤10 ng/ml as they considered that there is most debate over recommending a prostate biopsy in this group than in men with a higher PSA level. A genetic score was calculated by summing the number of risk alleles (0,1, or 2) at each of the 35 SNPs multiplied by the logarithm of the OR for that SNP. In univariate analysis, the OR associated with this score was 1.93 (95% CI, 1.85 to 2.01), with an AUC of 0.61 (95% CI, 0.59 to 0.63). In multivariate analysis, adjusting for PSA, the ratio of free-to-total PSA, age, and family history, the OR was 1.52 (95% CI, 1.45 to 1.59). The AUC for PSA, the ratio of free-to-total PSA, and age was 0.63 (95% CI, 0.60 to 0.65); the addition of family history increased this to 0.64 (95% CI, 0.62 to 0.66) and adding both family history and the genetic score increased the AUC to 0.67 (95% CI, 0.65 to 0.70).

Different risk cutoffs were assessed for: 1) the model comprising PSA, the ratio of free-to-total PSA, age, and family history; 2) the addition of the genetic score to this model; and, 3) a hypothetical genetic model based on a score variable constructed from SNPs explaining 100% of the population genetic risk. Comparisons were made of how these would affect the numbers of biopsies performed and cancer detected per 1,000 men with a clinical prostate biopsy (Table 7). The addition of the 35 SNPs (Model 2) to the factors included in Model 1 would reduce the number of biopsies conducted but increase the number of missed cancers. For the hypothetical genetic model (Model 3), the number of biopsies would be further reduced compared with Model 2, and the increase in proportion of missed cancers reduced.

Table 7. Comparison of effects on biopsies conducted and cancer detected per 1,000 men with a clinical prostate biopsy between three models of risk prediction for prostate cancer and two cutoffs

Model	Cutoff	Biopsies			Cancers		
		Conducted	Avoided	% Avoided	Detected	Missed	% Missed
Biopsies conducted and cancers detected		1000	0	0	365	0	0
1. PSA, the ratio of free-to-total PSA, age, and family history	20	949	51	5.1	352	13	3.6
	25	871	129	12.9	338	27	7.4
2. PSA, the ratio of free-to-total PSA, age, family history, and genetic score	20	878	122	12.2	344	21	5.8
	25	773	227	22.7	321	44	12.1
3. Hypothetical genetic model	20	745	255	25.5	348	17	4.7
	25	686	314	31.4	340	25	6.8

deCODE ProstateCancer test. The deCODE Prostate Cancer Web site states that the predictive accuracy of the 27-SNP ProstateCancer test panel, the 9-SNP subset for African-American men, and the 12-SNP subset for men of East Asian descent is essentially independent of, and therefore complements, the risk confirmed by family history of the disease.[208] The validity is reported to be based on the evaluation of risks associated with single SNPs; it is stated that the validity of multiplying together the risk conferred by different markers is based on the lack of significant interaction or overlap of impact between markers in two studies.[165,168]

b. Distinguishing between clinically important and latent/asymptomatic prostate cancer

5-SNP panel. In a case-only analysis of combined data from the Swedish, Johns Hopkins Hospital, and PLCO Trial participants, there was no statistically significant association between the five genetic variants, Gleason score, aggressiveness of prostate cancer,[214] or age at diagnosis.[190]

14-SNP panel. In the Swedish data investigated in the development of a prediction model of absolute risk for prostate cancer using 14 SNPs and family history, the OR for aggressive prostate cancer in men who had ≥14 risk alleles and positive family history compared with men with 11 risk alleles and no family history of prostate cancer was 4.77 (95% CI, 3.41 to 6.69).[193] The corresponding OR for nonaggressive prostate cancer was 5.05 (95% CI, 3.66 to 6.96). In addition, the risk associated with each increase in the number of risk alleles did not differ between aggressive and nonaggressive disease.

11-SNP panel. In the analysis of Zheng, et al.,[192] which developed a model comprising counts of risk alleles for 11 SNPs and family history, stratified analysis of data on sensitivity and specificity by number of risk factors did not show differences by disease aggressiveness or age at diagnosis.

35-SNP panel. In the study of Aly, et al.,[200] aggressive disease was defined as T3-4 N1 M1 or Gleason 4+3 and higher, and nonaggressive disease as T0-2 N 0/X M 0/X or Gleason 3 +=4 and lower. The increase in AUC for aggressive disease between a SNP-based model (35-SNPs) and a non-SNP-based model based on PSA, the ratio of free-to-total PSA, age, and family history was not statistically significant.

c. How well do available SNP-based genotyping panels predict prognosis in individuals with a clinical diagnosis of prostate cancer?

5-SNP panel (Focus 5) with and without inclusion of family history. In the study in King County,[189] described above, the predictive ability of the SNP panel for prostate cancer specific mortality over an average length of followup of 7.6 years was evaluated. There were 45 deaths among 1,207 men with followup data; there was no association with the SNPs individually or in combination, and they did not increase the AUC for a model that included age at diagnosis, serum PSA at diagnosis, Gleason score, and tumor stage (difference in AUC between model including SNPs compared to one without 0.5 percent, 95% CI, -1 to +2).

6-SNP test. In a survival analysis of the six SNPs found to be associated with prostate cancer in the data from the PHS and King County using the Cox proportional hazards model, there was no significant association between these variants and prostate cancer mortality.[197] In addition, comparison was made between prostate cancer deaths and men alive more than 10 years after diagnosis in a combined analysis that included both of these samples, together with a series of cases from the Dana-Farber Harvard Cancer Center diagnosed over the period from 1976 to 2007. The total number of risk alleles was not associated with mortality.

16-SNP panel. In a population-based study of survival after prostate cancer diagnosis in 2,875 men in Sweden over an average of 4.9 years (range 3.7 to 6.8 years), there was no association between prostate cancer mortality in a comparison with the average number of risk alleles, in a test for trend with an increasing number of risk alleles, or in relation to specific individual variants within the panel.[201]

None of the studies reported above presented data on risk reclassification or performance in simulation analyses.

3. ***What other factors (e.g., race/ethnicity, gene-gene interaction, gene-environment interaction) affect the predictive value of available panels and/or the interpretation of their results?***

Beuten, et al.,[196] developed separate tests for SNPs in steroid hormone pathway genes for non-Hispanic whites and Hispanic whites (see above).

deCODE markets the ProstateCancer test, which tests for 27 genetic variants (Table 13) associated with prostate cancer in men of European descent (including the five SNPs included in the Focus 5 test), a subset of nine variants for African-American men, and a subset of 12 variants for men of East Asian descent; the specific variants in the subsets are not specified in the Web site (www.decodhealth.com/prostate-cancer).[208]

KQ3. What is the clinical utility of available SNP-based panels designed for prostate cancer risk assessment?

Process of care

1. ***Does the use of panels alter processes of care and behavior?***
   a. ***screening or management decisions, and the appropriateness of these decisions, by patients and/or providers***
   b. ***alteration in health-related behaviors of patients (e.g., adherence to recommended screening interventions and/or other lifestyle changes)?***

No data addressing this question were identified.

Health outcomes

2. ***Does the use of panels lead to changes in health outcomes?***
   a. ***all-cause mortality***
   b. ***cancer-specific mortality***
   c. ***morbidity***

And do any changes vary by race or ethnicity?

No data addressing this question were identified.

Harms

3. ***Does the use of panels lead to harms?***
    a. ***psychological harms***
    b. ***other negative individual impacts (e.g., discrimination) and do any such harms vary by race or ethnicity?***

No data addressing this question were identified.

Costs

4. ***What is known about the costs, cost-effectiveness, and/or cost utility of using SNP-based panels for prostate cancer risk assessment, compared to current practice?***

No data addressing this question were identified.

Quality Assessment of Individual Studies

All included studies were related to clinical validity, which usually lends itself to a medical test framework for quality assessment. However, we decided to use the Newcastle-Ottawa Scale (NOS)[185] (Table 14a) because all but one of the studies had a case-control design (the exception being a cohort study of prostate cancer survival[201]), and because it is not clear how well the QUADAS[186] tool would apply to genetic tests. We supplemented this with selected items from the QUADAS[186] tool to assess the risk prediction aspect of the included studies. These were: (1) whether the spectrum of participants was representative of the patients who would receive the test in practice; (2) whether the selection criteria were clearly described; and, (3) whether un-interpretable, indeterminate, or intermediate test results were reported (Table 14b). Other QUADAS[186] criteria considered when assessing the risk of bias of the studies included whether or not: 1) the whole sample or a random selection of the sample received verification using the reference standard; 2) participants received the same reference standard regardless of the index test result; 3) the reference standard was independent of the index test; 4) the execution of the index test was described in sufficient detail to permit its replication; and, 5) the same clinical data were available when the test results were interpreted as would be available when the test is used in practice.

The reference standard for cases was histopathological diagnosis in all of the studies, but checking for latent or undiagnosed cancer was not conducted in control groups with two exceptions.[195,200] Autopsy studies in men over 50 years of age who had died from other causes have demonstrated a frequency of histologically proven prostate cancer of 30 to 40 percent.[54-60] However, there are clearly ethical constraints to taking prostate tissue samples in asymptomatic men in order to exclude an undiagnosed disease. In one of the studies, controls were selected from the same group of men referred to prostate cancer centers who had either a PSA value ≥4.0ng/ml or an abnormal DRE and who had no biopsy evidence of prostate cancer.[195] The results of the clinical validity evaluation of the 5-SNP panel in this study were similar to those of the other studies in which this panel was evaluated.[189-191] In all of the studies, it seems unlikely that the index test result affected the decision to undertake prostate biopsy, or the interpretation of histopathological examination of biopsy specimens. However, since all of the studies were conducted in research contexts, it is not clear that decisionmaking incorporated the same clinical data as would have been available in routine practice.

The execution of the genotyping component of the index test was adequately described in all but one[198] of the studies (see section on analytic validity). Almost all of the studies related to participants of European origin, and those that did not adjusted for ethnicity or conducted

analyses restricted to participants of European origin. This is likely to have limited the risk of bias resulting from population stratification; that is, the presence within a population of subgroups among which allele (or genotype, or haplotype) frequencies and disease risks differ.[215-218] However, some of the other variables included in risk scores may have been prone to differential error because of the retrospective case-control design used in all but the PLCO Trial,[193,203] the PHS,[197] and the San Antonio cohort.[196]

By combining the results of the NOS[185] evaluation and the QUADAS[186] criteria for the individual studies, all studies of the 5-SNP panel were found to have a moderate risk of bias. Based on three selected domains in the NOS[185] (selection of controls, comparability of cases and controls, method of ascertainment of cases and controls), along with limited data about genotyping methods and quality control, lack of specification of which candidate nongenetic variables were initially examined or considered for inclusion in the risk models, and lack of information about how these variables were assessed, the overall risk of bias of was assessed as being at least 'moderate'. Using the same approach, the assessments of the other 14 panels were based on single studies, reported in eleven articles,[191-201] and these were also all considered to have at least a moderate risk of bias.

Rating the Body of Evidence

Four domains were considered in the assessment of overall strength of evidence (SOE) for the SNP panels identified. These were risk of bias (internal validity of the studies), the consistency of findings, directness (how closely the tests were applied in a way which resembles routine practice), and precision (whether the estimates allow clinically useful conclusions).

For the domain of internal validity, all studies were assessed as having at least a moderate risk of bias. For the domain of consistency, it is impossible to assess results for panels evaluated in single studies only. For the Focus 5 panel, where there were several studies, the data did not permit development of an ROC curve, and therefore consistency could also not be assessed quantitatively. For models containing the five SNPs included in the Focus 5 panel, but with diverse other variables included, the AUC ranged between 63 percent and 73 percent.[188,193,195] Compared with the models that did not include the SNPs, the 5 SNPs increased the AUC by 1 to 3 percent.

For the domain of directness, all studies were conducted in a research context, no panel being applied in a setting that might be considered close to routine clinical practice. As well as presenting difficulty in assessing generalizability to a 'typical' clinical approach, this meant that none of the tests were explicitly evaluated in a medical test framework. Specifically, the case-control design meant there was no meaningful comparison of any SNP panel against a routine clinical alternative 'test'. Finally, the assessment of the precision domain requires a clear idea of clinically meaningful differences between levels of sensitivity, specificity, AUC, and other accuracy metrics (i.e., how much difference in one of these would make a 'real' difference in clinical or patient decisionmaking). This area of evaluation appears to be underdeveloped in the clinical literature, and the studies evaluated shed no light on this aspect. We were therefore unable to offer a valid assessment of this domain.

We are unable to assess the extent of publication bias in this review. We contacted a comprehensive list of companies we considered most likely to be developing SNP panels for commercial application, and received no responses. It is possible that unpublished data exist to support the clinical validity of one or more of the SNP panels reviewed here, or of other SNP panels which were not identified in this report. If so, this review's conclusions would be unduly

negative. However, this would be an unlikely scenario, since publication bias is usually considered to lead to selective reporting of studies with systematically larger effect sizes than is actually the case.[219] Only papers published in English were included. There is no empirical evidence of the effects of language restriction on genetic risk prediction studies. Although there is some empirical evidence of systematic differences in effect sizes of genetic associations reported in studies in Asian populations published in English and in Chinese, it is not clear that these differences are due to publication bias.[220] Moreover, there is evidence of considerable overlap of publications in English and Chinese medical journals on the same studies.[221] In the literature on randomized controlled trials, restriction to English language publications does not appear to bias estimates of effectiveness of conventional interventions.[222]

Overall, it is unlikely that any of the biases identified would be sufficient to alter the interpretation of the findings from (at best) inadequacy of evidence to clearly positive supporting evidence for any of the SNP panels reviewed.

For characteristics of included studies see Tables 8–10. The Focus 5 test is reported in Table 11. Summary of SNPs and other variables included in test panels is reported in Table 12. Table 13 reports genetic variants tested for by deCODE ProstateCancer and Table 14 reports case studies on the Newcastle-Ottawa Scale.

Table 8. Characteristics of included studies

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Aly[200] 2011	Model development Cohort	5,241 men who underwent prostate biopsy Stockholm, Sweden 2005 - 2007	Exclusion: age >80, deceased, no valid personal number or address, other cancer than prostate at biopsy, known prostate cancer before 2005, lack of consent Patient registries in 2 of 3 pathology departments in Stockholm, Sweden 8,088 identified, 7,035 invited, 5,241 accepted
Beuten[196] 2009	Model development Case-control	Screening center funded by national cancer institute Texas, U.S. NR but screening center opened in 2001	Cases had biopsy confirmed prostate cancer. 231 incident cases from San Antonio Center for Biomarkers of Risk of Prostate Cancer cohort + 655 prevalent cases; controls volunteers >45 years normal DRE and PSA <2.5ng/mL on all study visits 1,452 non-Hispanic Caucasians (cases = 609 , controls = 843); 709 Hispanic Caucasians (cases = 195, controls = 514); 291 African-Americans (cases = 82, controls = 209)
Helfand[191] 2010	Model Development Case-control	Hospital cases (90% treated by single surgeon); volunteer control group previously described matched on European descent Chicago, U.S. June 2002 - May 2008 (biopsy and pathological findings prospectively collected in cases)	Inclusion: European descent, with CaP who underwent radical prostatectomy at Northwestern Memorial Hospital Exclusion: lack of genetic data and/or incomplete clinical information Consecutive men with CaP who underwent radical prostatectomy. Controls were volunteers (PSA less than 2.5ng/mL, and normal digital rectal exam) 1,614 men

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Helfand[199] 2011	Model development Case-control	1,459 white men who underwent radical prostatectomy. 203 had normal screening examination at time of Dx, clinical stage T1C, PSA <4ng/mL and nonsuspicious DRE; Controls: 611 recruited as healthy control subjects for genetic studies from the national Prostate Cancer Coalition screening study (2007); controls had PSA<4.0ng/mL, normal DRE, no prior Hx of a prostate biopsy Washington University, St Louis, MO; and Northwestern University Chicago, IL. 97.5% treated by same surgeon 1997 - 2009	NR NR 1,459
Nam[195] 2009	Validation (models from Zheng, et al., 2008[188]) and model development Case-control	Recruited from prostate centers of the University of Toronto (Sunnybrook and Women's College Health Sciences Center and University Health Network) Toronto, Ontario, Canada. June 1999 - June 2007	Cases= Inclusion: PSA values ≥4.0ng/mL or an abnormal DRE; All patients underwent 1 or more transrectal ultrasonography-guided needle core biopsies; Primary endpoint was histological presence of adenocarcinoma of the prostate in biopsy specimen based on Gleason score Exclusion: PSA >50ng/mL (where the decision to biopsy would be considered unequivocal), not capable of giving consent to participate in the study, could not provide sufficient baseline information, or had a Hx of CaP Controls= Inclusion: no inclusion criteria reported aside from no presence of histologic adenocarcinoma of the prostate from biopsy Exclusion: Hx of CaP Source: men who were part of a screening program, selection was based on biopsy confirmed CaP; Samples were obtained using a systematic pattern and additional targeted samples were taken of suspicious areas; Those with histological presence of adenocarcinoma of the prostate were cases, while those that were not were controls 3,108

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Penney[197] 2009	Model development Physician Health Study (PHS) labeled nested case-control but also referred to as a prospective cohort by authors Dana Farber Harvard Cancer Center SPORE (Gelb center) case series; No controls FHCRC King County Case-control; 2 population-based case-controls	PHS: Randomized controlled trial of aspirin and beta carotene U.S. Blood samples 1982 – 1984; Followup through March ,1 2008 Gelb Center: Referral hospital-based case series Boston, U.S. 1976 - 2007 FHCRC: 2 population-based case-control; Incident cases with histologically confirmed prostate cancer ascertained from Seattle SEER cancer registry King County, Washington, U.S. Study I: Jan 1, 1993 – Dec 31, 1996; Study II: Jan 1, 2002 – Dec 31, 2005	PHS: Inclusion: Healthy U.S. physicians; Excluded at baseline if any serious medical conditions including all cancers except non-melanoma skin cancer; Restricted participation to self-reported Caucasians; Controls selected by risk-set sampling matched on age, smoking status & followup time; Caucasians only Self-reported prostate cancer cases verified through medical record and pathology review 1,438 Gelb Center: Inclusion: Healthy U.S. physicians; Excluded at baseline if any serious medical conditions including all cancers except nonmelanoma skin cancer; Restricted participation to self-reported Caucasians Self-reported prostate cancer cases verified through medical record and pathology review NR FHCRC: Inclusion: Healthy U.S. physicians; excluded at baseline if any serious medical conditions including all cancers except nonmelanoma skin cancer; Restricted participation to self-reported Caucasians Incident cases with histologically confirmed prostate cancer from SEER cancer registry Controls identified with one-step random digit dialing, matched by age; Only Caucasians included 2,448

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Salinas[189] 2009	Model development validation of Zheng[188] Case-control	Cases recruited from Seattle-Puget SEER cancer registry Participants from King County, Washington, U.S. (study I and II) Study I: Jan 1, 1993 - Dec 31, 1996; Study II: Jan 1, 2002 - Dec 31, 2005	Inclusion: Cases = histologically confirmed CaP from cancer registry, Caucasian Controls = residents of King County, no self-reported Hx of CaP, Caucasian Control selection: Residence of King County, without self-reported Hx of CaP, identified using a step random digit dialing frequently matched to cases by 5y age groups, recruited evenly throughout both ascertainment periods for case patients; Complete census information obtained for 94% and 81% of residential numbers contacted in Study I and II, respectively 2,244 CaP patients identified; 2,448 met control eligibility

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Sun[190] 2008	Model is validating previously reported model from Zheng, et al.[188] Case-control	JHH: Samples from JHH (Baltimore, MD), 1999 - 2006 CGEMS: Cases and controls from PLCO cancer screening trial (United States), 1992 - 2008 CAPS: Cases = 4 regional cancer registries; Controls = Swedish Population Registry Sweden July 2001 - October 2003	JHH: Cases = European-American men undergoing CaP treatment; Controls = European-American men undergoing CaP screening, >55 years of age, normal digital rectal exam, <4.0ng/mL PSA Cases = 1,562; Controls = 576 CGEMS: European-American men selected from PLCO Cancer Screening Trial using incidence density sampling strategy Cases = 1,172; Controls = 1,157 CAPS: Biopsy-confirmed or cytologically verified adenocarcinoma of the prostate, diagnosed between July 2001 and October 2003 Cases: 6 cancer registries; Method of selection apart from inclusion criteria not reported; Controls recruited concurrently and randomly selected from Swedish Population Registry Cases = 3,648; Controls = 3,153 Combined cumulative analysis (all three study populations): Cases = 5,628; Controls = 3,514

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Sun[194] 2008	Model development Case-control	HPC families were studied at Brady Urology Institute at Johns Hopkins Hospital; Non-HPC cases = same hospital; Controls = CaP screening from the hospital and greater Baltimore area. Baltimore, MD, U.S. HPC cases = described previously (Xu, et al., 2001[223]) Non-HPC = 1999 - 2006	Cases: HPC case criterion = prostate cancer (CaP) patients who have at least 2 first degree relatives diagnosed with CaP; non-HPC case criteria = patients undergoing radical prostatectomy for treatment of CaP at Johns Hopkins Hospital between 1999 to 2006 with DNA samples indicating normal seminal vesicle tissues; European Ancestry inclusion criterion for all cases; Controls: normal DRE, PSA <4.0ng/mL, and older than 55 years of age; Quality control checks: HPC cases = CaP was verified by medical records for each affected male studied; non-HPC cases = tumors from each patient were graded and staged using uniform criteria established and implemented by a single pathologist HPC Cases = 221 index CaP patients (probands) of European ancestry met the HPC criterion, while 168 of these probands had DNA sampled from affected and nonaffected relatives for linkage; Non-HPC cases = not specified, however 1,404 were collected DNA samples isolated from normal seminal vesicle tissue; Controls = 560 met eligibility Number assessed NR
Sun[198] 2011	Model development Cohort within a population case-control	Cases from regional cancer registries in Sweden, controls randomly selected from Swedish Population Registry and matched according to expected age distribution of cases (groups of 5 year intervals) and geographic region Sweden NR	Pathologically or cytologically verified adenocarcinoma of the prostate NR 2,899

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Wiklund[201] 2009	Model development Population-based case-control	CAPS: Cases = 4 of 6 regional cancer registries in Sweden Controls = Swedish population registry Sweden July 2001 - October 2003	Histologically or cytologically verified adenocarcinoma of the prostate (ICD-10:C61) NR 2,875 Cases
Xu[193] 2009	Model development and validation Case-control	CAPS: Cases = 4 of 6 cancer registries in Sweden Controls = Swedish population registry Sweden July 2001 - October 2003 PLCO: Independent Study Population from PLCO trial United States 1992 - 2009	CAPS: Cases = 2,899; Controls = 1,722 PLCO: Cases = 1,172; Controls = 1,157

Table 8. Characteristics of included studies (continued)

Author Year	Study Objective Study Design	Setting Location Dates of Data Collection	Study Participants Eligibility Source and Method of Selection Number Assessed for Eligibility
Zheng[192] 2009	Model development and validation Case-control (CAPS study)	Cases = 4 of 6 cancer registries in Sweden Controls = Swedish population registry Sweden July 2001 - October 2003	Case eligibility: Pathologic or cytologically verified adenocarcinoma of the prostate, Diagnosed between July 2001 and October 2003 Aggressive case eligibility: Consent to participate, T3/4, N+, M+, Gleason score sum ≥8, or PSA >50ng/mL; Otherwise they were classified as nonaggressive (localized) cases Control eligibility: consent to participate (PSA obtained but not used for exclusion) Cases: From 4 of 6 regional cancer registries in Sweden, method of selection not reported Controls: Recruited by invitation and randomly selected concurrently with case subjects, from Swedish Population Registry Cases = 3,648; Controls = 3,153
Zheng[188] 2008	Model Development Case-control	Cases = 4 regional cancer registries; Controls = Swedish Population Registry Sweden July 2001 - October 2003	Biopsy-confirmed or cytologically verified adenocarcinoma of the prostate, diagnosed between July 2001 and October 2003 Cases: 6 cancer registries; Method of selection apart from inclusion criteria not reported; Controls recruited concurrently and randomly selected from Swedish Cases = 3,648; Controls = 3,153

Abbreviations: CaP = prostate cancer; CAPS = cancer of the prostate in Sweden; CGEMS = cancer genetic markers of susceptibility; DNA = deoxyribonucleic acid; DRE = digital rectal examination; Dx = diagnosis; FHCRC = Fred Hutchinson cancer research center; GWA = genome-wide association; HPC = hereditary prostate cancer; Hx = history; JHH = Johns Hopkins Hospital; NR = not reported; PLCO = prostate lung cancer ovarian; PSA = prostate specific antigen; SEER = surveillance epidemiology and end results; SNP = single nucleotide polymorphism; SPORE = specialized programs of research excellence; y = year(s)

Table 9. Characteristics of included studies: SNPs

Author Year	SNP's Number genotyped and considered for inclusion in panel Was genotyping done blind to participant status?	Hardy Weinberg Equilibrium (HWE) Assessed? If yes, method? In controls? If no, in all participants? Result(s) [indicate whether this was for all SNPs considered for inclusion, or just those in the model(s) developed or evaluated	How were SNPs handled in analysis? (e.g., dominant or recessive effects per SNP, per allele, genotype categories, risk scores [explain which of alleles/genotypes is considered to be risk variant])	Other variables included in SNP panel
Aly[200] 2011	Cases = 2,135; Controls = 3,108 NR	HW calculations were performed to verify that each marker was within an allelic equilibrium in the control population.	NR	Nongenetic model included log total PSA, log free to total PSA ratio, age at biospy and family Hx of CaP. The genetic model also included the genetic risk score.
Beuten[196] 2009	2,452 samples NR	Checked for each SNP; rs6201 showed deviation from HW equilibrium in cases and controls of all 3 ethnic groups; In Caucasians, rs10923823 not in HW equilibrium in cases or controls and rs3751592 out of HW equilibrium in non-Hispanic Caucasians; SNPs not in HW equilibrium left out of further statistical analyses	OR and 95% CI was estimated by unconditional logistic regression as a measure of the association between genotype and CaP risk. Tested for additive, dominant, and recessive associations. Generalized linear model function with all SNPs were entered into a single multivariate logistic regression model (SNPs with additive effects). The random forest algorithm was applied. The generalized multifactor dimensionality reduction was also used.	NR
Helfand[191] 2010	Cases = 687; Controls = 777 Was done elsewhere and previously described	Yes, but methods not shown; all genetic variants were in HWE.	Differences in alleles between cases and controls were tested for each SNP using a logistic regression model; CaP risk OR was estimated from regression coefficients. For each genetic variant, genotype information was compared using Akaike's information criteria to choose the best fit genetic model (dominant or recessive).	No
Helfand[199] 2011	Cases = 203; Controls = 611 NR	Tests for HWE were performed for each SNP separately among control subjects with the use of Fisher's Exact Test. The genotypes and frequencies of the 17 different risk alleles were determined for all cases and controls and found to be in HW equilibrium.	The genotype information was compared using Aikake's Information Criteria to choose the best fit genetic model (dominant or recessive).	Positive family Hx

Table 9. Characteristics of included studies: SNPs (continued)

Author Year	SNP's Number genotyped and considered for inclusion in panel Was genotyping done blind to participant status?	Hardy Weinberg Equilibrium (HWE) Assessed? If yes, method? In controls? If no, in all participants? Result(s) [indicate whether this was for all SNPs considered for inclusion, or just those in the model(s) developed or evaluated	How were SNPs handled in analysis? (e.g., dominant or recessive effects per SNP, per allele, genotype categories, risk scores [explain which of alleles/genotypes is considered to be risk variant])	Other variables included in SNP panel
Nam[195] 2009	3,004 men underwent 1 or more biopsies (and had sufficient leukocyte DNA available for SNP analysis): Cases = 1,389; Controls = 1,615 NR	Yes, HWE assessed among controls; 6 of 25 SNPs (rs983085, rs6983561, rs7214479, rs6501455, rs4242382, ETV1) were not in HWE (p <0.001)	The authors examined 25 SNPs; 15 were reported by Zheng, et al., 2008,[188] from chromosomal regions 8q24 and 17q. They also examined 10 other SNPs previously shown to be associated with CaP, from KLK2, TNF, HOGG,9p22, and ETV1-rs2348763 and ETv1-rs13225697 genes and from locus of HPC1 on chromosome 1q24. Also included were 2 SNPs from ERG genes (TMPRSS2:ERG). Genotype groupings were tested based on additive, dominant, and recessive genetic models for each SNP and the one with the highest LRT was chosen as the best model. For SNPs examined by Zheng, et al., they used their genotype groupings.	SNP panels for independent assessment: no additional variables included; Model 1, 2, and 3: adjusted for age, family Hx of prostate cancer, ethnicity, presence of urinary voiding symptoms, PSA level, free: total PSA ratio, and DRE.
Penney[197] 2009	Physicians Health Study: Cases = 1,347; Controls = 1,462 SPORE: Cases = 3,714 FHCRC King County Case-control: Cases = 1,308; Controls = 1,266 Yes (all 3 studies)	No SNPs violated HWE in controls for Physicians Health Study or FHCRC King County case-control	SNPs that had a minor allele frequency of >10% were analyzed under a codominant model, whereas the less common SNPs were analyzed assuming a dominant inheritance model.	NR

Table 9. Characteristics of included studies: SNPs (continued)

Author Year	SNP's Number genotyped and considered for inclusion in panel Was genotyping done blind to participant status?	Hardy Weinberg Equilibrium (HWE) Assessed? If yes, method? In controls? If no, in all participants? Result(s) [indicate whether this was for all SNPs considered for inclusion, or just those in the model(s) developed or evaluated	How were SNPs handled in analysis? (e.g., dominant or recessive effects per SNP, per allele, genotype categories, risk scores [explain which of alleles/genotypes is considered to be risk variant])	Other variables included in SNP panel
Salinas[189] 2009	Cases = 1,457 genotyped of the 1,754 interviewed; Controls = 1,645 were interviewed; Included in panel: Caucasian cases =1308; Caucasian controls = 1,266 Yes	HWE for the 5 SNPs in Caucasian control was assessed using Fisher's Exact Test; pairwise linkage equilibrium (LD) between SNPs estimated based on r2	For each SNP genotype, models adjusted for age were used to test dominant, recessive and additive (0,1, or 2 copies of associated allele) genetic models.	Model 1 (Cumulative risk of 5 SNPs): adjusted for age and family Hx; Model 2: adjusted for age only
Sun[190] 2008a	JHH study: Cases = NR; Controls = <4.0ng/ml; CGEMS and CAPS study = NR Case-only analysis: data not shown	NR	NR	Not applicable (current study is validation study)
Sun[194] 2008b	HPC families = 168; Non-HPC cases = 1,404; Controls = 560 Duplicated and water sampled = yes; otherwise blinding not reported	Yes, for each SNP, tested whether observed genotype distributions were consistent with HWE expected proportions, separately for HPC probands, non-HPC, and controls using exact test, Tests for pairwise LD among SNPs in control subjects, and estimates for D' and r2 obtained using Haploview software. To minimize impact of multiple testing, for each SNP, only the "best" mode of inheritance model, suggested by earlier studies, was evaluated.	Comparisons of frequencies of alleles and genotypes between HPC probands and non-HPC patients and between HPC probands and unaffected controls were performed. For each SNP, homogeneity of allele frequencies was tested using a X2 test, with 1 degree of freedom. Genotype frequency differences, assuming an additive, dominant, or recessive mode-of-inheritance model, was tested using unconditional logistic regression models. Risk genotypes were compared to reference genotypes for each SNP (e.g., SNP: rs10086908, position 128,081,119 = TC/TT (risk) vs. TT and ORs produced for	Models 1 and 2: adjusted for age

Table 9. Characteristics of included studies: SNPs (continued)

Author Year	SNP's Number genotyped and considered for inclusion in panel Was genotyping done blind to participant status?	Hardy Weinberg Equilibrium (HWE) Assessed? If yes, method? In controls? If no, in all participants? Result(s) [indicate whether this was for all SNPs considered for inclusion, or just those in the model(s) developed or evaluated	How were SNPs handled in analysis? (e.g., dominant or recessive effects per SNP, per allele, genotype categories, risk scores [explain which of alleles/genotypes is considered to be risk variant])	Other variables included in SNP panel
			comparison between groups).	
Sun[198] 2011	Cases = 2,899 NR	NR	NR	Family Hx
Wiklund[201] 2009	Cases = 2,875 NR	Each of the SNPs in autosomal chromosomes was in HWE (P>=0.05).	NR	NR
Xu[193] 2009	CAPS: Cases = 2,899; Controls = 1,722 PLCO: Cases = 1,172; Controls = 1,157 NR	HWE for each SNP among control subjects in each study using Fisher's Exact Test.	The association between the number of risk alleles and family Hx with CaP risk was tested using a logistic regression model.	Family Hx
Zheng[192] 2009	Cases = 2,899; Controls = 1,722 NR	Yes; Each of the SNPs in the autosomal chromosomes was in HWE (p >0.05) among controls. Tests for HWE done for each SNP separately among cases and controls using Fisher's Exact Test. Pairwise disequilibrium (LD) was tested for SNPs within same chromosomal region in control subjects.	Allele frequency differences, between case patients and control patients were tested for each SNP using x2 test with 1 degree of freedom.	Independent association of prostate cancer risk with each of the SNPs: adjusted for other SNPs as well as age, geographic region, and family Hx. ROC for three models including one with age, family Hx and 11 SNPs.
Zheng[188] 2008	Cases = 2,893; Controls = 1,781 NR	Yes, for each SNP separately (cases and controls) using Fishers' Exact test. Pairwise linkage disequilibrium tested for SNPs within each of the 5 chromosomal	For genotypes, a series of tests assuming an additive, dominant, or recessive genetic model were performed for each of the 5 SNPs with the use of unconditional logistic regression. Differences in allele	Family Hx, age, and geographic region.

Table 9. Characteristics of included studies: SNPs (continued)

Author Year	SNP's Number genotyped and considered for inclusion in panel Was genotyping done blind to participant status?	Hardy Weinberg Equilibrium (HWE) Assessed? If yes, method? In controls? If no, in all participants? Result(s) [indicate whether this was for all SNPs considered for inclusion, or just those in the model(s) developed or evaluated	How were SNPs handled in analysis? (e.g., dominant or recessive effects per SNP, per allele, genotype categories, risk scores [explain which of alleles/genotypes is considered to be risk variant])	Other variables included in SNP panel
		regions (controls).	frequencies between cases and control subjects were tested for each SNP with the use of chi-square test with 1 degree of freedom.	

Abbreviations: CaP = prostate cancer; CAPS = cancer of the prostate in Sweden; CGEMS = cancer genetic markers of susceptibility; DNA = deoxyribonucleic acid; DRE = digital rectal examination; ERG = ETS related gene; ETS = E-twenty six; ETV1 = ETS translocation variant 1; FHCRC = Fred Hutchinson cancer research center; HOGG = human 8-oxoguanine glycosylase; HPC = hereditary prostate cancer; HPC1 = hereditary prostate cancer 1; HW = Hardy Weinberg HWE = Hardy Weinberg equilibrium; Hx = history; JHH = Johns Hopkins hospital; KLK2 = kallikrein-2; LD = linkage disequilibrium; LRT = likelihood ratio test; NR = not reported; OR = odds ratio; PLCO = prostate lung cancer ovarian; PSA = prostate specific antigen; ROC = receiver operating characteristic; SNP = single nucleotide polymorphism; SPORE = specialized programs of research excellence; TMPRSS2 = transmembrane protease serine 2; TNF = tumor necrosis factor

Table 10. Characteristics of included studies: Analysis and results

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Aly[200] 2011	35 SNPs, log total PSA, log free to total PSA ratio, age at biopsy, family Hx of CaP Allelic ORs were calculated using logistic regression models. For each man a genetic risk score was created by summing the number of risk alleles at each of the 35 SNPs multiplied by the log of that SNPs OR.	NR OR, AUC	Cases = 2,135; Controls = 3,108 Cases = 66; Controls = 64 Yes Cases = 29%; Controls = 22%	When using the nongenetic model the AUC was 64.2%; By using the genetic model the AUC was significantly improved to 67.4% (p=0.014). NR NR NR
Beuten[196] 2009	116 SNPs initially considered NR	Imputed for random forest and GMDR method. OR used for cumulative effects of risk variants. Testing accuracy & cross validation consistencies used for "best multi-genic models" .	2,452 samples genotyped Cases = 65.5 (8.5); Controls = 60.8 (8.8) NR	Non-Hispanic Caucasians # risk genotypes 0 ref, 1 OR 1.39 (1.0 to 1.9), 2 OR 1.56 (1.11 to 2.20), 3 OR 2.87 (1.64 to 5.02) trend OR 2.20 (1.44 to 3.38) Hispanic Caucasians 0 Ref, 1 OR 1.88 (1.17 to 3.02), 2 OR 4.58 (2.19 to 9.61), trend OR 4.29 (2.11 to 8.72) NR NR Best multigenic models. 13 significant non-Hispanic Caucasians rs1538989-rs2479827-rs17523880-rs2470164 testing accuracy 0.63 p0.001. 19 significant Hispanic. By ethnicity

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Helfand[191] 2010	CaP cumulative risk was analyzed. The determined best fit genetic model for each genetic variant was used to examine the cumulative relationship between the original 5 SNPs and CaP risk in the population.[204] NR	NR ROCs constructed with and without adjustment for age, compared as a ROC contrast statement in SAS for the models including 5 vs. 9 genetic variants; CaP cumulative risk on best fit genetic model measured by OR	Cases = 687; Controls = 777 Cases = 69.8 years; Controls = 58 years. No SDs given. NR	Age to adjusted ORs (95% CIs): 5 SNPs along 8q24 +17q + 0 to 1 carried variants = 1.00 (Ref); + 2 carried variants = 1.74 (1.32 to 2.29);+ 3 carried variants = 2.00 (1.47 to 2.71);+ 4 to 5 carried variants = 3.19(1.85 to 5.50); age to adjusted OR (95% CI): 2p15, 10q11, 11q13 + Xp11 SNPs + 0 to 1 carried variants = 1.00 (ref); + 2 carrier variants = 1.46 (0.74 to 2.86); +3 carrier variants = 2.46 (1.29 to 4.66); + 4 carrier variants = 3.05 (1.60 to 5.79); + 5 carrier variants = 4.39 (2.24 to 8.61); + 6 or more carrier variants = 5.75 (2.50 to 13.24) Model including all 9 variants = 0.61; model including 5 variants = 0.58 After adjustment for age, 9 variant model AUC = 0.66, and 5 variant model = 0.65 NR NR
Helfand[199] 2011	NR NR	NR AUC	Cases = 203 Controls = 611 Cases = 58 Controls = 58 Yes Cases = 36% Controls = 15%	When the presence of family Hx was included in the analysis, we found that carriers of >10 genetic risk factors had an 11.2 fold increased risk of having CaP (p<0.0001) compared with men who were carriers of ≤5 risk alleles. AUC for the model including all the carrier numbers of all 17 risk variants was 0.655 [p<0.000, OR 1.4 (1.3-1.6)] When family Hx was included AUC=0.706, p,0.001 NR NR

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Nam[195] 2009	A panel of 15 initially considered SNPs and independent comparisons of allele frequencies in cases/controls were examined. Based on those associated with CaP from Zheng, et al., 2008.[188] A second panel of SNPs for independent assessment was based on the authors' previous findings (Nam, et al., 2008;[224] Nam, et al., 2005;[225] Nam, et al., 2006[226]). Model 1 was based on 5 SNPs defined by Zheng, et al. Model 2 used a similar approach to Zheng, but the authors chose 4 SNPs with the most significant p-values from a panel based on their previous work. Model 3 used the two most significant SNPs selected from Zheng and two from Nam. NR	NR Independent association of prostate cancer risk with each of SNPs measured by OR and 95% CI; Cumulative effects of selected SNPs as seen in combination SNP Models 1, 2, and 3 measured using OR and 95% CI for prostate cancer using univariate and multivariate analyses; ROC constructed to estimate AUC of the various SNP models	Cases = 1,389;Controls = 1,615 At time of biopsy, mean age is prostate biopsies = 64.5 (range = 40 to 94 years); controls = NR (range ≤50 to ≥70 years Cases = 16.4%; Controls = 12.1%; obtained by research personnel through questionnaire and medical record review	Panel of SNPs (validation of Zheng, et al.): OR (95% CI) in order of SNPs as previously listed: rs4430796 = 1.04 (0.9 to 1.2), rs7501939 = 1.04 (0.8 to 1.3), rs3760511 = 1.02 (0.8 to 1.3), rs1859962 = 1.34 (1.1 to 1.6), rs16901979 = 1.07 (0.9 to 1.3), rs6983267 = 1.20 (1.0 to 1.4), rs7000448 = 1.16 (1.0 to 1.4), rs1447295 = 1.61 (1.3 to 1.9), rs7017300 = 1.50 (1.3 to 1.8), rs7837688 = 1.51 (1.2 to 1.8); Second Panel of SNPs from previous work. ERG rs2836431 = 1.36 (1.1 to 1.7), ERG rs8131855 = 1.34 (1.1 to 1.6), HOGG1 = 326 rs1052133 = 1.67 (1.2 to 2.3), KLK2 rs198972 = 1.16 (1.0 to 1.3), KLK2 rs2664155 = 1.24 (1.1 to 1.4), TNF rs1800629 = 1.27 (1.1 to 1.5), rs1552895 (9p22) = 1.21 (1.0 to 1.4), HPC1 (1q25,rs1930293) = 1.27 (1.1 to 1.5), ETV1 (7q21,rs2348763) = 1.25 (1.1 to 1.4); Combination models (0 associated genotypes (gt) = ref): model 1: 1 gt = 1.40 (1.1 to 1.7), 2 gt = 1.47 (1.2 to 1.9), 3 gt = 1.58 (1.1 to 2.2), ≤4 gt = 1.55 (0.9 to 2.8); model 2: 1 gt = 1.32 (0.9 to 1.9), 2 gt = 1.44 (1.0 to 2.0), 3 gt = 1.69 (1.2 to 2.4), ≥4 gt = 2.17 (1.3 to 3.6); model 3: 1 gt = 1.23 (1.0 to 1.5), 2 gt = 1.45 (1.1 to 1.8), 3 gt = 2.22 (1.5 to 3.2), ≥4 gt = 5.09 (1.6 to 16.5); From multivariate ROC analysis: AUC for baseline model including age, family Hx, ethnicity, presence of urinary voiding symptoms, PSA level, free: total PSA ratio, DRE = 0.72 (95% CI, 0.70 to 0.74). Adding SNPs from Zheng, et al. (model 1) to multivariate model, AUC = 0.73 (0.71 to 0.75). AUC from model 2 was 0.73 (0.71 to 0.74). AUC from model 3 was 0.74 (0.72 to 0.76, p = 0.0001). AUC of predictive model: Removing SNP genotype combination and compared it with incremental drops of variables: SNP combination from model 3 = drop of 0.014); age = 0.022; family Hx = 0.003; symptom score = 0.001; PSA =

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Nam[195] 2009 (cont'd)				0.001; Free: total PSA ratio = 0.066; DRE = 0.010 Positive predictive value (%) of PSA test based on established cut-off level of 4.0 ng/ml using genotype combination from model 3: 1 gt combinations = PPV Combination models (Caucasians only, OR, 95% CI): Model 1: 1 gt = 1.41 (1.2 to 1.7), 2 gt = 1.53 (1.2 to 1.9), 3 gt = 1.33 (0.9 to 2.0), ≥4 gt = 4.46 (1.4 to 13.9); Model 2: 1 gt = 1.22 (0.9 to 1.7), 2 gt = 1.49 (1.1 to 2.1), 3 gt = 1.76 (1.2 to 2.5), ≥4 gt = 2.38 (1.4 to 4.0); Model 3: 1 gt = 1.26 (1.0 to 1.6), 2 gt = 1.61 (1.3 to 2.1), 3 gt = 3.05 (2.0 to 4.6), ≥4 gt = 3.81 (1.2 to 12.3)
Penney[197] 2009	CaP incidence was investigated only in PHS and FHCRC, as there are no controls in GELB. NR	NR Data analyzed by unconditional logistic regression, adjusting for matching factors to estimate OR; OR combined into summary estimate across PHS and FHCRC using random effects model with cohort as random effect	PHS: Cases = 1,347; Controls = 1,462 GELB: Cases = 3,714 (not in CaP incidence) FHCRC: Cases = 1,308; Controls = 1,266 PHS: 70.5 (7.7) GELB: 62 (8.2) FHCRC: 59.9 (7.0) NR in any study	Combined in PHS and FHCRC: rs13254738 AA = OR 1.00, AC OR = 1.03 (0.92 to 1.16), CC OR 1.28 (1.06 to 1.54); rs6983561 AA OR 1.00, AC/CC OR 1.54 (1.13,2.08); rs5693267 TT 1.00, GT OR 1.22(1.04 to 1.44), GG 1.41 (1.20 to 1.64), rs7000448 CC 1.00, CT 1.04 (0.93 to 1.17), TT 0.92 (0.78 to 1.09), rs1447295 CC 1.00, CA/AA 1.40 (1.23, 1.61), rs4430796 GG 1.00, AG 1.31 (1.11 to 1.54), AA 1.60 (1.37 to 1.88), rs1859962 TT 1.00, GT 1.18 (0.90,1.54), 1.48 (1.27, 1.73) in PHS only rs7008482 TT 1.00, GT 0.91 (0.77,1.07), GG 0.87 (0.68,1.12) NR NR Comparison of CaP mortality (death vs. 10 year survival); Gleason score; Pathologic Stage; Age and PSA at Dx

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Salinas[189] 2009	The best fitting models for each SNP (using Zheng, et al., 2008[188]) was selected based on the model with the greatest LRT. Confounding was evaluated by considering whether inclusion of other covariates changed the risk estimates ≤10%. P-values were derived from LRT statistics obtained by comparison of nested models. Goodness of fit was evaluated using the Hosmer-Lemeshow Test. Gene-gene and gene-environment interaction was evaluated using the LRT test comparing the full model with the main effect and an interaction term. PAR% was calculated for each SNP based on the OR obtained from the multivariate models. Corrected PAR% was calculated by solving a quadratic equation in which the absolute risk is a function of the observed OR, exposure prevalence in controls, and background disease. NR	Men with missing genotype information for any SNP excluded from independent SNP analyses Models 1 and 2: OR and 95% CI; comparison of models (subset analysis): AUC; ROCs (shown in figure, not presented in report); prostate cancer-specific mortality associated with each of the SNPs = hazard ratios and 95% CI (data not within scope of current review)	Main analyses (study I and II participants): Cases = 1,308 Controls = 1,266 Subset AUC analysis from Study I only: Cases = 475 Controls = 364 At Dx: Cases = 59.9 Controls = 59.6 Cases = 21.6% Controls = 11.1%; (time of Dx) obtained by trained male interviewers using standardized questionnaire	Model 1 = cumulative effect of associated genotypes at 5 SNPs: 1st degree family Hx of CaP = 2.31 (1.84 to 2.91), (0 associated genotype (gt) = reference, 1 gt = 1.48 (1.09 to 2.01), 2 gt = 1.88 (1.38 to 2.56), 3 gt = 2.97 (2.08), ≥4 gt = 3.36 (1.90 to 6.08); Model 2: cumulative effect of genotypes at 5 SNPs and family Hx: 0 gt (reference), 1 gt = 1.41 (1.02 to 1.97), 2 gt = 2.25 (1.63 to 3.13), 3 gt = 3.43 (2.40 to 4.94), 4 gt = 3.65 (2.24 to 6.03), ≤5 gt = 4.92 (1.58 to 18.53); Independent SNP Effects Models (study I and II participants): family Hx = 2.32 (1.85 to 2.92), Region 7q12: rs4430796 = 1.43 (1.19 to 1.71), Region 17q24.3: rs1859962 = 1.25 (1.03 to 1.51), Region 8q24: rs6983561 = 1.76 (1.30 to 1.64), rs6983267 = 1.34 (1.10 to 1.64), rs1447295 = 1.34 (1.10 to 1.63) Model with age at reference date, serum PSA (at Dx for cases, interviews for controls), and 1st degree relatives with CaP = 0.63 compared to same model with 5 SNPs added = 0.66. This was based on random subset of Study I participants only (cases = 475/controls = 364). Difference between the curves = 0.03 (95% CI, -0.12 to +0.06) PAR(%) for SNPs in the 8q24, 17q12, and 17q24.3 chromosomal regions: 1st degree family Hx of CaP = 11.8%, rs4430796 (AA gt) = 9.4%, rs1859962 (GG gt) = 5.3%, rs6983561 (CC+CA gts) = 4.5%, rs6983267 (GG+GT gts) = 19.8%, rs1447295 (AA+AC gts) = 6.0%, all 5 at risk SNPs (as above) = 38.1%, all 5 SNPs & family Hx = 54.4% Subset analysis of Study I participants only, as reported under AUC scores

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Sun[190] 2008a	Multivariate analyses were done where all 5 SNPs, family Hx (excluding JHH), and age were included. Cumulative effects of the 5 SNPs were analyzed using the JHH study population and CGEMS study population (confirmation studies) using logistic regression. A subanalysis of the cumulative effect included family Hx because it was independent from the cumulative risk genotype effect. Cumulative effect of the 5 SNPs and family Hx on CaP in the CGEMS-prostate sample was estimated and compared to the CAPS sample and then combined, but not for the JHH sample, due to incomplete family Hx data. The combined analysis of 5 SNPs and family Hx was assessed by counting the number of prostate cancer associated genotypes (based on best fit genetic model from Zheng, et al., and coded as '1' if the individual carried the risk factors and '0' otherwise for each of the 6 factors in each subject. This model is validating the previously reported model from Zheng, et al., 2008[188]	One SNP (rs16901979) imputed from the adjacent genotyped SNPs at 8q24 using IMPUTE software; computed confidence scores to ensure reliable imputation Cumulative effect of 5 SNPs in three independent studies: OR for prostate cancer for men carrying any combination of 1,2,3, or ≥4 risk genotypes estimated by comparing to men carrying none of the risk genotypes using logistic regression	Combined cumulative analysis (all three study populations): Cases = 5,628 Controls = 3,514 NR JHH study - 'not complete'; CAPS and CGEMS studies - yes	Cumulative Combined Effect of 5 SNPs Model 1 from Combining data from Johns Hopkins Study + CGEMS-prostate study + CAPS study : ORs (95% CI) all compared to reference 0 SNPs: = 1 SNP: 1.41 (1.20 to 1.67), 2 SNP: 1.88 (1.59 to 2.22), 3 SNPs: 2.36 (1.95 to 2.85), and ≥4 SNPs: 3.80 (2.77 to 5.22); Cumulative Combined Effect of 6 Risk Variants (5 SNPs + family Hx) Model 2 from the CAPS and CGEMS studies = 1 SNP: 1.64 (1.34 to 2.00), 2 SNPs: 2.07 (1.70 to 2.51), 3 SNPs: 2.82 (2.28 to 3.50), 4 SNPs: 4.61 (3.40 to 6.25), ≥5 SNPs: 11.26 (4.74 to 24.75). Case-only analysis: no statistically significant association was found between 5 SNPs and Gleason score, age at Dx, presence of family Hx, (CGEMS only), or aggressiveness of prostate cancer NR Trend test was statistically significant in the CGEMS-prostate (p = 4.75 x 10 to 14) and in the combined CAPS and CGEMS-prostate (p = 1.94 x 10 to 39). NR

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Sun[194] 2008b	12 SNPs were selected based on the published literatureTo minimize the impact of multiple testing for each SNP, only the best mode-of-inheritance model, was evaluated. OR and 95% CI was estimated for men with previously identified risk genotypes, compared to men without, under these genetic models. Family-based association tests were performed utilizing data from nuclear families, sibships, or a combination of the two to test for linkage and linkage disequilibrium between traits and genotypes. An empirical variance estimator in FBAT was used to perform a valid test of association, accounting for the correlation of alleles among multiple affected individuals in the same family due to linkage. The LAMP computer program was used to jointly model linkage and association in the 168 families with HPC, and to calculate the LRT of marker data conditional on trait data under several models. LAMP uses a LRT to test for linkage and/or linkage disequilibrium. NR	NR Estimated genotype risk (Models 1) of 8q24: OR and 95% CI; Cumulative effects of 8q24 risk variants (Models 2): OR and 95% CI (and p-values)	Estimated Genotype Risk (models 1) : HPC = 221 Controls = 560; Non-HPC Cases = 1,404 Controls = 560 Cumulative effect of 8q24 (models 2) = HPC vs. controls; Non-HPC vs. controls: 0 risk genotypes: HPC probands = 96; Non-HPC cases = 678; Controls = 560; 1 risk genotypes: HPC = 97; Non-HPC = 559; Controls = 192; ≥2 risk genotypes: HPC = 28; Non-HPC cases = 167; Controls = 36; Described previously (Xu, et al., 2001)[223] 221 HPC cases (at least 2 additional 1st degree relatives diagnosed with prostate cancer) verified by medical records	Model 1 (genotype risk vs. ref) OR (95%CI) (HPC vs. Controls): Region 1 = rs1447295: 2.25 (1.52 to 3.32), rs4242382: 2.37 (1.61 to 3.50), rs7017300: 1.86 (1.29 to 2.67), rs10090154: 2.33 (1.57 to 3.45), rs7837688: 2.51 (1.71 to 3.70); Region 2 = rs10086908: 0.88 (0.63 to 1.22), rs13254738: 0.99 (0.68 to 1.32), rs6983561:1.76 (1.05 to 2.94), rs16901979: 1.70 (1.02 to 2.84); Region 3 = rs6983267: 1.29 (0.89 to 1.86) , rs7000448: 0.54 (0.30 to 0.96), Region c to MYC = rs6470572 : 1.09 (0.78 to 1.52); (Non to HPC vs. controls): Region 1 = rs1447295: 1.73 (1.33 to 2.26), rs4242382: 1.81 (1.38 to 2.34), rs7017300: 1.44 (1.14 to 1.82), rs10090154: 1.74 (1.33 to 2.27), rs7837688: 1.80 (1.38 to 2.36); Region 2: rs10086908: 0.92 (0.76 to 1.12), rs13254738: 1.00 (0.82 to 1.22), rs6983561:1.14 (0.80 to 1.62), rs16901979: 1.13 (0.79 to 1.60); Region 3 = rs6983267: 1.42 (1.14 to 1.78) , rs7000448:1.26 (0.95 to 1.67); Region c to MYC = rs6470572 : 0.91 (0.74 to 1.12); Model 2 (Cumulative Effect) OR (95% CI): HPC vs. Controls: 0 risk genotypes = ref., 1 risk genotype = 1.76 (1.24 to 2.49), ≥2 risk genotypes = 2.94 (1.67 to 5.15), Non to HPC vs. Controls: 1 genotype = 1.42 (1.15 to 1.75), = >2 genotypes = 2.23 (1.52 to 3.28) NR NR NR NR

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Sun[198] 2011	Family Hx, 5 SNPs, 11 SNPs, 28 SNPs sequentially discovered from GWAs in the 4 years preceding December 2009 Multiplicative model; Estimated sensitivity and specificity, PPV, and NPV, and used AUC statistic	NR AUC	Cases = 2,899; Controls = 1,722 Cases = 66; Controls = 67 Yes Cases = 19%; Controls = 9%	AUC was 0.60 for 5 SNPs, 0.61 for 11 SNPs and 0.62 for 28 SNPs NR NR NR
Wiklund[201] 2011	16 SNPs selected from 4 GWAs NR	NR Survival Analysis, Cox regression methods	Cases = 2,875 Age = 35 – 79 NR	NR NR NR NR

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Xu[193] 2009	The association of a number of risk alleles and family Hx with CaP risk was tested using a logistic regression model adjusted for age and geographic region (CAPS). NR	NR Absolute risk estimated based on OR, calibrated incidence rate of CaP for men with most common number of risk alleles, negative family Hx, and mortality rate for all causes excluding CaP in Sweden and the U.S.	CaPs: Cases = 2,899; Controls = 1,722 PLCO screening trial: Cases = 1,172; Controls = 1,157 NR 1st and 2nd degree relative +ve CaPs: Cases = 550/2,898; Controls = 163/1,721 PLCO: Cases = 1,36/1,176; Controls = 67/1,101	OR (95%CI) CaPs with no family Hx 0 to 7 risk alleles 0,71 (0.55 to 0.91), 8 risk alleles 0.78 (0.61 to 1.01), 9 r.a. 0.95 (0.76 to 1.21), 10 r.a. 0.99 (0.80 to 1.24), 11 r.a. 1.00 (baseline), 12 r.a.1.13 (0.91 to 1.41), 13 r.a. 1.41 (1.10 to 1.79), ≥14 2.26 (1.79 to 2.86) CaPs with family Hx 0 to 7 risk alleles 1.54 (1.12 to 2.12), 8 r.a.1.70 (1.24 to 2.33), 9 r.a. 2.07 (1.54 to 2.80), 10 r.a. 2.16 (1.61 to 2.89), 11 r.a., 2.17 (1.80 to 2.63),12 r.a. 2.45 (1.84 to 3.27), 13 r.a. 3.06 (2.25 to 4.15), ≥14 4.92 (3.64 to 6.64) NR NR NR NR

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Zheng[192] 2009	The panel consisted of the independent association of prostate cancer risk with each SNP (significantly associated from an allelic test). The model with the highest LRT was considered as the best-fitting genetic model for the respective SNP. Backward selection was used for independent association with each of the significantly associated SNPs (adjusting for age, geographic location and family Hx). To assess the utility of these SNPs and family Hx in predicting men with and without CaP, sensitivity and specificity for predicting CaP was estimated using various cutoffs of number of alleles and family Hx. AUC statistics were estimated for several predictive models after fitting a logistic regression, including model 3 = age, family Hx, and genetic variants. CaP risk and 19 SNPs identified from previous GWA studies imply its validation of previously reported significantly associated SNPs. No validation within the study was reported for ROCs and AUC statistics.	Missing data treated as missing values in the analyses Independent association of prostate cancer risk with each of SNPs measured by OR and 95% CI; Overall predictive performance of predictive models	Cases = 2,899; Controls = 1,722 At enrolment: Aggressive cases = 68.04 (7.32); Nonaggressive cases = 65.14 (6.74) All cases = 66.36 (7.13); Controls = 67.15 (7.39) [No family Hx: Aggressive cases = 82.29%; Nonaggressive cases = 79.99% All controls = 90.57%] Overall: Cases = 19.1%; Controls = 14% (same as Zheng, et al.)	Independent Association with each SNP: ORs (95% CI) = family Hx only = 2.19 (1.80 to 2.67); age only = 1.02 (1.00 to 1.03); geographic region = 0.46 (0.38 to 0.54); rs2660753 = 1.32 (1.12 to 1.55); rs9364554 = 1.08 (0.98 to 1.19); rs10486567 = 1.39 (1.04 to 1.85); rs6465657 = 1.14 (1.04 to 1.25); rs16901979 = 1.65 (1.32 to 2.08); rs6983267 = 1.22 (1.12 to 1.34); rs1447295 = 1.16 (1.01 to 1.34); rs1571801 = 1.15 (1.04 to 1.27); rs10993994A = 1.16 (1.06 to 1.27); rs10896449B = 1.12 (1.02 to 1.22); rs4430796 = 1.22 (1.11 to 1.33); rs1859962 = 1.17 (1.07 to 1.28); rs5945619C = 1.19 (1.05 to 1.36). No interactions were statistically significant (p >0.05) (data not shown). Predictive Models: model 1 (age) = 0.58 (0.56 to 0.59), model 2 (age and family Hx) = 0.61 (0.59 to 0.62), model 3 (age, family Hx, 11 SNPs = 0.65 (0.63 to 0.66), model 4 (age, family Hx, geographic region & 5 previously evaluated SNPs (Zheng 2008) = 0.63 (0.62 to 0.65) Difference AUC mode 2 to model 1 = 0.03 ; difference between model 3 and 2 = 0.04; Difference in AUC statistically significant between models 2 and 1 for additional effect of family Hx: p = 1.36 x 10 to 7, and between models 3 and 2: p = 2.3 x 10 to 10. Among 23 risk factors (22 risk alleles from 11 SNPs and family Hx), cutoff of 11 risk factors = sensitivity and specificity (0.25 and 0.86, respectively) which were similar to PSA level cutoff of 4.1ng/ml. Sensitivity and specificity of the genetic factors to predict specific types of this cancer: No differences were found for any specific types of prostate cancer

Table 10. Characteristics of included studies: Analysis and results (continued)

Author Year	Analysis Method of constructing SNP panel Method of validating SNP panel	Analysis Missing data Measures used to evaluate SNP panel	Results Number of participants included in analysis Mean age (SD) (by group) 1st degree family Hx CaP	Risk Score AUC ΔAUC Other Measure Subgroup analysis of risk score, AUC, delta AUC or other measure
Zheng[188] 2008	The likelihood ratio test (LRT) for the best fitting genetic model of individual SNPs, adjusting for age and geographic region were given. The independent effect of the 5 regions were given by including the most significant SNP from each of the 5 regions in a logistic regression model using backwards selection. Multiplicative interactions were tested for each pair of SNPs by including both main effects and an interaction term using logistic regression. Cumulative effect of the 5 SNPs was tested by counting the number of genotypes associated with prostate cancer (from single SNP analysis) for the 5 SNPs in each subject. Subanalysis included cumulative effect, including 5 SNPs and family Hx. NR	NR OR, AUC, PAR for each model	Aggressive disease cases = 1,231; Localized disease cases = 1,619; Controls = 1,781 Cases = 66.4 (7.1); Controls = 67.2 (7.2) Cases = 19.0%; Controls = 9.4%	OR (95% CI): Age + 0 SNPs = 1.01 (1.00 to 1.02); Geographic region + 0 SNPs = 0.47 (0.40 to 0.55); 1 SNp = 1.62(1.27 to 2.08); 2 SNPs = 2.07 (1.62 to 2.64); 3 SNPs = 2.71 (2.08 to 3.53); 4 SNPs = 4.76 (3.31 to 6.84); ≥5 SNPs = 9.46 (3.62 to 24.72) 63.3 (95% 61.7 to 65.0) for model 3 (age, region, family Hx, and # genotypes associated with CaP at the 5 SNPs) NR NR NR

Abbreviations: AUC = area under the curve; ΔAUC = change in the area under the curve; CaP = prostate cancer; CAPS = cancer of the prostate in Sweden; CGEMS = cancer genetic markers of susceptibility; DNA = deoxyribonucleic acid; DRE = digital rectal examination; Dx = diagnosis; ERG = ETS related gene; ETS = E-twenty six; ETV1 = ETS translocation variant 1; FBAT-family based association test; FHCRC = Fred Hutchinson cancer research center; GMDR = generalized multifactor dimensionality reduction; HOGG = human 8-oxoguanine glycosylase; HPC = hereditary prostate cancer; HPC1 = hereditary prostate cancer 1; HW = Hardy Weinberg HWE = Hardy Weinberg equilibrium; Hx = history; JHH = Johns Hopkins hospital; KLK2 = kallikrein-2; LAMP = linkage and association modeling for pedigrees; LD = linkage disequilibrium; LRT = likelihood ratio test; NR = not reported; OR = odds ratio; PAR = population attributable risk; PHS = physicians' health study; PLCO = prostate lung cancer ovarian; PPV = positive predictive value; PSA = prostate specific antigen; ROC = receiver operating characteristic; SAS = statistical analysis software; SD = standard deviation SNp = single nucleotide polymorphism; TNF = tumor necrosis factor

Table 11. Focus 5 test

5-SNP Panel (Focus 5)								
Chromosome	**rs Number**	**Replicated in GWA Studies**	**Zheng[188]**	**Salinas[189]**	**Sun[190]**	**Nam[195] model 1**	**Helfand[191]**	**Zheng[192]**
8q24 (region 1)	rs1447295	Yes	x	x	x	x	x	x
8q24(region2)	rs16901979	Yes	x	x[a]	x (imputed in PLCO)	x	x[b]	x
8q24(region3)	rs6983267	Yes	x	x	x	x	x[b]	x
17q12	rs4430796	Yes	x	x	x	x	x[c]	x
17q24	rs1859962	yes	x	x[c]	x	x	x	x
Variables adjusted for			Age, geographic region and family Hx	Age (and serum PSA, family Hx in AUC analysis)		None and age, family Hx, ethnicity, urinary symptoms, PSA, free: total PSA ratio and DRE	Age	In AUC analysis, age and family Hx
Variables added to model containing SNPs			Family Hx	Family Hx	Family Hx			

[a] substituted by rs6983561, with which it was perfectly correlated
[b] additive model, in contrast to other five studies in which 5-SNP panel assessed
[c] dominant model, in contrast to other five studies in which 5-SNP panel assessed
Abbreviations: AUC = area under the curve; DRE = digital rectal exam; GWA = genome-wide association studies; Hx = history; PLCO = Prostate Lung Colon and Ovarian Cancer Screening Trial; PSA = prostate specific antigen; SNP = single nucleotide polymorphism

Table 12. Summary of SNPs and other variables included in test panels

SNP			9-SNP Panel[191]	17-SNP Panel[199]	11-SNP Panel[192]	14-SNP Panel	16-SNP Panel	28-SNP Panel	3 SNPs in 8q24	4-SNP Test	4-SNP Test	3-SNP Test	2-SNP Test	6-SNP Panel	35-SNP Panel
Chromosome	**rs number**	**Replicated in GWA studies[§]**	**Helfand [191]**	**Helfand [199]**	**Zheng[192]**	**Xu[193]**	**Wiklund[201]**	**Sun[198]**	**Sun[194]**	**Nam[195] model 2**	**Nam[195] model 3**	**Beuten [196]**	**Beuten [196]**	**Penney [197]**	**Aly[200]**
1q25	rs1930293									x					
2p15	rs2710646		x												
	rs721048	yes		x	(ass)		x	x							x
2p21	rs1465618							x							x
2p21 *THADA*	rs1465618	yes													
2q31	rs10207654														
2q31.1	rs12621278							x							x
3	rs10934853							x							
3p12	rs2660753	yes			x	x									
3q21.3	rs4857841														x
3q21.3	rs10934853	yes		x											
4q22 PDLIM5	rs17021918														
4q22.3	rs12500426														x
	rs17021918							x							x
4q24	rs7679673	yes													
5p15	Rs2736098			x											
5p15	Rs401681			x											
6q25	rs9364554	yes			x										
6q25.3	rs9364554						x	x							x
7p15.2	rs10486567						x								x
7q21.3	rs6465657						x								x
7p15	rs10486567	yes			x	x									
7q21	rs6465657	yes			x	x									
	rs2348763									x	x				

Table 12. Summary of SNPs and other variables included in test panels (continued)

SNP			9-SNP Panel[191]	17-SNP Panel[199]	11-SNP Panel[192]	14-SNP Panel	16_SNP Panel	28-SNP Panel	3-SNPs in 8q24	4-SNP Test	4-SNP Test	3-SNP Test	2-SNP Test	6-SNP Panel	35-SNP Panel
Chromosome	**rs number**	**Replicated in GWA studies[§]**	**Helfand[191]**	**Helfand[199]**	**Zheng[192]**	**Xu[193]**	**Wiklund[201]**	**Sun[198]**	**Sun[194]**	**Nam[195] model 2**	**Nam[195] model 3**	**Beuten[196]**	**Beuten[196]**	**Penney[197]**	**Aly[200]**
8	rs2928679							x							
	rs1512268							x							
8p21	rs1512268	yes													
8p21.2	rs1512268														x
8q24	rs7008482													x	
8q24	Rs16902094	yes		x				x							x
8q24 (region 1)	rs1447295	yes	x	x	x	x	x		x		x			x	x
	rs4242382	yes							(ass)						
	rs7017300								(ass)	x					
	rs10090154								(ass)						
	rs7837688	yes							(ass)	x					
	rs6470572								(ass)						
8q24 (region 2)	rs16901979	yes	x	x	x	x (imputed in PLCO)	x		x						x
	rs10086908								(ass)						x
	rs13254738								(ass)					x	
	rs6983561													x	x
8q24 (region 3)	rs6983267	yes	x	x	x	x	x		x	x				x	
	rs7000448								(ass)	x				x	
8q24.21	rs12543663														x
	rs1016343														x
	rs13252298														x
	rs445114														x
	rs620861							x							x
	rs6983267														x

Table 12. Summary of SNPs and other variables included in test panels (continued)

SNP			9-SNP Panel[191]	17-SNP Panel[199]	11-SNP Panel[192]	14-SNP Panel	16_SNP Panel	28-SNP Panel	3-SNPs in 8q24	4-SNP Test	4-SNP Test	3-SNP Test	2-SNP Test	6-SNP Panel	35-SNP Panel
Chromosome	**rs number**	**Replicated in GWA studies[§]**	**Helfand[191]**	**Helfand[199]**	**Zheng[192]**	**Xu[193]**	**Wiklund[201]**	**Sun[198]**	**Sun[194]**	**Nam[195] model 2**	**Nam[195] model 3**	**Beuten[196]**	**Beuten[196]**	**Penney[197]**	**Aly[200]**
	rs16902104														
	rs445114	yes		x											
9p22	rs1552895									x					
9q33	rs1571801				x										
10q11	rs10993994	yes	x	x	x	x									
	rs7920517				(ass)										
10q11.23	rs10993994						x								x
10q26	rs4962416	yes			(ass)										
10q26.13	rs4962416						x	x							x
11p15.5	rs7127900							x							x
11q13	rs7931342	yes			(ass)										
	rs10896450		x	x											
	rs11228565			x											
11q13 (region1)	rs10896449	yes			x										
11q13 (region2)	rs12418451														
11q13.2	rs12418451							x							x
	rs11228565														x
	rs10896449						x								x
17q12	Rs11649743			x											x
17q12	rs4430796	yes	x	x	x[b]	x	x			x				x	x
17q12	rs7501939	yes								x					
17q12	rs3760511									x					
17q24	rs1859962	yes	x	x	x[b]	x	x				x			x	x
19q13.2	rs8102476	yes		x				x							x

Table 12. Summary of SNPs and other variables included in test panels (continued)

SNP			9-SNP Panel[191]	17-SNP Panel[199]	11-SNP Panel[192]	14-SNP Panel	16_SNP Panel	28-SNP Panel	3-SNPs in 8q24	4-SNP Test	4-SNP Test	3-SNP Test	2-SNP Test	6-SNP Panel	35-SNP Panel
Chromosome	**rs number**	**Replicated in GWA studies[§]**	**Helfand[191]**	**Helfand[199]**	**Zheng[192]**	**Xu[193]**	**Wiklund[201]**	**Sun[198]**	**Sun[194]**	**Nam[195] model 2**	**Nam[195] model 3**	**Beuten[196]**	**Beuten[196]**	**Penney[197]**	**Aly[200]**
19q13 (KLK2/KLK3)	rs2735839	yes			(ass)		x	x							x
	rs5759167	yes													
22q13						x									
22q13.1	rs9623117														x
22q13.2	rs5759167							x							x
ERG	rs2836431									x					
ERG	rs8131855									x					
CYP19	rs12439137											x (nHW)			
CYP19	rs2470152											x (nHW)			
CYP19	rs10459592												x (HW)		
CYP24A11	rs3787554												x (HW)		
HOGG1-326	rs1052133									x					
HSD3B2	rs1819698											x (nHW)			
KLK2	rs198972									x					
KLK2	rs2664155									x					
Region c-MYC	rs6470572								(ass)						
TERT	rs401681	With serum PSA levels													
TNF	rs1800629									x	x				
Xp11.22	rs5945619						x								x
Xp11	rs5945572	yes	x	x	(ass)										
	rs5945619	yes			x										
11p15	rs7127900	yes													

Table 12. Summary of SNPs and other variables included in test panels (continued)

SNP			9-SNP Panel[191]	17-SNP Panel[199]	11-SNP Panel[192]	14-SNP Panel	16_SNP Panel	28-SNP Panel	3-SNPs in 8q24	4-SNP Test	4-SNP Test	3-SNP Test	2-SNP Test	6-SNP Panel	35-SNP Panel
Chromosome	**rs number**	**Replicated in GWA studies[§]**	**Helfand[191]**	**Helfand[199]**	**Zheng[192]**	**Xu[193]**	**Wiklund[201]**	**Sun[198]**	**Sun[194]**	**Nam[195] model 2**	**Nam[195] model 3**	**Beuten[196]**	**Beuten[196]**	**Penney[197]**	**Aly[200]**
Variables adjusted for			Age		In AUC analysis, age, and family Hx						age, family Hx, ethnicity, US, PSA, free: total PSA ratio and DRE				
Variables added to model containing SNPs						Family Hx									

[§] based on information in Table 1
[a] substituted by rs6983561, with which it was perfectly correlated
[b] additive model, in contrast to other five studies in which 5-SNP panel assessed
[c] dominant model, in contrast to other five studies in which 5-SNP panel assessed
Abbreviations: AUC = area under the curve; ass = assessed in single SNP analysis, but not included in panel; DRE = digital rectal exam; HW = Hispanic whites; nHW = Non-Hispanic whites; Hx = history; PSA = prostate specific antigen; rs = Reference SNP; US=urinary symptoms

Table 13. Genetic variants tested for by deCODE ProstateCancer

Chromosome	rs Number
8q24 (region 1)	rs1447295
8q24 (region2)	rs16901979
	rs10086908
8q24 (region3)	rs6983267
17q12	rs4430796
17q24	rs1859962
19q13.2	rs8102476
19q13 (KLK2/KLK3)	rs2735839
	rs5759167
2p15	rs2710646
3p12	rs2660753
6q25	rs9364554
7p15	rs10486567
7q21	rs6465657
10q11	rs10993994
11q13 (region1)	rs10896449
Xp11	rs5945572
4q22 PDLIM5	rs17021918
TERT	rs401681
11p15	rs7127900
8p21	rs1512268
4q24	rs7679673
2q31	rs10207654
3q21.3	rs10934853
8q24.21	rs16902104
2p21 *THADA*	rs1465618
8q24.21	rs445114

Table 14a. Newcastle-Ottawa Scale:[185] Case-control studies

	Study														
Question	**Zheng** [188]	**Salinas** [189]	**Sun** [190]	**Sun** [190] **JHH**	**Helfand** [191]	**Zheng** [192]	**Xu** [193]	**Sun** [194]	**Nam** [195]	**Beuten** [196]	**Penney** [197] **PHS & FHCRC**	**Penney** [197] **Gelb Center companion** [227]	**Aly** [200]	**Helfand** [199]	**Sun** [198]
Is the case definition adequate? A* = yes, with independent validation B = yes, e.g., record linkage or based on self-reports C = no description	A*	A*	C	C	A*	A*	PR	B	A*	A*	A*	C	B	C	A*
Representativeness of the cases A* = consecutive or obviously representative series of cases B = potential for selection biases or not stated	B	A*	A*	A*	A*	A*	PR	A*	A*	B	B	B	B	B	B
Selection of Controls A* = community controls B = hospital controls C = no description	A*	A*	A*	B	C	A*	PR	B	B	A*	A*	C	A*	C	A*
Definition of Controls A* = no Hx of disease (endpoint) B = no description of source	B	A*	B	B	B	B	PR	B	A*	A*	A*	B	A*	A*	B
Comparability of cases and controls on the basis of the design of analysis A* = study controls for (select most important factor) B* = study controls for any additional factor	A*B	A*&B*	A*&B*	A*	A*	A*&B*	PR	A*&B*	A*&B	A*&B*	A*&B*	A*	A*&B*	A*	A*&B*

Table 14a. Newcastle-Ottawa Scale:[185] Case-control studies (continued)

	Study														
Question	**Zheng** [188]	**Salinas** [189]	**Sun** [190]	**Sun** [190] **JHH**	**Helfand** [191]	**Zheng** [192]	**Xu** [193]	**Sun** [194]	**Nam** [195]	**Beuten** [196]	**Penney** [197] **PHS & FHCRC**	**Penney** [197] **Gelb Center companion** [227]	**Aly** [200]	**Helfand** [199]	**Sun** [198]
Ascertainment of exposure: quality control & blinding A* = secure record (e.g., surgical records) B = structured interview where blind case/control status C = interview not blinded to case/control status D = written self-report or medical record only E = no description	A*	A*	E	E	E	E	PR	A*	E	D	A*	A*	A*	A*	E
Same method of ascertainment for cases & controls A* = yes B = no	B	B	A*	A*	B	B	PR	B	A*	A*	A*	A*	A*	B	PR
Non-Response rate A* = same rate for both groups B = nonrespondents described C = rate different and no designation	B	B	C	C	C	B	PR	C	C	C	C	C	C	C	C
NOS Star Rating (out of 9)	5	7	5	3	3	5	NA	4	6	6	7	3	6	2	4

Abbreviations: FHCRC = Fred Hutchinson Cancer Research Center; Hx = history; JHH = Johns Hopkins Hospital; NA = not available; PHS = Physician's Health Study; PR = previously reported

Table 14b. Newcastle-Ottawa Scale:[185] Cohort studies

Study	Representativeness of the exposed cohort A* truly representative of the average prostate cancer patient in the community B* somewhat representative C selected group of users (volunteers) D no description of derivation of cohort	Selection of the non exposed cohort A* from same community as exposed B from different source C no description	Ascertainment of exposure A* secure records (surgical) B* structured interview C written self report D no description	Demonstration that outcome of interest was not present at start of study A* yes B no	Comparability of cohorts on the bases of the design or analysis A* most important factor study controls for B* additional factor	Assessment of outcome A* independent blind assessement B* record linkage C self report D no description	Was follow-up long enough for outcomes to occur A* yes B no	Adequacy of follow up of cohorts A* complete follow up B*small number lost (%) or description of those lost, C % lost and no description of lost D no statement	NOS Star Rating (out of 9)
Wiklund[201]	A* (PR)	A*	A*	A* (PR)	A*	B*	A*	A*	8

Table 14c. Selected items from QUADAS[186]

Question	Zheng 188	Salinas 189	Sun 190	Helfand 191	Zheng 192	Xu 193	Sun 194	Nam 195	Beuten 196	Penney 197	Penney 197	Penney 197	Aly 200	Helfand 199	Sun 198	Wiklund 201
Spectrum of participants representative of the patients who would receive the test in practice	yes	yes	yes	no	yes	NA	no	no	yes	no (PHS)	yes (FHCRC)	UC (Gelb Center)	yes	yes	yes	yes
Selection criteria clearly described	yes	yes	yes	no	yes	NA	UC	yes	yes	yes	yes	yes*	yes	yes	yes	yes
Reporting of uninterpretable indeterminate, or intermediate test results	yes	yes	no	no	yes	NA	no	UC	no	no	no	no	yes	yes	yes	yes

* yes, if look at companion

Abbreviations: FHCRC = Fred Hutchinson Cancer Research Center; NA=not applicable; PHS = Physician's Health Study, UC=unclear

Discussion

The purpose of this review was to establish the evidence base behind using single nucleotide polymorphism-based panels in prostate cancer risk assessment, which includes risk stratification, screening for undiagnosed disease, and assessing prognosis. The high incidence of prostate cancer, the problems associated with current test methods (particularly prostate-specific antigen [PSA] screening in asymptomatic men), the difficulty of determining prognosis in many affected men, and the lack of clarity on the utility of different therapeutic approaches, mean that other avenues need to be explored with some energy. Even fairly modest improvements in risk classification could translate into large health gains in absolute terms.

It is of crucial conceptual importance to recognize that this review is based on a framework of risk prediction, as distinct from causal inference. In the situation of risk prediction, it is relevant to compare models that include standard risk factors with models that include the same risk factors together with single nucleotide polymorphisms (SNPs). This contrasts with the situation of causal inference in which the SNP status of an individual is "assigned" at birth (and is by definition unconfounded). In a clinically-oriented, test evaluation approach, such concerns are secondary to assessing performance as a predictor of a particular outcome.

The review was structured around the ACCE framework, which emphasizes technical assessment as well as clinical performance, although the intent was always to draw conclusions to guide current clinical practice. This was not achieved because of the dearth of evidence relating to most of the questions of interest.

We identified a number of SNP panels that we considered fulfilled the definition of "close to commercially available". They were widely variable in their makeup, containing a range of different SNPs, many combined with other risk factor data in predictive algorithms. There was a lack of published data describing the technical protocols and analytical accuracies achieved for the specific SNPs by panel, and of information describing the laboratory protocols used to demonstrate the analytical validity of SNP panels used for clinical service testing. The limited data available suggest that the analytic validity of genotyping of the 5-SNP panel is high in research settings, but questions remain about potential errors which could influence test results in a clinical setting. This concern also applies to the other panels assessed, for which data were only available from single studies.

With regard to the clinical validity of the 5-SNP panel, the studies were predominantly done with participants of European origin, and so the generalizability of these findings to men of other ancestral or ethnic groups is limited. None of the analyses showed any substantial increment in AUC when the SNPs were added to other risk factors in the models evaluated. The AUCs with the inclusion of SNPs ranged between 63 and 73 percent, and would not in themselves be considered useful for individual risk prediction. In general, proposed tests with an AUC of 75 percent or less are unlikely to be clinically useful.[228,229] In the single study of the 5-SNP panel that investigated mortality, there was no difference between SNP-based and non-SNP-based models. In the single study of the panel that addressed differences by Gleason score, and aggressive and nonaggressive disease, there was no association with scores derived from the 5-SNP panel.

There were only single studies of the other panels, almost all of which reported on panel development, with no information on internal or external validation. When AUC was reported, it was in the range of 62 to 74 percent, and would not in itself be considered useful for individual risk prediction. Any increase in AUC compared with models not incorporating the SNP combinations was small. In the few studies that investigated the distinction between clinically

important and latent/asymptomatic prostate cancer or prognosis, no associations were observed with risk scores derived from the SNP panels.

Thus currently available or documented SNP panels proposed for prediction of risk for prostate cancer have poor discriminative ability. Only one of the panels was tested in data independent of the data in which the panel was developed, and by independent teams of investigators. None of the articles considered calibration, that is, the agreement between the proportion predicted to have the outcome and the proportion observed in the participants in which the panel was tested. Evaluation of calibration is important if predictions based on a test panel are used to inform those tested or health professionals in making decisions.[230] Moreover, discrimination and calibration have limited usefulness for clinical decisionmaking. On the one hand, a panel with good discrimination in a research context may not be clinically useful if the threshold for clinical decision making is outside the range of predictions provided by the panel.[230] On the other hand, a model with relatively poor discrimination may be clinically useful if there is little evidence or consensus to guide clinical choice between alternative managements; none of the studies use a decision-analytic approach.[231]

No evidence was found which addressed the important questions of clinical utility. This is unsurprising, given that this field is in the early stages of development.[232,233] However, even if the review had identified more compelling evidence to support clinical validity (the ability to accurately predict or detect prostate cancer), this would not in itself provide any direct evidence of the value of SNP-based test panels in reducing morbidity and mortality.

Even if SNP-based panels were determined to be useful in improving prostate cancer screening (i.e., the detection of undiagnosed but clinically important cancer), the overall benefits would also depend on the consistent application of appropriate diagnostic strategies, which in turn would depend at least partly on clinicians' willingness to trust the results of initial screening. The most important limitation with PSA-based screening is its lack of specificity (i.e., high rate of false positives).[88,102,103] Improving on this by using SNP-based panels would reduce unnecessary diagnostic investigations and their associated morbidity and costs. However, this will only be successful if patients are willing to trust in negative screen results, given a prevailing culture that seems to promote higher levels of screening as 'better' screening practice.[234-239] Thus, SNP-based screening panels will need not only to demonstrate increased specificity, but may also need to demonstrate superior levels of sensitivity compared with PSA-based screening in order for patients and their physicians to have confidence in their use.

SNP-based panels may also have a role in stratifying future risk of prostate cancer in men who are currently unaffected. This would permit tailoring of surveillance strategies according to risk category: those at highest risk would presumably be offered more frequent screening and those at lowest risk could avoid unnecessary surveillance. However, this assumes that it would be possible to optimize surveillance strategies and ensure valid screening tests. It might also be assumed that men at higher risk would be more motivated to make positive lifestyle changes, although there is no evidence that this actually occurs from studies based on other forms of risk stratification (family history or genetic testing).[240,241] It has also been argued that while the risk of a disease outcome varies between risk strata, the risk of harm from treatment is more uniform.[242] Thus, some individuals could benefit more from treatment than others, but all would be at similar risk of harm.

It is also hoped that SNP-based panels may improve the overall tailoring of treatment so that only those men who are at risk of aggressive disease are offered radical surgical interventions. Evaluations of the prognostic accuracy of such panels would be a first step, but definitive

evidence from rigorous trial would still be required to determine the overall utility of such an approach. To date, there is limited evidence from randomized controlled trials (RCTs) about the efficacy of radical prostatectomy compared with watchful waiting in men with clinically localized prostate cancer,[70,71,81] and syntheses of observational evidence are significantly hampered by serious methodological issues.[243] Two RCTs comparing watchful waiting with radical prostatectomy are ongoing, one in the U.K.,[82] and one in the United States.[84]

Taken together, therefore, benefits from improvements in prostate cancer risk prediction, screening, and prognostic stratification will depend to a large extent on clearer evidence that surveillance, diagnostic, and treatment strategies in themselves lead to reductions in morbidity and mortality.

Applicability

At present it would be premature to apply the results of this review to a clinical population.

Conclusion

The potential value of using single nucleotide polymorphism-based panels in prostate cancer risk assessment includes risk stratification, screening for undiagnosed disease, and assessing prognosis. We identified 15 single nucleotide polymorphism (SNP) panels that we considered fulfilled the definition of 'close to commercially available'. They were widely variable in their makeup, containing 2-35 different SNPs, many combined with other risk factor data in predictive algorithms.

With regard to stratifying future risk and/or screening for current disease, a 5-SNP panel was evaluated in six articles. The other 14 panels were investigated in single studies only. Areas under the curve (AUCs) across all panels ranged between 58 and 74 percent. Thus, all of the panels had AUCs below 75 percent, the threshold below which tests are in general considered unlikely to be clinically useful. Moreover, within individual studies, the incremental gain in AUC observed when the predictive model including the SNP data was compared against the best alternative non-SNPs model (i.e., the absolute improvement in AUC) was very small.

Evaluations of the use of SNP-panels to distinguish between clinically important and latent/asymptomatic prostate cancer were available for four panels. None of the evaluations suggested that any of the four panels performed well in distinguishing between more and less aggressive disease. Prediction of prostate cancer mortality in affected men was evaluated for three panels. There was no association between risk alleles and prostate cancer mortality for any of the panels.

Not surprisingly, given that this field is in the early stages of development, no evidence was found which addressed the important questions of clinical utility. However, even if the review had identified more compelling evidence to support clinical, this would not in itself provide any direct evidence of the value of SNP-based test panels in reducing morbidity and mortality. Any benefit from improvements in prostate cancer risk prediction, screening, and prognostic stratification will depend to a large extent on clearer evidence that surveillance, diagnostic, and treatment strategies in themselves lead to reductions in morbidity and mortality.

Future Research

We identified a number of evaluations of diverse single nucleotide polymorphism (SNP) panels. We could not draw robust conclusions regarding their analytic validity. These studies showed statistically significant associations between combinations of SNPs and risk of prostate cancer. However, when assessed using test evaluation designs, the risk models which incorporated the SNP panels improved the area under the curve only marginally compared with non-SNP-based tests in their ability to distinguish cases from noncases, clinically meaningful from latent or asymptomatic cancer, or in stratifying the prognosis of confirmed cases. These evaluations were not conducted in routine clinical settings. No evidence was identified to address the question of clinical utility.

Future research should focus on evaluating the clinical validity of SNP-based panels more extensively and robustly, in participants more representative of general clinical populations, and compared directly with existing standards of care. In addition to the consideration of discrimination and calibration, it would be helpful to use decision-analysis methods.[219] Incorporation of additional SNPs that increase the proportion of the polygenic variance accounted for by measured genetic variants would be expected to increase the absolute difference in risk between extreme tails of the distribution of a SNP panel.[244] It has also been observed that adding a polygenic risk score (that is, a score based on SNP alleles associated with disease that do not achieve either nominal statistical significance ($p<0.05$) or stringent genome-wide statistical significance) does not improve risk prediction for prostate cancer over replicated SNPs from genome-wide association (GWA) studies.[245] These observations would suggest a need to identify and validate further genetic markers to enable larger SNP panels to be developed. However, it is also the case that SNPs identified from GWA studies are markers for the region of risk in which the causal SNP is located. The magnitude of risk associated with truly causal variants would be expected to be greater than with the risk markers so far identified. Therefore, the quest to develop future panels useful in risk stratification will depend on further characterization of the regions of genetic risk already identified, as well as possible additional markers. More emphasis needs to be placed on distinguishing aggressive and nonaggressive disease, and investigators should consider the possibility for subgroup analyses at the planning stage of studies.

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Appendix A. Search Strings

Search Strategy SNPs

Medline
1. Prostatic Neoplasms/
2. *Neoplasms/
3. ((prostate or prostatic) adj2 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti,ab.
4. 1 or 2 or 3
5. Polymorphism, Single Nucleotide/
6. SNP?.tw.
7. *Genetic Predisposition to Disease/ge [Genetics]
8. or/5-7
9. 4 and 8
10. limit 9 to english language
11. limit 10 to (comment or editorial)
12. 10 not 11

EMBASE
1. Polymorphism, Single Nucleotide/
2. SNP?.tw.
3. exp *genetic predisposition/
4. 1 or 2 or 3
5. exp prostate cancer/
6. *Neoplasms/
7. ((prostate or prostatic) adj2 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti,ab.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to english language
11. limit 10 to (editorial or note)
12. 10 not 11

Cochrane Central Register of Controlled Trials
1. Prostatic Neoplasms/
2. *Neoplasms/
3. ((prostate or prostatic) adj2 (cancer$ or neoplasm$ or carcinom$ or tumo?r$)).ti,ab.
4. 1 or 2 or 3
5. Polymorphism, Single Nucleotide/
6. SNP?.tw.
7. *Genetic Predisposition to Disease/ge [Genetics]
8. or/5-7
9. 4 and 8

Appendix B. Data Abstraction Forms

SNP Screening Forms

<u>Level 1 Title and Abstract Screening Form</u>

1. Is this citation in **English**?

◯ YES/Can't tell

◯ NO (STOP)

2. Is this citation a **full report of a research study** and does it include the use of the acronym or phrase **SNP (single nucleotide polymorphism) testing**? (NOT a commentary, editorial, or narrative review; nor GWAS or family study)

OR include genetic testing AND polymorphic variants of multiple genes AND (not) gene expression

◯ YES/Can't tell

◯ NO (STOP)

3. Is this citation a full report of a SINGLE research study? (**NOT** a systematic review)

◯ YES/Can't Tell

◯ NO (an SR, so STOP)

4. Does this citation focus on **human** SNPs research? (rather than an animal model, such as mouse)

◯ YES/Can't tell

◯ NO (STOP)

5. Does this citation include some proportion of subjects who do **not** have prostate cancer?

◯ YES/Can't tell

◯ NO (continue)

Full Text Screening Level 1 Form

1. **Is this study about Prostate Cancer**?

◯ YES

◯ NO (exclude)

2. Does this study include a test panel of human SNPs?
A test panel is defined as a list of SNPs (or other genetic sequence analytes) included in the assay. The included SNPs can either be informative (i.e., provide test results utilize in the interpretation of the result), or controls used to assist in determining the accuracy and conclusiveness of the test result.

◯ YES

◯ NO (exclude)

◯ Other (exclude, but specify…) [ ]

3. **Is the SNP test commercially available**?

Yes = Affymetrix, Illumina, Seqnenome iPlex, ABI SNplex, other multi-plex arrays

NO = Sequencing for a single SNP, TaqMan assay, RFLP (restriction length fragment polymorphism)

Can't tell = anything that doesn't seem to fit above, but please record the name if you can find it

◯ YES

◯ Don't know (provide name) [ ]

◯ NO (exclude)

4. **Is the study design of this publication**…..?

◯ COMPARATIVE design (case-control, population cohort, RCT, 2 or more group simulation study)

◯ SINGLE GROUP design (pre/post; no comparator)

◯ LABORATORY STUDY evaluating analytic validity/accuracy of SNP panel/platform

◯ Case report (exclude)

◯ Qualitative study (exclude)

◯ Diagnostic test evaluation

◯ Systematic review

◯ Other (exclude) – what kind – GWAs? Family? Other? _____

Full Text Screening Level 2 Form

1. **Does this study address SNP discovery in genes linked to Prostate Cancer cases only**?

◯ YES, Genome wide association study GWAS (agnostic, hypothesis testing) approach; "Fishing expedition". (Stop, Exclude)

◯ YES, By candidate gene approach (hypotheses about effects of variants of genes, or about genetic variation in a gene being associated with risk. The latter would be associated with terms like "tagging and/or "haplotypes". (Stop, Exclude)

◯ No, This study is about gene-characterization containing SNPs associated with Prostate Cancer in previous studies (Continue)

◯ UNSURE (Specify and describe in box provided below this question) (Continue)

2. **Does this SNP study address the following**?

◯ SNP(s) assessment in single gene only (Stop, Exclude)

◯ SNP(s) assessment ACROSS more than one gene (this may or may not include investigation of gene-gene or gene-environment interaction. (Continue)

3. **The aim of this study is to address the following**?

◯ To determine whether a panel of specific SNPs (across genes) predicts risk (Stop, Include)

◯ Whether genetic variation in general at a specific genetic locus is associated with risk (Stop, Include)

Full Text Screening Level 3 Form

Does this study use a SNP assembled panel to assess clinical validity (risk prediction)?

◯ YES (included)

◯ NO (excluded)

SNP Data Abstraction Form

Name: _____ Date: _____

Please answer the following questions with regard to the selected articles:

Author: _____

Publication Year: _____

Refid: _____

Study Objective:

- ◯ Model development
- ◯ Validation
- ◯ Both

Study Design

1. Key elements (e.g., single or multiple case-control, nested case-control, cross-sectional, cohort, newly incident or prevalent cases, nature of control group[s])

_____

_____

2. Setting (in which participants were recruited):

- ◯ Hospitals
- ◯ Outpatient clinics
- ◯ Screening centers
- ◯ Registries
- ◯ Other (Specify) _____

3. Location (country, region, city):

_____

_____

4. Dates of data collection:_____to_____

Study Participants

1. Eligibility (i.e., inclusion and exclusion) criteria for participants:

_____

_____

2. Sources and methods of selection:

_____

_____

3. Number assessed for eligibility: [ ][ ][ ][ ][ ]

SNPs

1. Number genotyped and considered for inclusion in panel: [ ][ ][ ][ ][ ]

2. Type of laboratory in which genotyping done: _____

3. Genotyping method: _____

4. Was genotyping done blind to participant status?

   ◯ Yes

   ◯ No

   ◯ Unsure

5. Genotyping call rate (range; or > % threshold; coverage [SNPs that were considered for inclusion but assay failed so not carried in to analysis])

_____

_____

6. Concordance rate for duplicate samples:

_____

_____

7. Any other quality control checks (Specify):

_____

_____

8. Hardy Weinberg equilibrium (HWE):

   Assessed? Yes No

   If yes, method? _____

   In controls? Yes No

   If no, in all participants? _____

   Result(s) [indicate whether this was for all SNPs considered for inclusion, or just those in the model(s) developed or evaluated] _____

   _____

   _____

9. SNPs (rs number and chromosomal region; if used in paper, please record alternative name for SNP as well) included in each model. When more than one model is developed or evaluated in a paper, the list of SNPs for each model should be given separately.

_____

_____

10. How were SNPs handled in analysis? (e.g., dominant or recessive effects per SNP, per allele, genotype categories, risk scores [explain which of alleles/genotypes is considered to be risk variant])

_____

_____

_____

11. Other variables included in SNP panel

_____

_____

Analysis

1. Method of constructing SNP panel (number of SNPs and number of other variables initially considered; variable selection procedure; horizon of risk protection [e.g., 5-year risk])

_____

_____

2. Method of validating SNP panel (procedure and data)

_____

_____

3. Missing data (imputation, other)

_____

_____

4. Measures used to evaluate SNP panel (e.g., OR(s) by risk score, AUC, ΔAUC, maximum test accuracy and cross-validation consistency)

_____

_____

Results

1. Number of participants included in analysis (by group; one entry per analysis) ☐☐☐☐☐

2. Mean age (SD) (by group) Age: ☐☐ SD:_____

3. Ethnicity: _____

4. First degree family history of prostate cancer?

   ◯ Yes

   ◯ No

5. PSA: _____

6. Gleason score: _____

7. Pathologic stage (TNM): _____

8. Aggressive Disease

   a. Definition: _____

   _____

   b. Proportion of cases with aggressive disease: _____%

9. Risk Score: _____

10. AUC: _____

11. ΔAUC: _____

12. Other measure: _____

13. Subgroup analysis of risk score, AUC, ΔAUC or other measure:

_____

_____

14. Results of validation (if relevant):

_____

_____

Funding

15. Specified?

- ◯ Yes
- ◯ No

16. Public or other? _____

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE-CONTROL STUDIES

Note: A study can be awarded a maximum of one star (*****) for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation *****
   b) yes, e.g., record linkage or based on self reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases *****
   b) potential for selection biases or not stated
3) Selection of Controls
   a) community controls *****
   b) hospital controls
   c) no description
4) Definition of Controls
   a) no history of disease (endpoint) *****
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) *****
   b) study controls for any additional factor ***** (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) *****
   b) structured interview where blind to case/control status *****
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) yes *****
   b) no
3) Non-Response rate
   a) same rate for both groups *****
   b) non respondents described
   c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community*
   b) somewhat representative of the average _____ in the community
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort*
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g, surgical records)*
   b) structured interview*
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) *
   b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment*
   b) record linkage*
   c) self report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) *
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for*
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Wells, G. A, Shea, B., O'Connel, D. et al. The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses. http://www ohri ca/programs/clinical_epidemiology/oxford htm 2009 Feb 1

The QUADAS tool

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2.	Were selection criteria clearly described?	( )	( )	( )
3.	Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	( )	( )	( )
6.	Did patients receive the same reference standard regardless of the index test result?	( )	( )	( )
7.	Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?	( )	( )	( )
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13.	Were uninterpretable/ intermediate test results reported?	( )	( )	( )
14.	Were withdrawals from the study explained?	( )	( )	( )

Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25

Appendix C. Excluded Studies

Anonymous Association of carboxylesterase 1A genotypes with irinotecan pharmacokinetics in Japanese cancer patients. Br J Clin Pharmacol. 2010;70(2):222-3. PMID:20653675.OVID-Medline.
Exclude: Not about prostate cancer

Anonymous Matrix metalloproteinase-2 polymorphism is associated with prognosis in prostate cancer. Urol Oncol. 2010;28(6):624-7. PMID:19117773.OVID-Medline.
Exclude: Did not use SNP assembled panel

Abe M, Xie W, Regan MM, et al. Single-nucleotide polymorphisms within the antioxidant defence system and associations with aggressive prostate cancer. BJU Int. 2011;107(1):126-34. PMID:20477822 OVID-Medline.
Exclude: Did not use SNP assembled panel

Adank MA, van Mil SE, Gille JJ, et al. PALB2 analysis in BRCA2-like families. Breast Canc Res Treat. 2011;127(2):357-62. PMID:20582465 OVID-Medline.
Exclude: Not about prostate cancer

Adeyemo A, Rotimi C. Genetic variants associated with complex human diseases show wide variation across multiple populations. Publ Health Genomics. 2010;13(2):72-9. PMID:19439916 OVID-Medline.
Exclude: Did not use SNP assembled panel

Agalliu I, Leanza SM, Smith L, et al. Contribution of HPC1 (RNASEL) and HPCX variants to prostate cancer in a founder population. Prostate. 2010;70(15):1716-27. PMID:20564318 OVID-Medline.
Exclude: Test not commercially available

Agalliu I, Suuriniemi M, Prokunina-Olsson L, et al. Evaluation of a variant in the transcription factor 7-like 2 (TCF7L2) gene and prostate cancer risk in a population-based study. Prostate. 2008;68(7):740-7. PMID:18302196 OVID-Medline.
Exclude: Test not commercially available

Agalliu I, Kwon EM, Salinas CA, et al. Genetic variation in DNA repair genes and prostate cancer risk: Results from a population-based study. Canc Causes Contr. 2010;21(2):289-300. PMID:19902366 OVID-Medline.
Exclude: Did not use SNP assembled panel

Agalliu I, Lin DW, Salinas CA, et al. Polymorphisms in the glutathione S-transferase M1, T1, and P1 genes and prostate cancer prognosis. Prostate. 2006;66(14):1535-41. OVID-Embase.
Exclude: Candidate gene study

Agalliu I, Karlins E, Kwon EM, et al. Rare germline mutations in the BRCA2 gene are associated with early-onset prostate cancer. Br J Canc. 2007;97(6):826-31. PMID:17700570 OVID-Medline.
Exclude: Did not use SNP assembled panel

Ahn J, Kibel AS, Park JY, et al. Prostate cancer predisposition loci and risk of metastatic disease and prostate cancer recurrence. Clin Canc Res. 2011;17(5):1075-81. OVID-Embase.
Exclude: Did not use SNP assembled panel

Ahn J, Schumacher FR, Berndt SI, et al. Quantitative trait loci predicting circulating sex steroid hormones in men from the NCI-Breast and Prostate Cancer Cohort Consortium (BPC3). Hum Mol Genet. 2009;18(19):3749-57. PMID:19574343 OVID-Medline.
Exclude: Test not commercially available

Ahn J, Berndt SI, Wacholder S, et al. Variation in KLK genes, prostate-specific antigen and risk of prostate cancer. Nat Genet. 2008;40(9):1032-4. OVID-Embase.
Exclude: Study Design

Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis. 2009;30(5):769-76. PMID:19255064 OVID-Medline.
Exclude: Did not use SNP assembled panel

Al Khaldi RM, Al MF, Al AS, et al. Associations of single nucleotide polymorphisms in the adiponectin gene with adiponectin levels and cardio-metabolic risk factors in patients with cancer. Dis Markers. 2011;30(4):197-212. PMID:21694446 OVID-Medline.
Exclude: Not about prostate cancer

Al Olama AA, Kote-Jarai Z, Giles GG, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. Nat Genet. 2009;41(10):1058-60. PMID:19767752 OVID-Medline.
Exclude: Did not use SNP assembled panel

Albayrak S, Canguven O, Goktas C, et al. Role of MMP-1 1G/2G promoter gene polymorphism on the development of prostate cancer in the Turkish population. Urol Int. 2007;79(4):312-5. PMID:18025848 OVID-Medline.
Exclude: Test not commercially available

Alcazar LP, Arakaki PA, Godoy-Santos A, et al. Estrogen receptor polymorphism and its relationship to pathological process. Am J Med Sci. 2010;340(2):128-32. OVID-Embase.
Exclude: Study Design

Allin KH, Nordestgaard BG, Zacho J, et al. C-reactive protein and the risk of cancer: A mendelian randomization study. J Natl Canc Inst. 2010;102(3):202-6. PMID:20056955 OVID-Medline.
Exclude: Not about prostate cancer

Alvarez K, Kash SF, Lyons-Weiler MA, et al. Reproducibility and performance of virtual karyotyping with SNP microarrays for the detection of chromosomal imbalances in formalin-fixed paraffin-embedded tissues. Diagn Mol Pathol. 2010;19(3):127-34. PMID:20736741 OVID-Medline.
Exclude: Not about prostate cancer

Amankwah EK, Wang Q, Schildkraut JM, et al. Polymorphisms in stromal genes and susceptibility to serous epithelial ovarian cancer: A report from the Ovarian Cancer Association Consortium. PLoS One. 2011;6(5):e19642. OVID-Embase.
Exclude: Not about prostate cancer

Amankwah EK, Kelemen LE, Wang Q, et al. Prostate cancer susceptibility polymorphism rs2660753 is not associated with invasive ovarian cancer. Canc Epidemiol Biomarkers Prev. 2011;20(5):1028-31. PMID:21415361 OVID-Medline.
Exclude: Not about prostate cancer

Amirian ES, Ittmann MM, Scheurer ME. Associations between arachidonic acid metabolism gene polymorphisms and prostate cancer risk. Prostate. 2011;71(13):1382-9. OVID-Embase.
Exclude: Candidate gene study

Amundadottir LT, Sulem P, Gudmundsson J, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet. 2006;38(6):652-8. PMID:16682969 OVID-Medline.
Exclude: Candidate gene study

Andreassen CN, Alsner J. Genetic variants and normal tissue toxicity after radiotherapy: A systematic review. Radiother Oncol. 2009;92(3):299-309. OVID-Embase.
Exclude: Study Design

Angele S, Falconer A, Edwards SM, et al. ATM polymorphisms as risk factors for prostate cancer development. Br J Canc. 2004;91(4):783-7. OVID-Embase.
Exclude: Test not commercially available

Anghel A, Narita D, Seclaman E, et al. Estrogen receptor alpha polymorphisms and the risk of malignancies. Pathol Oncol Res. 2010;16(4):485-96. PMID:20383761 OVID-Medline.
Exclude: Not about prostate cancer

Arslan S, Pinarbasi H, Silig Y. Myeloperoxidase G-463A polymorphism and risk of lung and prostate cancer in a Turkish population. Mol Med Rep. 2011;4(1):87-92. PMID:21461569 OVID-Medline.
Exclude: Test not commercially available

Arsova-Sarafinovska Z, Matevska N, Petrovski D, et al. Manganese superoxide dismutase (MnSOD) genetic polymorphism is associated with risk of early-onset prostate cancer. Cell Biochem Funct. 2008;26(7):771-7. OVID-Embase.
Exclude: Test not commercially available

Ashtiani ZO, Hasheminasab SM, Ayati M, et al. Are GSTM1, GSTT1 and CAG repeat length of androgen receptor gene polymorphisms associated with risk of prostate cancer in Iranian patients? Pathol Oncol Res. 2011;17(2):269-75. PMID:21089003 OVID-Medline.
Exclude: Candidate gene study

Assie G, LaFramboise T, Platzer P, et al. Frequency of germline genomic homozygosity associated with cancer cases. JAMA. 2008;299(12):1437-45. PMID:18364486 OVID-Medline.
Exclude: No test panel of human SNP

Azria D, Ozsahin M, Kramar A, et al. Single nucleotide polymorphisms, apoptosis, and the development of severe late adverse effects after radiotherapy. Clin Canc Res. 2008;14(19):6284-8. PMID:18829510 OVID-Medline.
Exclude: Not about prostate cancer

Bachmann N, Hoegel J, Haeusler J, et al. Mutation screen and association study of EZH2 as a susceptibility gene for aggressive prostate cancer. Prostate. 2005;65(3):252-9. PMID:16015586 OVID-Medline.
Exclude: Test not commercially available

Baffoe-Bonnie AB, Smith JR, Stephan DA, et al. A major locus for hereditary prostate cancer in Finland: Localization by linkage disequilibrium of a haplotype in the HPCX region. Hum Genet. 2005;117(4):307-16. PMID:15906096 OVID-Medline.
Exclude: Test not commercially available

Balistreri CR, Caruso C, Carruba G, et al. A pilot study on prostate cancer risk and pro-inflammatory genotypes: Pathophysiology and therapeutic implications. Curr Pharmaceut Des. 2010;16(6):718-24. OVID-Embase.
Exclude: Test not commercially available

Balistreri CR, Caruso C, Carruba G, et al. Genotyping of sex hormone-related pathways in benign and malignant human prostate tissues: Data of a preliminary study. OMICS. 2011;15(6):369-74. OVID-Embase.
Exclude: Test not commercially available

Balistreri CR, Caruso C, Listi F, et al. LPS-mediated production of pro/anti-inflammatory cytokines and eicosanoids in whole blood samples: Biological effects of +896A/G TLR4 polymorphism in a Sicilian population of healthy subjects. Mech Ageing Dev. 2011;132(3):86-92. OVID-Embase.
Exclude: Not about prostate cancer

Bao B-Y, Pao J-B, Lin VC, et al. Individual and cumulative association of prostate cancer susceptibility variants with clinicopathologic characteristics of the disease. Clinica Chimica Acta. 2010;411(17-18):1232-7. OVID-Embase.
Exclude: Doesn't include test panel

Bao B-Y, Pao J-B, Huang C-N, et al. Polymorphisms inside MicroRNAs and MicroRNA target sites predict clinical outcomes in prostate cancer patients receiving androgen-deprivation therapy. Clin Canc Res. 2011;17(4):928-36. OVID-Embase.
Exclude: Doesn't include test panel

Bao S, Yang W, Zhou S, et al. Relationship between single nucleotide polymorphisms in -174G/C and -634C/G promoter region of interleukin-6 and prostate cancer. J Huazhong U Sci Tech. 2008;Medical(6):693-6. PMID:19107369 OVID-Medline.
Exclude: Test not commercially available

Beebe-Dimmer JL, Levin AM, Ray AM, et al. Chromosome 8q24 markers: Risk of early-onset and familial prostate cancer. Int J Canc. 2008;122(12):2876-9. PMID:18360876 OVID-Medline.
Exclude: Test not commercially available

Beebe-Dimmer JL, Zuhlke KA, Ray AM, et al. Genetic variation in adiponectin (ADIPOQ) and the type 1 receptor (ADIPOR1), obesity and prostate cancer in African Americans. Prostate Canc P Dis. 2010;13(4):362-8. PMID:20697428 OVID-Medline.
Exclude: Test not commercially available

Beebe-Dimmer JL, Lange LA, Cain JE, et al. Polymorphisms in the prostate-specific antigen gene promoter do not predict serum prostate-specific antigen levels in African-American men. Prostate Canc P Dis. 2006;9(1):50-5. PMID:16247489 OVID-Medline.
Exclude: Test not commercially available

Benn M, Tybjaerg-Hansen A, Stender S, et al. Low-density lipoprotein cholesterol and the risk of cancer: A mendelian randomization study. J Natl Canc Inst. 2011;103(6):508-19. PMID:21285406 OVID-Medline.
Exclude: Not about prostate cancer

Berndt SI, Sampson J, Yeager M, et al. Large-scale fine mapping of the HNF1B locus and prostate cancer risk. Hum Mol Genet. 2011;20(16):3322-9. OVID-Embase.
Exclude: SNP assessment in single gene

Berndt SI, Chatterjee N, Huang W-Y, et al. Variant in sex hormone-binding globulin gene and the risk of prostate cancer. Canc Epidemiol Biomarkers Prev. 2007;16(1):165-8. OVID-Embase.
Exclude: Test not commercially available

Bessarabova M, Pustovalova O, Shi W, et al. Functional synergies yet distinct modulators affected by genetic alterations in common human cancers. Canc Res. 2011;71(10):3471-81. PMID:21398405 OVID-Medline.
Exclude: Not about prostate cancer

Beuten J, Gelfond JA, Martinez-Fierro ML, et al. Association of chromosome 8q variants with prostate cancer risk in Caucasian and Hispanic men. Carcinogenesis. 2009;30(8):1372-9. PMID:19528667 OVID-Medline.
Exclude: Candidate gene study

Beuten J, Gelfond JA, Byrne JJ, et al. CYP1B1 variants are associated with prostate cancer in non-Hispanic and Hispanic Caucasians. Carcinogenesis. 2008;29(9):1751-7. PMID:18544568 OVID-Medline.
Exclude: Test not commercially available

Beuten J, Garcia D, Brand TC, et al. Semaphorin 3B and 3F single nucleotide polymorphisms are associated with prostate cancer risk and poor prognosis. J Urol. 2009;182(4):1614-20. PMID:19683737 OVID-Medline.
Exclude: Test not commercially available

Beuten J, Gelfond JA, Franke JL, et al. Single and multivariate associations of MSR1, ELAC2, and RNASEL with prostate cancer in an ethnic diverse cohort of men. Canc Epidemiol Biomarkers Prev. 2010;19(2):588-99. PMID:20086112 OVID-Medline.
Exclude: Candidate gene study

Bignell G, Smith R, Hunter C, et al. Sequence analysis of the protein kinase gene family in human testicular germ-cell tumors of adolescents and adults. Gene Chromosome Canc. 2006;45(1):42-6. OVID-Embase.
Exclude: Not about prostate cancer

Bochum S, Paiss T, Vogel W, et al. Confirmation of the prostate cancer susceptibility locus HPCX in a set of 104 German prostate cancer families. Prostate. 2002;52(1):12-9. OVID-Embase.
Exclude: Test not commercially available

Bock CH, Schwartz AG, Ruterbusch JJ, et al. Results from a prostate cancer admixture mapping study in African-American men. Hum Genet. 2009;126(5):637-42. PMID:19568772 OVID-Medline.
Exclude: GWA study

Bonilla C, Mason T, Long L, et al. E-cadherin polymorphisms and haplotypes influence risk for prostate cancer. Prostate. 2006;66(5):546-56. OVID-Embase.
Exclude: Test not commercially available

Bonilla C, Hooker S, Mason T, et al. Prostate cancer susceptibility loci identified on chromosome 12 in African Americans. PLoS One. 2011;6(2):e16044. OVID-Embase.
Exclude: Candidate gene study

Brajuskovic G, Mircetic J, Savic PD, et al. Analysis of five single nucleotide polymorphisms at locus 8q24 associated with prostate cancer in Serbian population. Virchows Archiv. 2011;Conference: 23rd European Congress of Pathology: Pathology - Diagnostic, Prognostic, Predictive Helsinki Finland.:S319. OVID-Embase.
Exclude: Study Design

Brand TC, Bermejo C, Canby-Hagino E, et al. Association of polymorphisms in TGFB1 and prostate cancer prognosis. J Urol. 2008;179(2):754-8. PMID:18082198 OVID-Medline.
Exclude: Test not commercially available

Breyer JP, McReynolds KM, Yaspan BL, et al. Genetic variants and prostate cancer risk: Candidate replication and exploration of viral restriction genes. Canc Epidemiol Biomarkers Prev. 2009;18(7):2137-44. PMID:19567509 OVID-Medline.
Exclude: Did not use SNP assembled panel

Brooks J. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. Urol Oncol. 2008;26(5):569-70. OVID-Embase.
Exclude: Study Design

Brooks J. Multiple loci identified in a genome-wide association study of prostate cancer. Urol Oncol. 2008;26(5):571. OVID-Embase.
Exclude: Study Design

Brooks J. Multiple newly identified loci associated with prostate cancer susceptibility. Urol Oncol. 2008;26(5):570. OVID-Embase.
Exclude: Study Design

Burmester JK, Suarez BK, Lin JH, et al. Analysis of candidate genes for prostate cancer. Hum Hered. 2004;57(4):172-8. PMID:15583422 OVID-Medline.
Exclude: Test not commercially available

Burri RJ, Stock RG, Cesaretti JA, et al. Association of single nucleotide polymorphisms in SOD2, XRCC1 and XRCC3 with susceptibility for the development of adverse effects resulting from radiotherapy for prostate cancer. Radiat Res. 2008;170(1):49-59. PMID:18582155 OVID-Medline.
Exclude: Candidate gene study

Cai D, Ning L, Pan C, et al. Association of polymorphisms in folate metabolic genes and prostate cancer risk: A case-control study in a Chinese population. J Genet. 2010;89(2):263-7. PMID:20861582 OVID-Medline.
Exclude: Test not commercially available

Camp NJ, Tavtigian SV. Meta-analysis of associations of the Ser217Leu and Ala541Thr variants in ELAC2 (HPC2) and prostate cancer. Am J Hum Genet. 2002;71(6):1475-8. PMID:12515253 OVID-Medline.
Exclude: Study Design

Camp NJ, Farnham JM, Wong J, et al. Replication of the 10q11 and Xp11 prostate cancer risk variants: Results from a Utah pedigree-based study. Canc Epidemiol Biomarkers Prev. 2009;18(4):1290-4. PMID:19336566 OVID-Medline.
Exclude: Did not use SNP assembled panel

Campa D, Husing A, Chang-Claude J, et al. Genetic variability of the fatty acid synthase pathway is not associated with prostate cancer risk in the European Prospective Investigation on Cancer (EPIC). Eur J Canc. 2011;47(3):420-7. PMID:20965718 OVID-Medline.
Exclude: Candidate gene study

Campa D, Husing A, Dostal L, et al. Genetic variability of the forkhead box O3 and prostate cancer risk in the European Prospective Investigation on Cancer. Oncol Rep. 2011;26(4):979-86. OVID-Embase.
Exclude: Test not commercially available

Campa D, Husing A, Stein A, et al. Genetic variability of the mTOR pathway and prostate cancer risk in the European Prospective Investigation on Cancer (EPIC). PLoS One. 2011;6(2):e16914. OVID-Embase.
Exclude: Candidate gene study

Campa D, Kaaks R, Le ML, et al. Interactions between genetic variants and breast cancer risk factors in the breast and prostate cancer cohort consortium. J Natl Canc Inst. 2011;103(16):1252-63. OVID-Embase.
Exclude: Not about prostate cancer

Cancel-Tassin G, Latil A, Valeri A, et al. No evidence of linkage to HPC20 on chromosome 20q13 in hereditary prostate cancer. Int J Canc. 2001;93(3):455-6. PMID:11433415 OVID-Medline.
Exclude: Study Design

Cancel-Tassin G, Latil A, Valeri A, et al. PCAP is the major known prostate cancer predisposing locus in families from south and west Europe. Eur J Hum Genet. 2001;9(2):135-42. PMID:11313747 OVID-Medline.
Exclude: Test not commercially available

Canzian F, Cox DG, Setiawan VW, et al. Comprehensive analysis of common genetic variation in 61 genes related to steroid hormone and insulin-like growth factor-I metabolism and breast cancer risk in the NCI breast and prostate cancer cohort consortium. Hum Mol Genet. 2010;19(19):3873-84. PMID:20634197 OVID-Medline.
Exclude: Not about prostate cancer

Castro P, Creighton CJ, Ozen M, et al. Genomic profiling of prostate cancers from African American men. Neoplasia (New York). 2009;11(3):305-12. PMID:19242612 OVID-Medline.
Exclude: Candidate gene study

Chae YK, Huang HY, Strickland P, et al. Genetic polymorphisms of estrogen receptors alpha and beta and the risk of developing prostate cancer. PLoS One. 2009;4(8):e6523. PMID:19654868 OVID-Medline.
Exclude: Did not use SNP assembled panel

Chang BL, Zheng SL, Isaacs SD, et al. A polymorphism in the CDKN1B gene is associated with increased risk of hereditary prostate cancer. Canc Res. 2004;64(6):1997-9. PMID:15026335 OVID-Medline.
Exclude: Did not use SNP assembled panel

Chang BL, Zheng SL, Isaacs SD, et al. Evaluation of SRD5A2 sequence variants in susceptibility to hereditary and sporadic prostate cancer. Prostate. 2003;56(1):37-44. PMID:12746845 OVID-Medline.
Exclude: Test not commercially available

Chang BL, Cramer SD, Wiklund F, et al. Fine mapping association study and functional analysis implicate a SNP in MSMB at 10q11 as a causal variant for prostate cancer risk. Hum Mol Genet. 2009;18(7):1368-75. PMID:19153072 OVID-Medline.
Exclude: SNP assessment in single gene

Chang BL, Liu W, Sun J, et al. Integration of somatic deletion analysis of prostate cancers and germline linkage analysis of prostate cancer families reveals two small consensus regions for prostate cancer genes at 8p. Canc Res. 2007;67(9):4098-103. PMID:17483320 OVID-Medline.
Exclude: Did not use SNP assembled panel

Chang BL, Zheng SL, Hawkins GA, et al. Joint effect of HSD3B1 and HSD3B2 genes is associated with hereditary and sporadic prostate cancer susceptibility. Canc Res. 2002;62(6):1784-9. PMID:11912155 OVID-Medline.
Exclude: Test not commercially available

Chang BL, Zheng SL, Isaacs SD, et al. Polymorphisms in the CYP1A1 gene are associated with prostate cancer risk. Int J Canc. 2003;106(3):375-8. PMID:12845676 OVID-Medline.
Exclude: SNP assessment in single gene

Chang BL, Zheng SL, Isaacs SD, et al. Polymorphisms in the CYP1B1 gene are associated with increased risk of prostate cancer. Br J Canc. 2003;89(8):1524-9. PMID:14562027 OVID-Medline.
Exclude: SNP assessment in single gene

Chang C-H, Chiu C-F, Wu H-C, et al. Significant association of XRCC4 single nucleotide polymorphisms with prostate cancer susceptibility in Taiwanese males. Mol Med Rep. 2008;1(4):525-30. OVID-Embase.
Exclude: Test not commercially available

Chaturvedi AK, Caporaso NE, Katki HA, et al. C-reactive protein and risk of lung cancer. J Clin Oncol. 2010;28(16):2719-26. OVID-Embase.
Exclude: Not about prostate cancer

Chau CH, Permenter MG, Steinberg SM, et al. Polymorphism in the hypoxia-inducible factor 1alpha gene may confer susceptibility to androgen-independent prostate cancer. Canc Biol Ther. 2005;4(11):1222-5. PMID:16205110 OVID-Medline.
Exclude: Test not commercially available

Chavan SV, Maitra A, Roy N, et al. Genetic variants in the distal enhancer region of the PSA gene and their implication in the occurrence of advanced prostate cancer. Mol Med Rep. 2010;3(5):837-43. OVID-Embase.
Exclude: SNP assessment in single gene

Chen H, Hernandez W, Shriver MD, et al. ICAM gene cluster SNPs and prostate cancer risk in African Americans. Hum Genet. 2006;120(1):69-76. PMID:16733712 OVID-Medline.
Exclude: Test not commercially available

Chen J, Rodriguez C. Conditional likelihood methods for haplotype-based association analysis using matched case-control data. Biometrics. 2007;63(4):1099-107. PMID:18078481 OVID-Medline.
Exclude: Not about prostate cancer

Chen M, Huang Y-C, Yang S, et al. Association between the prostate-specific antigen gene and the risk of prostate cancer in a Taiwanese population. Urol Sci. 2011;22(1):28-31. OVID-Embase.
Exclude: Test not commercially available

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Exclude: SNP assessment in single gene

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Exclude: Doesn't include test panel

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Exclude: Study Design

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Exclude: SNP assessment in single gene

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Exclude: SNP assessment in single gene

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Exclude: Did not use SNP assembled panel

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Exclude: GWA study

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Exclude: Did not use SNP assembled panel

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Exclude: SNP assessment in single gene

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Exclude: SNP assessment in single gene

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Exclude: Study Design

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Exclude: Did not use SNP assembled panel

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Exclude: SNP assessment in single gene

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Exclude: No test panel of human SNP

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Exclude: GWA study

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Exclude: Did not use SNP assembled panel

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Exclude: Candidate gene study

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Exclude: Test not commercially available

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Exclude: Did not use SNP assembled panel

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Exclude: Candidate gene study

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Exclude: Did not use SNP assembled panel

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Exclude: Study Design

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Exclude: SNP assessment in single gene

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Exclude: Test not commercially available

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Exclude: Study design

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Exclude: Study Design

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Exclude: Did not use SNP assembled panel

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Exclude: SNP assessment in single gene

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Exclude: Did not use SNP assembled panel

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Exclude: Candidate gene study

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Exclude: SNP assessment in single gene

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Exclude: Study Design

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Exclude: Doesn't include test panel

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Exclude: Study design

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Exclude: SNP assessment in single gene

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Exclude: Test not commercially available

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Exclude: No test panel of human SNP

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Exclude: Did not use SNP assembled panel

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Exclude: Study Design

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Exclude: Candidate gene study

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