

## *Draft Evidence Review*

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Number XX

# **Use of Multi-Gene Panels Involving Single Nucleotide Polymorphisms (SNPs) for Prostate Cancer Risk Assessment**

**Prepared for:**

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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 healthcare in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

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AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare 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 e-mail to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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## **Acknowledgments**

### **Technical Expert Panel**

# Use of Multi-Gene Panels Involving Single Nucleotide Polymorphisms (SNPs) for 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 risk of prostate cancer.

**Data Sources:** MEDLINE<sup>®</sup>, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and EMBASE, from the beginning of each database to September 2010. Search strategies used combinations of controlled vocabulary (medical subject headings, keywords) and text words. Grey literature was identified. Excluded populations included nonhumans or studies with all subjects diagnosed with prostate cancer.

**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 (TEP) appointed by the Agency for Healthcare Research and Quality (AHRQ). Standard systematic review methodology was applied, with eligibility criteria developed separately for each KQ.

**Results:** From 1,513 unique citations, ten 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 11 individual panels with 3-27 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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# Use of Multi-Gene Panels Involving Single Nucleotide Polymorphisms (SNPs) for Prostate Cancer Risk Assessment

## *Executive Summary*

### **Background**

Prostate cancer is the fifth most common malignancy in the world,<sup>1</sup> 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.<sup>2,3</sup> These numbers are likely to increase with the ageing of the population.<sup>4</sup> 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-late 1990s, and disparity between ethnic groups in cancer stage at diagnosis decreased.<sup>5</sup>

The risk factors associated with prostate cancer are unclear,<sup>6</sup> which makes 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, and African-American men have a poorer prognosis than other groups, independent of co-morbidity or access to health services.<sup>7</sup> First-degree relatives of men with prostate cancer have a two- to three-fold increased risk for developing the disease,<sup>6,8,9</sup> and its estimated heritability is high.<sup>10</sup> 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.<sup>11,12</sup> 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.

The natural history of prostate cancer is highly variable.<sup>13</sup> In a large proportion of men, the disease is indolent, and it is difficult to predict which tumors will be aggressive. 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 United States Food and Drug Administration (FDA) in 1986 for monitoring progression in patients with prostate cancer, and later approved for the detection of disease in symptomatic men (but not for screening asymptomatic men).<sup>14</sup> A meta-analysis of seven randomized controlled trials (RCTs) of screening using PSA testing alone, or in combination with digital rectal examination, suggested no evidence of benefit in reducing mortality,<sup>15,16</sup> and some evidence of harms from overdiagnosis.<sup>16</sup> Amidst substantial debate,<sup>17-23</sup> the argument has been made for developing more accurate screening tests, including possible genetic markers.

SNPs are minute inherited variations in DNA sequence. SNPs occur about once in every 800 base pairs<sup>24</sup> 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.<sup>25-34</sup> The magnitude of the odds ratios (ORs) in these studies was in the range 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,<sup>35-38</sup> but a small to moderate number of common, low penetrance variants, in combination, may account for a high proportion of a disease<sup>36,39,40</sup> and may be useful in predicting risk for disease.<sup>41</sup> 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.

## 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 ES. Table 1).

**ES. Table 1. Elements and key components of evaluation framework for SNP-based panels in prostate cancer risk assessment [reproduced from Yoon, Scheuner, and Khoury, 2003]<sup>42</sup>**

Element	Definition	Components
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (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) <sup>43</sup>
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

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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 a 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 therefore 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<sup>®</sup>, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, and EMBASE databases were searched from their inception to September 2010 inclusive.

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

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.

## Results

Our comprehensive search yielded 1,513 unique citations. In total, 1,092 (72 percent) were excluded from further review following the initial level of title and abstract screening. The remaining 421 citations were screened at full text and from these a total of 10 articles<sup>44-53</sup> 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 2011, as were companies known to offer genetic testing more generally. As of 27 June 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 eleven test panels were considered eligible for KQ2, 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 reported usually in the range of 98 to 99 percent (with a low of 90 percent), and reported concordance on retesting was usually >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?**

Ten articles, describing eleven distinct SNP-based panels, were identified as eligible for KQ2. The properties of a 5-SNP panel were investigated in five articles, three of which also considered family history. The other ten panels included between three and 27 SNPs, but each was investigated in single studies only; several of these considered family history and age in the risk prediction model. All 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’. None of the studies were performed in routine clinical settings.

**1. How well do available panels predict the risk of prostate cancer?**

**a. calibration**

**b. discriminative accuracy**

The range of observed diagnostic ORs for the 5-SNP panel across studies, 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 0.58 to 0.73, depending on the study and inclusion of other variables. AUCs across all panels ranged between 0.58 and 0.74. 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.

**c. ability to distinguish clinically important from latent/asymptomatic prostate cancer**

Data pertaining to this question were available for four panels.<sup>45,48,49,53</sup> Regardless of the operational definition of clinically important prostate cancer, none of the evaluations suggested that the panels performed well in distinguishing between more and less aggressive disease.

**2. How do available panels predict the risk of prostate cancer when substituted for, or added to, PSA based and other clinical risk assessment tests?**

**a. change in the area under the receiver operator characteristics curve (AUC)**

Data pertaining to this question were available for two panels.<sup>44,45,48</sup>

For the Focus 5 panel, three analyses were available. The first<sup>44</sup> suggested an improvement in the AUC from 0.61 to 0.63 when the SNP data were added to a risk model based on age, geographic region, and family history. In the second,<sup>51</sup> the results were 0.72 for a risk model based on age, family history of prostate cancer, ethnicity, urinary symptoms, PSA, free: total PSA ratio, and digital rectal examination and 0.73 when the SNP data were added. For the third,<sup>45</sup> the AUC was 0.63 for a risk model including age, serum PSA level, and history of prostate cancer in first degree relative and 0.66 when the SNP data were added. The improvements were not statistically significant for any of these comparisons.

For the 11-SNP panel,<sup>48</sup> the AUC for a risk model based on age and family history was 0.61 and increased to 0.65 when the complete SNP data were included. This improvement was not statistically significant.

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<sup>52</sup> 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 descent, African American men, and men of East Asian descent.<sup>54</sup>

**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**

Quality assessment was performed using The Newcastle Ottawa Scale (NOS)<sup>55</sup> supplemented by selected items from the QUADAS tool.<sup>56</sup> 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.

**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. Clinical validity analyses showed statistically significant associations between the panels and prostate cancer diagnosis. However, when assessed using AUC analyses, the SNP components of the models improved on the nongenomic components only marginally in their ability to distinguish cases from noncases, and in distinguishing clinically meaningful from latent or asymptomatic cancer. 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 is also a need to identify and validate

further genetic markers to enable larger SNP panels to be developed. 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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## Executive Summary References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-917. PMID:21351269
2. American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.  
<http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-026238.pdf>
3. Canadian Cancer Society. *Canadian Cancer Statistics 2010*. Toronto: Canadian Cancer Society; 2010 Apr.  
<http://www.cancer.ca/~media/CCS/Canada%20wide/Files%20List/English%20files%20heading/pdf%20not%20in%20publications%20section/Canadian%20Cancer%20Statistics%202010%20-%20English.ashx>
4. 2008 National Population Projections  
<http://www.census.gov/population/www/projections/2008projections.html>. U.S.Census Bureau. 2011.
5. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst*. 2009;101(18):1280-3. PMID:19713548
6. Gronberg H. Prostate cancer epidemiology. *Lancet*. 2003;361(9360):859-64. PMID:12642065
7. Evans S, Metcalfe C, Ibrahim F, et al. Investigating Black-White differences in prostate cancer prognosis: A systematic review and meta-analysis. *Int J Cancer*. 2008;123(2):430-5. PMID:18452170
8. Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. *Int J Cancer*. 2003;107(5):797-803. PMID:14566830
9. Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. *Cancer*. 2003;97(8):1894-903. PMID:12673715
10. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343(2):78-85. PMID:10891514
11. Carter BS, Beaty TH, Steinberg GD, et al. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A*. 1992;89(8):3367-71. PMID:1565627
12. Carter BS, Bova GS, Beaty TH, et al. Hereditary prostate cancer: epidemiologic and clinical features. *J Urol*. 1993;150(3):797-802. PMID:8345587
13. Cuzick J, Fisher G, Kattan MW, et al. Long-term outcome among men with conservatively treated localised prostate cancer. *Br J Cancer*. 2006;95(9):1186-94. PMID:17077805
14. Boyle P, Brawley OW. Prostate cancer: current evidence weighs against population screening. *CA Cancer J Clin*. 2009;59(4):220-4. PMID:19564244
15. Djulbegovic M, Beyth RJ, Neuberger MM, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2010;341:c4543 PMID:20843937
16. Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer: an updated Cochrane systematic review. *BJU Int*. 2011;107(6):882-91. PMID:21392207
17. Barry MJ. Screening for prostate cancer--the controversy that refuses to die. *N Engl J Med*. 2009;360(13):1351-4. PMID:19297564
18. Neal DE, Donovan JL, Martin RM, et al. Screening for prostate cancer remains controversial. *Lancet*. 2009;374(9700):1482-3. PMID:19664817
19. Stark JR, Mucci L, Rothman KJ, et al. Screening for prostate cancer remains controversial. *BMJ*. 2009;339:b3601 PMID:19778971

20. Roobol MJ, Carlsson S, Hugosson J. Meta-analysis finds screening for prostate cancer with PSA does not reduce prostate cancer-related or all-cause mortality but results likely due to heterogeneity - the two highest quality studies identified do find prostate cancer-related mortality reductions. *Evid Based Med.* 2011;16(1):20-1. PMID:21228057
21. Pinsky PF, Blacka A, Kramer BS, et al. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Clin Trials.* 2010;7(4):303-11. PMID:20571134
22. Lunn RM, Bell DA, Mohler JL, et al. Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis.* 1999;20(9):1727-31. PMID:10469617
23. Chou R, Crosswell JM, Dana T, et al. Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011; PMID:21984740
24. Feero WG, Gutmacher AE, Collins FS. Genomic medicine--an updated primer. *N Engl J Med.* 2010;362(21):2001-11. PMID:20505179
25. Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet.* 2007;39(5):645-9. PMID:17401363
26. Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet.* 2007;39(5):631-7. PMID:17401366
27. Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet.* 2007;39(8):977-83. PMID:17603485
28. Thomas G, Jacobs KB, Yeager M, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet.* 2008;40(3):310-5. PMID:18264096
29. Gudmundsson J, Sulem P, Rafnar T, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nat Genet.* 2008;40(3):281-3. PMID:18264098
30. Eeles RA, Kote-Jarai Z, Giles GG, et al. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet.* 2008;40(3):316-21. PMID:18264097
31. Sun J, Zheng SL, Wiklund F, et al. Sequence variants at 22q13 are associated with prostate cancer risk. *Cancer Res.* 2009;69(1):10-5. PMID:19117981
32. Gudmundsson J, Sulem P, Gudbjartsson DF, et al. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. *Nat Genet.* 2009;41(10):1122-6. PMID:19767754
33. Takata R, Akamatsu S, Kubo M, et al. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. *Nat Genet.* 2010;42(9):751-4. PMID:20676098
34. Haiman CA, Chen GK, Blot WJ, et al. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. *Nat Genet.* 2011;43(6):570-3. PMID:21602798
35. Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. *Lancet.* 2001;357(9257):709-12. PMID:11247571
36. Khoury MJ, Yang Q, Gwinn M, et al. An epidemiologic assessment of genomic profiling for measuring susceptibility to common diseases and targeting interventions. *Genet Med.* 2004;6(1):38-47. PMID:14726808
37. Madlensky L, McLaughlin JR, Carroll JC, et al. Risks and benefits of population-based genetic testing for Mendelian subsets of common diseases were examined using the example of colorectal cancer risk. *J Clin Epidemiol.* 2005;58(9):934-41. PMID:16085197

38. Janssens AC, Gwinn M, Bradley LA, et al. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. *Am J Hum Genet.* 2008;82(3):593-9. PMID:18319070
39. Yang Q, Khoury MJ, Friedman JM, et al. On the use of population attributable fraction to determine sample size for case-control studies of gene-environment interaction. *Epidemiology.* 2003;14(2):161-7. PMID:12606881
40. Yang Q, Khoury MJ, Friedman J, et al. How many genes underlie the occurrence of common complex diseases in the population? *Int J Epidemiol.* 2005;34(5):1129-37. PMID:16043441
41. Yang Q, Khoury MJ, Botto L, et al. Improving the prediction of complex diseases by testing for multiple disease-susceptibility genes. *Am J Hum Genet.* 2003;72(3):636-49. PMID:12592605
42. Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med.* 2003;24(2):128-35. PMID:12568818
43. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med.* 2009;11(1):3-14. PMID:18813139
44. Zheng SL, Sun J, Wiklund F, et al. Cumulative association of five genetic variants with prostate cancer. *N Engl J Med.* 2008;358(9):910-9. PMID:18199855
45. Salinas CA, Koopmeiners JS, Kwon EM, et al. Clinical utility of five genetic variants for predicting prostate cancer risk and mortality. *Prostate.* 2009;69(4):363-72. PMID:19058137
46. Sun J, Chang BL, Isaacs SD, et al. Cumulative effect of five genetic variants on prostate cancer risk in multiple study populations. *Prostate.* 2008;68(12):1257-62. PMID:18491292
47. Helfand BT, Fought AJ, Loeb S, et al. Genetic prostate cancer risk assessment: common variants in 9 genomic regions are associated with cumulative risk. *J Urol.* 2010;184(2):501-5. PMID:20620408
48. Zheng SL, Sun J, Wiklund F, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen. *Clin Cancer Res.* 2009;15(3):1105-11. PMID:19188186
49. Xu J, Sun J, Kader AK, et al. Estimation of absolute risk for prostate cancer using genetic markers and family history. *Prostate.* 2009;69(14):1565-72. PMID:19562736
50. Sun J, Lange EM, Isaacs SD, et al. Chromosome 8q24 risk variants in hereditary and non-hereditary prostate cancer patients. *Prostate.* 2008;68(5):489-97. PMID:18213635
51. Nam RK, Zhang WW, Trachtenberg J, et al. Utility of incorporating genetic variants for the early detection of prostate cancer. *Clin Cancer Res.* 2009;15(5):1787-93. PMID:19223501
52. Beuten J, Gelfond JA, Franke JL, et al. Single and multigenic analysis of the association between variants in 12 steroid hormone metabolism genes and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1869-80. PMID:19505920
53. Penney KL, Salinas CA, Pomerantz M, et al. Evaluation of 8q24 and 17q risk loci and prostate cancer mortality. *Clin Cancer Res.* 2009;15(9):3223-30. PMID:19366828
54. deCODEhealth <http://www.decodehealth.com/prostate-cancer>. 2011.
55. Wells, G. A, Shea, B., O'Connell, D. et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). 2009 Feb 1.

56. 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 PMID:14606960

# Introduction

## Prostate Cancer

Worldwide, over 900,000 cases of prostate cancer were diagnosed in 2008, making its incidence second only to lung cancer in men.<sup>1</sup> 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.<sup>1</sup> 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.<sup>2,3</sup> The risk for prostate cancer increases with age; the median age of diagnosis in the United States during 2004-2008 was 67 years.<sup>4</sup> With the ageing 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-late 1990s, and the disparity between ethnic groups in cancer stage at diagnosis decreased.<sup>5</sup>

The risk factors associated with prostate cancer are unclear,<sup>6</sup> which makes 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.<sup>7</sup> In parts of sub-Saharan Africa, the incidence of prostate cancer in black populations lies in the range of 14-25 per 100,000 per year, compared with 40-70 per 100,000 per year in white populations in these areas.<sup>8</sup> A high incidence of prostate cancer has also been observed in populations of African descent in Brazil, the Caribbean, and France.<sup>9</sup> 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 higher incidence populations. 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.

## Risk factors

First-degree relatives of men with prostate cancer have a two- to three-fold increased risk for developing the disease.<sup>6,10,11</sup> In addition, the risk of developing prostate cancer in relatives 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.<sup>12</sup> 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.<sup>13</sup>

A subset of familial prostate cancers 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.<sup>14,15</sup>

Compared with other common types of cancer, the risk factors associated with prostate cancer are unclear.<sup>6</sup> 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.<sup>16</sup>

Several studies have investigated the possible association between diabetes mellitus and the risk for prostate cancer. Meta-analyses indicate an inverse relationship.<sup>17,18</sup>

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 in 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.<sup>19</sup> 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.<sup>20</sup> However, in a large, long-term trial of male physicians, neither vitamin E nor C supplementation reduced the risk of prostate or total cancer,<sup>21</sup> 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.<sup>22</sup> While observational studies have suggested a protective role for selenium, this was not confirmed in a large randomized controlled trial.<sup>23</sup> Inverse associations with consumption of tomatoes/lycopene<sup>24,25</sup> and soy products<sup>26,27</sup> have been reported. Positive associations with consumption of dairy products and calcium have been reported.<sup>24,28,29</sup> The evidence of association with alcohol,<sup>24,30</sup> coffee,<sup>31</sup> dietary fibre,<sup>32</sup> fish consumption,<sup>33</sup> and beta-carotene supplementation<sup>34</sup> has been interpreted as null.

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

## Natural history

The natural history of prostate cancer is highly variable.<sup>53</sup> In studies of autopsy series, histologically proven prostate cancer was found in approximately 30-40 percent of men over 50 years of age who died of other causes.<sup>54-59</sup> This is three to four times higher than the lifetime risk of prostate cancer diagnosis in American men (approximately 11 percent),<sup>53</sup> 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 of the tumor, the extent of involved lymph nodes, presence of metastasis, and histological features of the tumor. 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) 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.<sup>60</sup> 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,<sup>61</sup> which resulted in a shift of the most commonly found score from 6 to 7.<sup>60</sup> 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.<sup>53,62-71</sup> 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.<sup>72-77</sup> Only a small proportion of men with prostate cancer diagnosed at an early clinical stage (Gleason scores  $\leq 4$ ) 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.<sup>65,68</sup> The greatest variation in outcome is for men with moderately differentiated tumors (Gleason scores 5 to 7).<sup>53,65,68</sup> The natural history over longer periods of observation is uncertain. A study in Sweden,<sup>68</sup> 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.<sup>65</sup> Numerous differences between these cohorts could account for this inconsistency.<sup>78</sup> 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.<sup>79</sup>

## **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.<sup>7</sup>

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.<sup>80</sup> 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.<sup>69,70</sup>

## **PSA screening**

PSA was discovered in the 1960s and 1970s,<sup>81</sup> and the work identifying it as a serum marker for adenocarcinoma of the prostate was published in 1987.<sup>82</sup> 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 disease in symptomatic men (but not for screening asymptomatic men).<sup>83</sup> 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.<sup>84</sup> 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.<sup>85</sup>

Seven randomized trials (12 publications) of screening using PSA testing alone, or in combination with digital rectal examination, have been reported, in the United States,<sup>86,87</sup> Canada,<sup>88-90</sup> and Europe,<sup>91-97</sup> 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,<sup>98,99</sup> and that overdiagnosis resulted in harms that are frequent, often persist, and are at least moderate in severity.<sup>99</sup> The individual trials and meta-analyses have generated substantial debate,<sup>100-106</sup> with many commentaries arguing for the development of more accurate markers to use in screening. Investigation of genetic variants associated with prostate cancer has been considered a promising route to the identification of such markers.

## Single Nucleotide Polymorphisms (SNPs)

SNPs are minute variations in the DNA sequence that are passed on from parents to children. Thus, SNP variants are inherited, and 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.<sup>107</sup> 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 once in about every 800 base pairs.<sup>108</sup> 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*<sup>109</sup>); androgen metabolism (*AR*,<sup>110</sup> *ESR2*,<sup>111</sup> *SRDA2*<sup>112,113</sup>); angiotensin conversion (*ACE*<sup>114</sup>); base-excision repair (*XRCC1*<sup>115</sup>); inflammation and immune response (*IL10*,<sup>116,117</sup> *MSR1*,<sup>118</sup> *PTGS2*,<sup>119</sup> *TNF*<sup>120</sup>); inhibition of cell growth (*FGFR4*,<sup>121,122</sup> *TGFB1*,<sup>123</sup> *TGFBRI*<sup>124</sup>); insulin-like growth factor metabolism (*IGF1*,<sup>125</sup> *IGFBP3*<sup>126</sup>); one carbon metabolism (*MTHFR*,<sup>127</sup> diverse genes<sup>128</sup>); oxidative response (*MnSOD*<sup>129</sup>); substrate metabolism (*CYP1A1*,<sup>130</sup> *CYP3A4*,<sup>131</sup> *CYP17*,<sup>132</sup> *GSTM1*, *GSTT1*, *GSTP1*,<sup>133</sup> and *Nat1 and NAT2*<sup>115</sup>); vitamin D metabolism (*VDR*<sup>134</sup>); and, common variants of genes for which rare mutations are associated with increased cancer risk (*ELAC/HPC2*,<sup>135</sup> *RNASEL*,<sup>136</sup> *TP53*<sup>137</sup>). In general, the results of candidate gene studies have been inconclusive, for reasons discussed in many commentaries.<sup>138,139</sup> However, when associations have been confirmed, they have been modest, with odds ratios (ORs) in the range of 1.1 to 2.2.<sup>140</sup> 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.<sup>108</sup> In genome-wide association (GWA) studies, a dense array of genetic markers, which capture a substantial proportion of common variation in genome sequence, is typed in a set of DNA samples and tested for association with the trait of interest without specific prior hypotheses.<sup>141</sup> In most investigations of this type, the ability to validate findings in independent samples is built in to the study.<sup>141</sup> As of 14 June 2011, GWA studies have identified replicated associations between prostate cancer

and almost 40 specific SNPs (Table 1).<sup>142-148,148-152</sup> 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,<sup>153-156</sup> 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<sup>154,157,158</sup> in a population and may be useful in predicting risk for disease.<sup>159</sup> 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 2 to 3 loci could be 50 to 100 percent in the presence of a modifiable exposure.<sup>154</sup> 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,<sup>160,161</sup> 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 in intron <sup>60</sup>	Reported gene	Reference
2p15	721048	Intronic	<i>EHBP1</i>	Gudmundsson, et al., 2008 <sup>146</sup>
2p15	6545977	Intergenic		Eeles, et al., 2009 <sup>152</sup>
2p21	651164	Intronic	<i>LOC1002891682</i>	Eeles, et al., 2009 <sup>152</sup>
2p24.1	13385191	Intronic	<i>C2orf43</i>	Takata, et al., 2010 <sup>150</sup>
2q31.1	12621278	Intronic	<i>ITGA6</i>	Eeles, et al., 2009 <sup>152</sup>
3p12.1	2660753	Intergenic		Eeles, et al., 2008 <sup>147</sup>
3p12.1	17181170	Intergenic		Eeles, et al., 2009 <sup>152</sup>
3p12.1	9284813	Intergenic		Takata, et al., 2010 <sup>150</sup>
3q21.3	10934853	Intronic		Gudmundsson, et al., 2009 <sup>149</sup>
4q22.3	17021918 and 12500426	Intronic	<i>PDLIM5</i>	Eeles, et al., 2009 <sup>152</sup>
4q24	7679673	Intergenic	<i>TET2</i>	Eeles, et al., 2009 <sup>152</sup>
5p15.33	12653946	Intergenic		Takata, et al., 2010 <sup>150</sup>
6p21.1	1983891	Intronic	<i>FOXP4</i>	Takata, et al., 2010 <sup>150</sup>
6q22.1	339331	Intergenic	<i>GPRC6A, RFX6</i>	Takata, et al., 2010 <sup>150</sup>
6q25.3	9364554	Intronic	<i>SLC22A3</i>	Eeles, et al., 2008 <sup>147</sup>
7p15.2	10486567	Intronic	<i>JAZF1</i>	Thomas, et al., 2008 <sup>145</sup>
7q21.3	6465657	Intronic	<i>LMTK2</i>	Eeles, et al., 2008, <sup>147</sup> 2009 <sup>152</sup>
8p21.2	1512268	Intergenic	<i>NKX3.1</i>	Eeles, et al., 2009; <sup>152</sup> Takata, et al., 2010 <sup>150</sup>
8q24.21	1447295	Intergenic		Yeager, et al., 2007; <sup>142</sup> Gudmundsson, et al., 2007a; <sup>143</sup> Gudmundsson, et al., 2009 <sup>149</sup>
8q24.21	6983267	Intergenic		Yeager, et al., 2007; <sup>142</sup> Thomas, et al., 2008; <sup>145</sup> Eeles, et al., 2008 <sup>147</sup>
8q24.21	1690179	Intergenic		Gudmundsson, et al., 2007a; <sup>143</sup> Gudmundsson, et al., 2009 <sup>149</sup>
8q24.21	Hap C	Intergenic		Gudmundsson, et al., 2007a <sup>143</sup>
8q24.21	4242382	Intergenic		Thomas, et al., 2008; <sup>145</sup> Eeles, et al., 2008; <sup>147</sup> Eeles, et al., 2009 <sup>152</sup>
8q24.21	1016343	Intergenic		Eeles, et al., 2008 <sup>147</sup>
8q24.21	16902094	Intergenic		Gudmundsson, et al., 2009 <sup>149</sup>

**Table 1. Replicated associations between prostate cancer and SNPs in GWA studies (cont'd)**

Chromosomal region	rs number	Intergenic or in intron <sup>60</sup>	Reported gene	Reference
8q24.21	445114	Intergenic		Gudmundsson, et al., 2009 <sup>149</sup>
8q24.21	1456315	Intergenic		Takata, et al., 2010 <sup>150</sup>
8q24.21	7837688	Intergenic		Takata, et al., 2010 <sup>150</sup>
10q11.23	10993994	Intronic	<i>MSMB</i>	Thomas, et al., 2008; <sup>145</sup> Eeles, et al., 2008 <sup>147</sup>
10q26.13	4962416	Intronic	<i>CTBP2</i>	Thomas, et al., 2008 <sup>145</sup>
11p15.5	7127900	Intronic	<i>ASCL2</i>	Eeles, et al., 2009 <sup>152</sup>
11q13.3	10896449	Intergenic		Thomas, et al., 2008 <sup>145</sup>
11q13.3	7931342	Intergenic		Eeles, et al., 2008 <sup>147</sup>
11q13.3	7130881	Intergenic		Eeles, et al., 2009 <sup>152</sup>
11q13.3	11228565	Intergenic		Gudmundsson, et al., 2009 <sup>149</sup>
13q22.1	9600079	Intergenic		Takata, et al., 2010 <sup>150</sup>
17q12	4430796	Intronic	<i>TCF2</i>	Gudmundsson, et al., 2007b; <sup>144</sup> Thomas, et al., 2008; <sup>145</sup> Gudmundsson, et al., 2009 <sup>149</sup>
17q12	7501939	Intronic	<i>HNF1B</i>	Eeles, et al., 2008, <sup>147</sup> 2009; <sup>152</sup> Takata, et al., 2010 <sup>150</sup>
17q21.33	7210100	Intronic	<i>ZNF652</i>	Haiman, et al., 2011 <sup>151</sup>
17q24.3	1859962	Intergenic		Gudmundsson, et al., 2007b; <sup>144</sup> Eeles, et al., 2008, <sup>147</sup> 2009 <sup>152</sup>
19q13.2	8102476	Intergenic		Gudmundsson, et al., 2009 <sup>149</sup>
19q13.33	2735839	Intronic	<i>KLK3</i>	Eeles, et al., 2008 <sup>147</sup>
22q13.1	9623117	Intronic	<i>TCNC613</i>	Sun, et al., 2009 <sup>148</sup>
22q13.2	4242384	Intronic	<i>RPS25P10</i>	Eeles, et al., 2009 <sup>152</sup>
22q13.2	5759167	Intergenic		Eeles, et al., 2009 <sup>152</sup>
Xp11.22	5945572, 5945619	Intronic	<i>NUDT11</i>	Gudmundsson, et al., 2008; <sup>146</sup> Eeles, et al., 2008, <sup>147</sup> 2009 <sup>152</sup>

## Scope and Purpose of the 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 panels to assess risk of prostate cancer. The overall goal of the EGAPP is to facilitate the use of evidence-based decision making that will assist health care providers, consumers, policy makers, and payers to distinguish genetic tests that are safe and useful, and to guide 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.<sup>162</sup> The synthesis of the evidence will be used by EGAPP to develop evidence-based recommendations on the use of the test. An initial set of questions was proposed by the EGAPP to guide the development of the evidence report, focusing on all aspects of SNP use. The intent of the original questions was to encompass all areas of test use, including analytic and clinical validity of SNP-based genotyping panels and associated algorithms for prostate cancer risk assessment, and the clinical utility of these tests to bring about change in clinical decision making and to assess potential for harms. The overarching goal of the use of this test is to enhance the ability to target, screen, and subsequently facilitate early detection of men at increased risk for prostate cancer.

**Table 2. Elements and key components of evaluation framework for SNP-based panels in prostate cancer risk assessment [reproduced from Yoon, Scheuner, and Khoury, 2003]<sup>163</sup>**

Element	Definition	Components
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (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) <sup>164</sup>
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

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## Objectives of the 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 (KQ) of the Review

The original key questions articulated in the Task Order were revised and re-articulated for the purposes of clarity.

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. calibration

- b. discriminative accuracy
  - c. ability to distinguish clinically important from latent/asymptomatic prostate cancer?
- 2. How do available panels alter risk assessment for prostate cancer when substituted for, or added to, PSA based and other clinical risk assessment tests, in terms of
  - a. change in the area under the receiver-operator characteristics curve (AUC)
  - b. risk reclassification
  - c. predicted performance in published 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?

**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

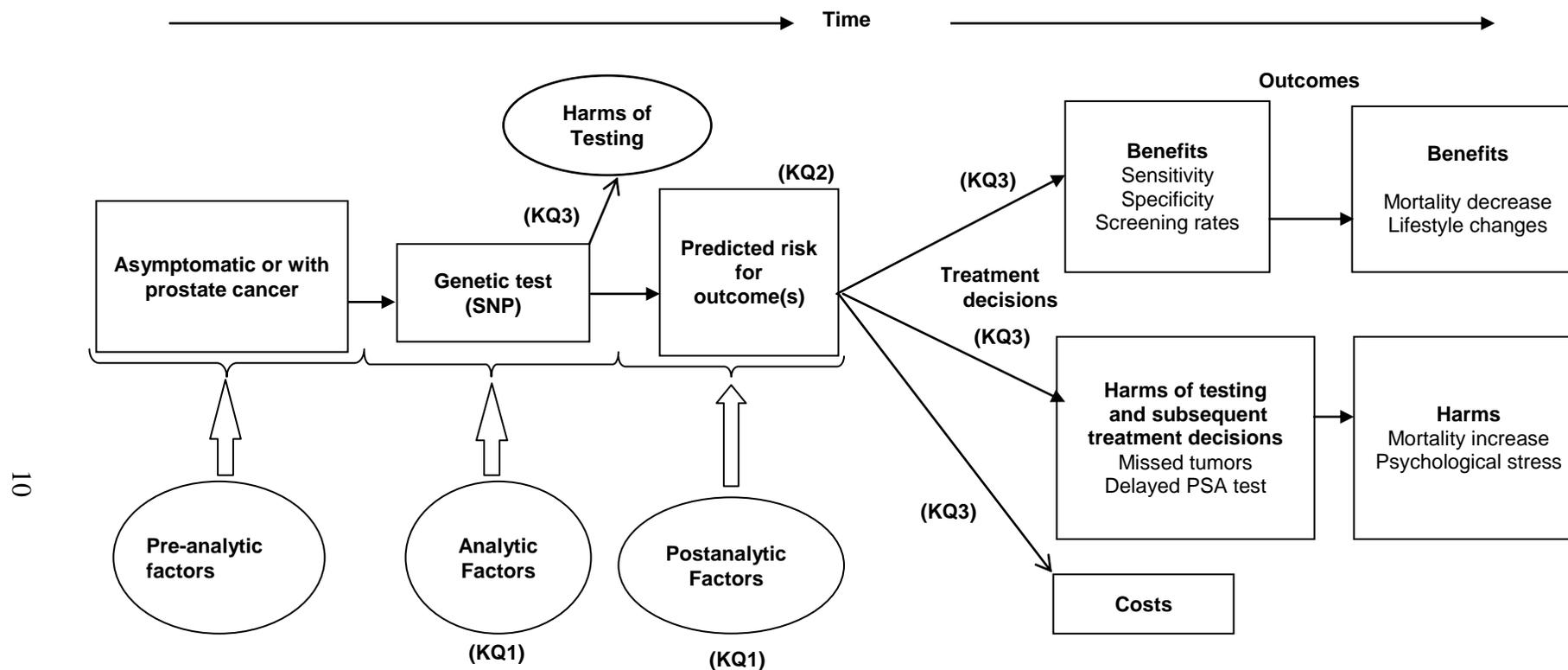
## Topic Development

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 identified and approved by the Task Order Officer at the Agency for Healthcare Research and Quality (AHRQ). The TEP advised MU-EPC on aspects of the 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 SNP test panels may result in different types of intermediate and final outcomes, including adverse events.

Figure 1. Use of multi-gene panels involving SNPs for prostate cancer risk assessment



Abbreviations: KQ = key question; PSA = prostate-specific antigen

## Search Strategy

Studies were limited to those published in English, from the beginning of each database to September 2010. The following databases were searched: MEDLINE<sup>®</sup>, 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).

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.

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.

### *Updating of the search*

Prior to submission of the final report, an updating of our search in all specified databases will be undertaken.

### *Incorporation of Public and Peer Review suggestions for literature*

Any relevant studies identified by the TEP, peer reviewers, or from public comment will be documented and verified within our citation database. Any references not included within our citation database will be retrieved and screened at full text.

## 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 been found not to be replicated.<sup>138,139</sup> 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.<sup>165</sup> Validation required observation of association in one or more independent data sets with a significance level of  $p < 10^{-5}$ . 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**

	<b>Eligibility</b>	<b>Population/ Participants</b>	<b>Study designs</b>	<b>Comparators</b>	<b>Outcome</b>
<b>KQ1: Analytic validity</b>	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	-
<b>KQ2: Clinical validity</b>	Inclusion	Males only	Clinical test evaluations Controlled/uncontrolled trials Cohort studies Case-control studies	N/A	Prostate cancer diagnosis Prostate cancer stage/type Prostate cancer mortality
	Exclusion		Case reports Gene discovery studies (e.g., GWA studies <sup>1</sup> )	N/A	-
<b>KQ3: Clinical utility</b> <i>Process</i>	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		
<b>KQ3: Clinical utility</b> <i>Health outcomes</i>	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		-
<b>KQ3: Clinical utility</b> <i>Harms</i>	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		

**Table 3. Eligibility Criteria (cont'd)**

	Eligibility	Population/ Participants	Study designs	Comparators	Outcome
<b>KQ3: Clinical utility</b>  <i>Economics</i>	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: 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, AUC,  $\Delta$ AUC, 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, 1<sup>st</sup> 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,  $\Delta$ AUC, 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)<sup>166</sup> to assess risk of bias for observational studies (case-control). The study design elements evaluated with this tool include: selection of the study population, appropriate means for measuring exposures (case-control studies), and comparability of groups (controlling for confounding). We also selected some items from the QUADAS<sup>167</sup> 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.<sup>168</sup> 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; that is that 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);
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. At the time of publication of this draft review, no information had been received from any 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 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 studies.

For KQ1, the analysis focused on assembling the 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 correctly 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 area under the receiver operator characteristics curve (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. These peer reviewers represent stakeholder groups including physicians, researchers and other professional representatives with knowledge of the topic. Additional peer reviewers include the Task Order Officer (TOO), associate editors and members of the AHRQ internal editorial staff. The peer reviewer comments on this draft of the report will be considered by the EPC in preparation of the final report. The responses to the peer reviewers will be documented and will be published three months after the publication of the final evidence report.

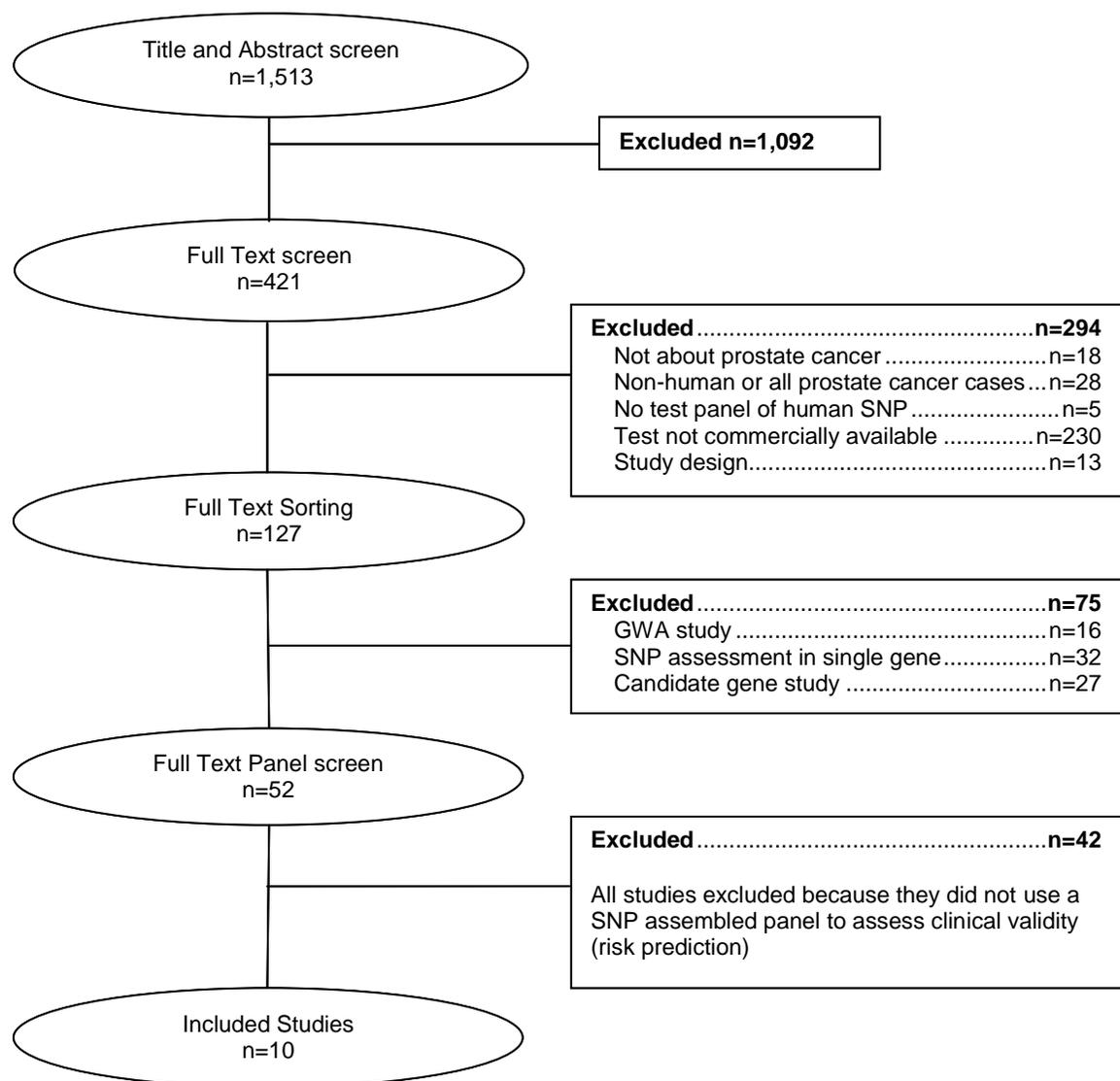


## Results

The literature search yielded 1,513 unique citations. In total, 1,092 (72 percent) were excluded from further review following the initial level of title and abstract screening. Out of the 421 citations promoted to full text screening, 294 were excluded and 127 proceeded to full text sorting. Of the 127 articles, 75 were excluded and 52 proceeded to a single nucleotide polymorphism (SNP) panel screen. Out of these, 42 were excluded and 10 articles<sup>169-178</sup> passed to final full text screen and proceeded to data abstraction and quality assessment. These 10 articles all focused on the assessment of clinical validity. Figure 2 depicts the flow of studies through the screening process, and reasons for study exclusion. The remainder of this chapter contains sections describing 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 relative lack of published data describing the technical protocols and analytical accuracies achieved for specific SNPs, and in particular, the analytical validation of panels of SNPs. 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 identified as focused on clinical validity, we abstracted information that was relevant to the assessment of analytic validity.

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



## Characteristics of the studies

All of the studies were of case-control design with the number of cases ranging from 687 to 2,893 and the number of controls from 560 to 1,781 (Tables 4 through 7). The studies were carried out in Canada,<sup>176</sup> Sweden,<sup>169,173</sup> the United States,<sup>170,175,177,178</sup> in both Sweden and the United States<sup>171,174</sup> and in one study, cases were recruited in the United States but it was unclear if controls had been recruited solely in the United States.<sup>172</sup>

There was complete overlap in the participants included from Sweden: a risk model was initially developed for a panel of five SNPs,<sup>169</sup> extended to 11 SNPs<sup>173</sup> in data from the same participants and then 14 SNPs.<sup>174</sup> For the initial 5-SNP model, validation was undertaken in King County (Washington, United States),<sup>170</sup> and a combined estimate of the cumulative effect of the five risk variants was made which incorporated these data and the Swedish data.<sup>171</sup> For the 14-

SNP model, data from the United States were used for confirmation;<sup>174</sup> the U.S. data in this study was based on the same participants (in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Trial)<sup>86</sup> as in one of the U.S. studies used to validate the 5-SNP model.<sup>171</sup> There was also overlap between the studies in the United States, first of participants recruited at the Johns Hopkins Hospital, Baltimore 1999-2006<sup>171,175</sup> and second in participants recruited in King County, Washington 1993-2002 to 2002-2005.<sup>170,178</sup>

Four of the studies were concerned solely with the development of models for the prediction of risk for prostate cancer,<sup>169,175,177,178</sup> two solely with model validation<sup>170,171</sup> and four with both model development and validation.<sup>172-174,176</sup>

Most of the studies relate to participants of European origin. In the studies of Swedish participants,<sup>169,171,173,174</sup> the ethnicity was not specified explicitly. All but one of the studies of U.S. participants were limited to men of European origin.<sup>170-172,174,175,178</sup> The exception to this presented a stratified analysis for Non-Hispanic European origin (54 percent of controls), Hispanic origin (33 percent) and African-American (13 percent).<sup>177</sup> 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.<sup>176</sup>

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.<sup>175</sup>

Five studies presented information on the proportion of cases and controls with a family history of prostate cancer. In three, this was specified as relating to first-degree relatives – in two different analyses of the same Swedish participants, the proportion of cases with a family history was 19 percent and controls 9.4 percent<sup>169,173</sup> and in a study in King County, Washington, the proportions were 21.6 percent and 11.1 percent respectively.<sup>170</sup> 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.<sup>174</sup> In the fifth study, the degree of relationships included in “family history” were not defined – the proportion for cases was 16.4 percent and for controls 12.1 percent.<sup>176</sup>

Seven articles were based on newly incident cases, one that related to the Canadian study (cases detected following referral for prostate-specific antigen (PSA)  $\geq$  or abnormal digital rectal examination without previous history of prostate cancer),<sup>176</sup> four to data on the same participants from Sweden,<sup>169,171,173,174</sup> and two to partially overlapping studies from the United States.<sup>170,178</sup>

Two publications (one of which also reported on participants from Sweden, as just mentioned) reported analyses on prevalent cases from overlapping studies in the United States.<sup>171,175</sup> One study in the United States was based on a mixture of newly incident and prevalent cases.<sup>177</sup> In another, it was unclear whether the cases were newly incident or prevalent – it was stated only that the cases were recruited after radical prostatectomy.<sup>172</sup>

The mean age of cases ranged from 56.8 years<sup>174</sup> to 70.5 years.<sup>178</sup> There was no obvious pattern according to inclusion of newly incident or prevalent cases.

As might be expected, there appeared to be a pattern that the median or means PSA level at diagnosis of cases became less when study periods were more recent. The proportion of cases with a PSA level of 4ng/ml or less varied between under 8 percent in Canada 1999-2007,<sup>176</sup> and Sweden 2001-2003,<sup>169,173</sup> to 13.6 percent in Washington State (United States) 1993-1996 and 2002-2005,<sup>179</sup> and 22 percent in Chicago 2002-2008.<sup>172</sup>

When reported (n=5), the proportion of cases with a Gleason score at diagnosis  $\leq 6$  ranged from 51 percent (Physicians' Health Study) 1982-2008<sup>178</sup> to 69 percent (Chicago 2002-2008).<sup>172</sup> Only one study<sup>171</sup> explicitly referred to having used the revised scoring as described by Epstein, et al.,<sup>61</sup> for the Johns Hopkins Hospital component of the study. The stage at diagnosis was reported for the Swedish cases,<sup>169,173</sup> in the study comprising three sets of cases and controls in the United States,<sup>178</sup> and the Chicago study;<sup>172</sup> over two-thirds of the cases were stage T2 or less at diagnosis.<sup>173</sup>

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  $\geq 4.0$ ng/ml or an abnormal digital rectal examination and who had no biopsy evidence of prostate cancer.<sup>176</sup> In the studies including Swedish cases, the controls were population-based, selected from the Swedish population registry.<sup>169,171,173,174</sup> The cases from the PLCO Trial were compared with controls participating in this trial.<sup>174,180</sup> Cases arising in the Physicians' Health Study<sup>178</sup> and cases from the San Antonio cohort<sup>177</sup> 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 country and identified by random digit dialing (participation rate 44.5 to 51.6 percent).<sup>170,178</sup> 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 digital rectal examination, PSA  $< 4.0$ ng/ml, and were aged  $> 55$  years.<sup>171,175</sup> 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, but it is not stated where this occurred.<sup>172,181</sup>

## Source of funding and conflict of interest

All of the studies were publicly funded. In addition, one study received support from deCODE Genetics.<sup>172</sup> All but three studies<sup>170,171,175</sup> included conflict of interest statements. Of the seven studies in which there was such a statement, two referred to the filing of a patent application<sup>169,173</sup> and two indicated specific nonpublic funding received by one of the authors.<sup>172,178</sup>

## Overview of the tests

There were 11 tests identified from these articles (Table 7). The number of SNPs included in the panels ranged from two to 14. Almost all of the individual SNPs had been discovered and replicated as 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 8).

The first test is for five SNPs and was described in the article of Zheng, et al.,<sup>169</sup> and is the basis of the Focus 5 predictive test for prostate cancer, and a patent application has been filed by Xu, et al.,<sup>182</sup> "Methods and compositions for correlating genetic markers with prostate cancer risk". The test has been marketed by Proactive Genomics.<sup>183</sup> Four other articles assessed this test in independent data.<sup>170-172,176</sup>

The second test, again initially proposed by Zheng, et al.,<sup>169</sup> included family history with the five SNPs included in the first test, and two of the articles that assessed the first test also assessed this test.<sup>170,171</sup> In two of these studies, family history was defined to include first degree relatives.<sup>169,170</sup>

The other nine tests were reported in seven articles<sup>172-178</sup> (Table 7). Two of these included family history, one in first degree relatives,<sup>173</sup> and one in first- and second-degree relatives.<sup>174</sup>

deCODE markets the deCODE ProstateCancer test, which tests for 27 genetic variants (Table 9) 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](http://www.decodhealth.com/prostate-cancer)).<sup>184</sup> 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).<sup>185</sup> A patent application was filed by Gudmundsson, et al., in May, 2010.<sup>186</sup>

## **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 was 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 27 June 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 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.<sup>169</sup> The same method was applied in samples from the Johns Hopkins Hospital<sup>171</sup> and Canada.<sup>176</sup> Some of the analytic validity information relevant to the initial study in Swedish samples<sup>169</sup> are reported in other articles which relate to the same platform, including the initial five SNPs but also additional SNPs, in the same samples.<sup>173,174</sup> A call rate of 98.3 percent was reported,<sup>173,174</sup> with a concordance rate for duplicate SNPs of >99 percent, and the genotypes for each SNP conformed to Hardy-Weinberg equilibrium in controls.<sup>169,173,174</sup> It was not reported whether genotyping was done blind to case-control status. (For the purpose of this report, call rate was defined as the proportion of samples for which genotypes are called for a converted marker).

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 one study using the Applied Biosystems (ABI) SNPLex Genotyping System.<sup>170</sup> 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 Hardy-Weinberg equilibrium.

One of the sets of samples used to assess the 5-SNP panel was the PLCO trial.<sup>171</sup> Four of the SNPs had already been genotyped as part of a GWA.<sup>143</sup> The genotyping had been undertaken by means of Sentrix HumanHap300 and Sentrix HumanHap240 platforms (Illumina).<sup>142,145</sup> The fifth SNP (rs16901979 in 8q24) was imputed from the adjacent genotyped SNPs at 8q24.<sup>171</sup>

**9-SNP panel.** In the study of Helfand, et al.,<sup>172</sup> 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).<sup>143,144,146,149,187</sup> 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.<sup>143,144,146,149</sup> In addition, the Centaurus (Nanogen) platform was used<sup>143,144,146,149,187</sup> and the concordance rate of SNPs genotyped by both the Illumina and Centaurus methods was stated to be >99.5 percent.<sup>143,144</sup> It is also stated that all genetic variants were in Hardy-Weinberg equilibrium.<sup>172</sup>

**11-SNP panel.** This panel was genotyped using the Mass ARRAY QGE iPLEX system (Sequenom).<sup>173</sup> A call rate of 98.3 percent was reported, with an average concordance rate for duplicate SNPs of 99.8 percent, and the genotypes for each SNP conformed to Hardy-Weinberg equilibrium in controls.<sup>173</sup> 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).<sup>174</sup> 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,<sup>145</sup> and one (rs16901979 in 8q24) was imputed. In the PLCO samples, genotyping was undertaken by means of Sentrix® HumanHap300 and Sentrix HumanHap240 platforms (Illumina).<sup>142,145</sup> It is stated that tests for Hardy-Weinberg equilibrium 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.

**3-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.<sup>175</sup> Genotype proportions were consistent with Hardy-Weinberg equilibrium in controls.

**4-SNP test: KLK2, HPC1, TNF, ETV1 and 8q24, 17q24, TNF, ETV1.** The SequenomPLEX 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 Hardy-Weinberg equilibrium and were excluded from further analysis.<sup>176</sup> 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 genotyping of 120 SNPs in the steroid hormone pathway by different methods.<sup>177</sup> 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.<sup>105,188-190</sup> 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 Hardy-Weinberg equilibrium 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 genotyping of 120 SNPs in the steroid hormone pathway by different methods.<sup>177</sup> 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.<sup>105,188-190</sup> 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 Hardy-Weinberg equilibrium in Hispanic whites and were excluded from the analysis of this ethnic group.

**6-SNP test.** This test 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.<sup>178</sup> The SequenomPLEX 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.<sup>178</sup> The Applied Biosystems (ABI) SNPlex Genotyping System was used to genotype the samples from King County, Washington. None of the eight SNPs violated Hardy-Weinberg equilibrium in either set (Physicians' Health Study or King County, Washington) of controls. The call rate for the eight SNPs genotyped was >94 percent.

**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.<sup>184</sup> 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***
  - a. *calibration***
  - b. *discriminative accuracy***
  - c. *ability to distinguish clinically important from latent/asymptomatic prostate cancer***

**5-SNP panel (Focus 5) with and without inclusion of family history.** Zheng, et al.,<sup>169</sup> 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 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 63.3 percent (95% CI, 61.7 to 65.0).

The model was tested in independent data from men of European origin in King County, Washington,<sup>170</sup> in data from the Johns Hopkins Hospital and the PLCO Cancer Screening Trial,<sup>171</sup> in a Canadian study,<sup>176</sup> and in a study in which cases underwent radical prostatectomy in a hospital in Chicago.<sup>172</sup> The pattern of association with risk score was attenuated compared with the original study in Swedish data,<sup>169</sup> 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 digital rectal examination was 72 percent (95% CI, 70 to 74), and with the addition of five SNPs, 73 percent (95% CI, 71 to 75).<sup>176</sup> In these studies, the proportion of controls with four or more risk genotypes ranged between 1.6 percent<sup>171</sup> and 3.4 percent,<sup>172</sup> 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.<sup>169-171</sup>

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,<sup>170</sup> and 20.68 (95% CI, 2.61 to 163.85) for the PLCO trial.<sup>171</sup> In the King County data, the AUC for a model including age, serum PSA level, and history of prostate cancer in 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.<sup>170</sup>

**9-SNP panel.** Helfand, et al.,<sup>172</sup> 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.

**11-SNP panel.** Zheng, et al.,<sup>173</sup> examined the effect of including 14 additional SNPs in the same Swedish study participants as in the original 5-SNP model.<sup>169</sup> 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 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”.<sup>173</sup> 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 61 percent (95% CI, 59 to 62), and for age, family history, and all eleven SNPs 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.

**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, using data for the PLCO trial for confirmation.<sup>174</sup> The number of risk alleles could range from 0 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  $\geq 14$  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 non-aggressive disease. With regard to absolute risk in Sweden, a 55 year old man with  $\geq 14$  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 7 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.

**3-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.<sup>175</sup> 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) for men, and for prostate cancer without such a family history 2.23 (95% CI, 1.52 to 3.28).

**4-SNP test: *KLK2*, *HPC1*, *TNF*, *ETV1*.** In a Canadian study,<sup>176</sup> in addition to examining the 5-SNP model of Zheng, et al.,<sup>169</sup> a model comprising four SNPs, one each in *KLK2*, *HPC1*, *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 proportions 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 digital rectal examination was 72 percent (95% CI, 70 to 74), and with the addition of the four SNPs 73 percent (95 percent 71 to 74).

**4-SNP test: 8q24, 17q24, *TNF*, *ETV1*.** In the same Canadian study,<sup>176</sup> 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 proportions 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 digital rectal exam 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 digital rectal examination (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.,<sup>177</sup> 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 sub-section, Beuten, et al.,<sup>177</sup> 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.,<sup>178</sup> evaluated eight SNPs, six in 8q24 and two in 17q, in data from the Physicians' Health Study (PHS) and from King County, Washington (KCW). 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 KCW.

**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.<sup>184</sup> 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 lack of significant interaction or overlap of impact between markers in two studies.<sup>149,152</sup>

#### *d. Distinguishing clinically important from latent/asymptomatic prostate cancer*

**5-SNP panel (Focus 5) with and without inclusion of family history.** In the study in King County,<sup>170</sup> 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).

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 and Gleason score, aggressiveness of prostate cancer,<sup>191</sup> or age at diagnosis.<sup>171</sup>

**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  $\geq 14$  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).<sup>174</sup> 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.,<sup>173</sup> 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.

**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 KCW using the Cox proportional hazards model, there was no significant association between these variants and prostate cancer mortality.<sup>178</sup> In addition, comparison was made between prostate cancer deaths and men alive more than ten 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.

2. *How do available panels alter risk assessment tests for prostate cancer when substituted for, or added to, PSA based and other clinical risk assessment tests?*
  - a. *change in the AUC*
  - b. *risk reclassification*
  - c. *predicted performance in published simulation analyses*

**5-SNP panel (Focus 5).** In the analysis of Zheng, et al.,<sup>169</sup> who presented the model for the cumulative effect of five SNPs (see above), the AUC for a model including age, geographic region, and family history was 60.8 percent (95% CI, 59.1 to 62.4), and for a model adding in the number of genotypes associated with prostate cancer, 63.3 percent (95% CI, 61.7 to 65.0). 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 digital rectal examination was 72 percent (95% CI, 70 to 74), and with the addition of five SNPs, 73 percent (95% CI, 71 to 75).<sup>176</sup> In the King County data, the AUC for a model including age, serum PSA level and history of prostate cancer in 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.<sup>170</sup>

**11-SNP panel.** In the analysis of Zheng, et al.,<sup>173</sup> which developed a model comprising counts of risk alleles for 11 SNPs and family history, the AUC for a model involving age and family history was 61 percent (95% CI, 59 to 62), and for age, family history, and all eleven SNPs, 65 percent (95% CI, 63 to 66).

No data were identified 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.,<sup>177</sup> 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 9) 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](http://www.decodhealth.com/prostate-cancer)).<sup>184</sup>

**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)<sup>166</sup> (Table 10a) because all studies had a case-control design, and because it is not clear how well the QUADAS<sup>167</sup> tool would apply to genetic tests. We supplemented this with selected items from the QUADAS<sup>167</sup> 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 10b). Other QUADAS<sup>167</sup> 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 one exception.<sup>176</sup> Autopsy studies in men over 50 dying from other causes have demonstrated a frequency of histologically proven prostate cancer of 30 to 40 percent.<sup>54-59</sup> However, there are clearly ethical constraints to taking prostate tissue samples in asymptomatic men to exclude 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  $\geq 4.0$ ng/ml or an abnormal digital rectal examination and who had no biopsy evidence of prostate cancer.<sup>176</sup> 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.<sup>170-172</sup> 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 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.<sup>192-195</sup> 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,<sup>174,180</sup> the PHS,<sup>178</sup> and the San Antonio cohort.<sup>177</sup>

By combining the results of the NOS<sup>166</sup> evaluation and the QUADAS<sup>167</sup> criteria for the individual studies, all studies were found to have a moderate risk of bias. Based on three selected domains in the NOS<sup>166</sup> (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, and lack of specification of which candidate non-genetic 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'. The

assessments of the other nine panels were based on single studies, reported in seven articles<sup>172-178</sup> and these were also all considered to have at least moderate risk of bias, using the same approach.

## 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).

All studies included in the review were based on case-control (association study) designs, with risk prediction model building and model testing components.

For the first domain, as indicated above, all studies were assessed as having at least moderate risk of bias. It is impossible to assess consistency of results for panels assessed in single studies only. For the Focus 5 panel, the data did not permit development of an ROC curve, therefore consistency could 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.<sup>169,174,176</sup> Compared with the models that did not include the SNPs, the 5 SNPs increased the AUC by 1 percent to 3 percent.

For directness, all 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. It is difficult to assess whether the way they were used resembles a 'typical' clinical approach, and they were not evaluated explicitly in a medical test framework. Specifically, the case-control design means that 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, (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 we were unable to offer a valid assessment of this domain.

**Table 4. Characteristics of included studies**

Author Year	Study Objective  Study Design	Setting  Location  Dates of data collection	<u>Study Participants</u>  Eligibility  Source and method of selection  Number assessed for eligibility
Beuten <sup>177</sup> 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 <sup>172</sup> 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 between June 2002 and May 2008; 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 4. Characteristics of included studies (cont'd)**

Author Year	Study Objective  Study Design	Setting  Location  Dates of data collection	Study Participants  Eligibility  Source and method of selection  Number assessed for eligibility
Nam <sup>176</sup> 2009	Validation (models from Zheng, et al., 2008 <sup>169</sup> ) and model development  Case-control study	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 $\geq 4.0$ ng/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 $>50$ ng/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 history of CaP Controls: Inclusion = no inclusion criteria reported aside from no presence of histologic adenocarcinoma of the prostate from biopsy Exclusion = history 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 4. Characteristics of included studies (cont'd)**

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 <sup>178</sup> 2009	<p>Model development</p> <p>Physician Health Study (PHS) labeled nested case-control but also referred to as a prospective cohort by authors; controls selected by risk-set sampling matched on age, smoking status &amp; followup time; Caucasians only</p> <p>Dana Farber Harvard Cancer Center SPORE (Gelb center) case series; no controls</p> <p>FHCRC King County Case-control. 2 population based case-controls.</p>	<p>PHS: Randomized controlled trial of aspirin and beta carotene</p> <p>U.S.</p> <p>blood samples 1982-1984. followup through March 1 2008</p> <p>Gelb Center: Referral hospital-based case series</p> <p>Boston U.S.</p> <p>1976-2007</p> <p>FHCRC: 2 population based case-control. incident cases with histologically confirmed prostate cancer ascertained from Seattle SEER cancer registry</p> <p>King county Washington U.S.</p> <p>1993(study 1) and 2002 (study II ) to 2005</p>	<p>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.</p> <p>Self-reported prostate cancer cases verified through medical record and pathology review</p> <p>1,438</p> <p>Gelb Center: 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.</p> <p>Self-reported prostate cancer cases verified through medical record and pathology review</p> <p>NR</p> <p>FHCRC: 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.</p> <p>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</p> <p>2,448</p>

**Table 4. Characteristics of included studies (cont'd)**

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 <sup>170</sup> 2009	Model development validation of Zheng <sup>169</sup>  Case-control	Cases recruited from Seattle-Puget SEER cancer registry  Participants from King County, Washington (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 history of CaP, Caucasian  Control selection: residence of King County, without self-reported history of CaP, identified using a 1 step random digit telephone 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 4. Characteristics of included studies (cont'd)**

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 <sup>171</sup> 2008	<p>Model is validating previously reported model from Zheng, et al.,<sup>169</sup></p> <p>Case-control</p>	<p>JHH: Samples from JHH (Baltimore, MD), 1999 to 2006</p> <p>CGEMS: Cases and controls from PLCO cancer screening trial (United States), 1992-2008</p> <p>CAPS: Cases - 4 regional cancer registries; controls - Swedish Population Registry</p> <p>Sweden</p> <p>July 2001 - October 2003</p>	<p>JHH: Cases: European-American men undergoing CaP treatment Control: European-American men undergoing CaP screening, &gt;55 years of age, normal digital rectal exam, &lt;4.0ng/mL PSA</p> <p>Cases = 1,562; Controls = 576</p> <p>CGEMS: European-American men selected from PLCO Cancer Screening Trial using incidence density sampling strategy</p> <p>Cases = 1,172; Controls = 1,157</p> <p>CAPS: Biopsy-confirmed or cytologically verified adenocarcinoma of the prostate, diagnosed between July 2001 and October 2003</p> <p>Cases: 6 cancer registries; method of selection apart from inclusion criteria not reported. Controls recruited concurrently and randomly selected from Swedish</p> <p>Cases = 3,648; Controls = 3,153</p> <p>Combined cumulative analysis (all three study populations): Cases = 5,628; Controls = 3,514</p>

**Table 4. Characteristics of included studies (cont'd)**

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 <sup>175</sup> 2008	Model development  Case-control study	<p>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.</p> <p>Baltimore, MD, U.S.</p> <p>HPC cases = described previously (Xu, et al., 2001<sup>196</sup>)                      Non-HPC                      Cases = 1999 to 2006                      Controls = 1999 to 2006</p>	<p>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 &lt;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 &amp; implemented by a single pathologist</p> <p>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</p>

**Table 4. Characteristics of included studies (cont'd)**

Author Year	Study Objective  Study Design	Setting  Location  Dates of data collection	Study Participants  Eligibility  Source and method of selection  Number assessed for eligibility
Xu <sup>174</sup> 2009	Model development and validation  Case-control	CAPS: Cases: 4 of the 6 cancer registries in Sweden Controls = Swedish population registry  Sweden  July 2001 to October 2003  PLCO: Independent Study Population from PLCO trial  United States  1992 to 2009	CAPS: Cases: 2,899 Controls: 1,722  PLCO: Cases: 1,172 Controls: 1,157  Previously reported in Thomas, et al., 2008. <sup>145</sup>
Zheng <sup>173</sup> 2009	Model development and validation  Case-control study (CAPS study)	Cases: 4 of the 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 non-aggressive (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

**Table 4. Characteristics of included studies (cont'd)**

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 <sup>169</sup> 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; FHCRC = Fred Hutchinson cancer research center; GWA = genome-wide association; HPC = hereditary prostate cancer; 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 5. 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
Beuten <sup>177</sup> 2009	2,452 samples  NR	Checked for each SNP; rs6201 showed deviation from HW equilibrium in cases & 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.	
Helfand <sup>172</sup> 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
Nam <sup>176</sup> 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, <sup>169</sup> 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 history of prostate cancer, ethnicity, presence of urinary voiding symptoms, PSA level, free: total PSA ratio, and DRE.

Table 5. Characteristics of included studies: SNPs (cont'd)

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
Penney <sup>178</sup> 2009	Physicians Health Study: Cases = 1,347 Controls = 1,462 SPORE: Cases = 3,714 FHCRC King County Case-control: Cases = 1,308 cases 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.	
Salinas <sup>170</sup> 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 r <sup>2</sup>	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 history; Model 2: adjusted for age only
Sun <sup>171</sup> 2008a	JHH study: Cases not reported in this study Controls = <4.0ng/ml; CGEMS and CAPS study: not reported in this study  Case-only analysis: data not shown	NR	NR	Not applicable (current study is validation study)

**Table 5. Characteristics of included studies: SNPs (cont'd)**

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
Sun <sup>175</sup> 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, & estimates for D' and r2 obtained using Haploview software; to minimize impact of multiple testing, for each SNP, only "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 comparison between groups)	Models 1 and 2: adjusted for age
Xu <sup>174</sup> 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 history with CaP risk was tested using a logistic regression model.	Family history of CaP

**Table 5. Characteristics of included studies: SNPs (cont'd)**

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
Zheng <sup>173</sup> 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 $\chi^2$ 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 history; ROC for three models including one with age, family history and 11 SNPs
Zheng <sup>169</sup> 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 regions (controls)	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 frequencies between cases and control subjects were tested for each SNP with the use of $\chi^2$ test with 1 degree of freedom.	Family history, age, geographic region

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; 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 6. 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
Beuten <sup>177</sup> 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"	2452 samples genotyped  Cases = 65.5 (8.5) Controls = 60.8 (8.8)  NR	Non to 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 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>172</sup> 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. <sup>181</sup>  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  No

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>176</sup> 2009	<p>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.<sup>169</sup> A second panel of SNPs for independent assessment was based on the authors' previous findings (Nam, et al., 2008;<sup>197</sup> Nam, et al., 2005;<sup>198</sup> Nam, et al., 2006<sup>199</sup>). 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.</p> <p>NR</p>	<p>NR</p> <p>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</p>	<p>Cases = 1,389 Controls = 1,614</p> <p>At time of biopsy, mean age is prostate biopsies = 64.5 (range = 40 to 94); cases =</p> <p>Cases = 16.4% Controls = 12.1%; obtained by research personnel through questionnaire and medical record review</p>	<p>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); 3. 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);</p> <p>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).</p> <p>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 =</p>

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>176</sup> 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 <sup>178</sup> 2009	CaP incidence was investigated only in PHS & 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& PSA at Dx

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>170</sup> 2009	<p>The best fitting models for each SNP (using Zheng, et al., 2008<sup>169</sup>) was selected based on the model with the greatest LRT. Confounding was evaluated by considering whether inclusion of other covariates changed the risk estimates <math>\leq 10\%</math>. 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 percent 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.</p> <p>NR</p>	<p>Men with missing genotype information for any SNP excluded from independent SNP analyses</p> <p>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)</p>	<p>Main analyses (study I and II participants): Cases = 1,308 Controls = 1,266 Subset AUC analysis from Study I only: Cases = 475 Controls = 364</p> <p>At Dx: Cases = 59.9 Controls = 59.6</p> <p>Cases = 21.6% Controls = 11.1%; (time of Dx) obtained by trained male interviewers using standardized questionnaire</p>	<p>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), <math>\geq 4</math> 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), <math>\leq 5</math> 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)</p> <p>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)</p> <p>Difference between the curves = 0.03 (95% CI, -0.12 to +0.06)</p> <p>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 &amp; family Hx = 54.4%</p> <p>Subset analysis of Study I participants only, as reported under AUC scores</p>

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>171</sup> 2008a	<p>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.</p> <p>This model is validating the previously reported model from Zheng, et al., 2008<sup>169</sup></p>	<p>One SNP (rs16901979) imputed from the adjacent genotyped SNPs at 8q24 using IMPUTE software; computed confidence scores to ensure reliable imputation</p> <p>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</p>	<p>Combined cumulative analysis (all three study populations): Cases = 5,628 Controls = 3,514</p> <p>NR</p> <p>JHH study - 'not complete'; CAPS and CGEMS studies - yes</p>	<p>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: Ref same as above = 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 (data not shown).</p> <p>NR</p> <p>NR</p> <p>Trend test was statistically significant in the CGEMS-prostate (p = 4.75 x 10<sup>-14</sup>) and in the combined CAPS and CGEMS-prostate (p = 1.94 x 10<sup>-39</sup>).</p> <p>NR</p>

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>175</sup> 2008b	<p>12 SNPs were selected based on the published literature, suggesting CaP susceptibility loci at 8q24 regions as noted by Witte (2007). Their role in HPC is not yet considered (rationale). To 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.</p> <p>NR</p>	<p>NR</p> <p>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)</p>	<p>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</p> <p>Described previously (Xu, et al., 2001)</p> <p>221 HPC cases (at least 2 additional 1st degree relatives diagnosed with prostate cancer) verified by medical records</p>	<p>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), = &gt;2 genotypes = 2.23 (1.52 to 3.28)</p> <p>NR</p> <p>NR</p> <p>NR</p> <p>NR</p>

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>174</sup> 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, & 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  1 <sup>st</sup> and 2 <sup>nd</sup> 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 NO FAMILY HISTORY 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 YES FAMILY HX 0 to 7risk 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 6. Characteristics of included studies: analysis and results (cont'd)**

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 <sup>173</sup> 2009	<p>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.</p> <p>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.</p>	<p>Missing data treated as missing values in the analyses</p> <p>Independent association of prostate cancer risk with each of SNPs measured by OR and 95% CI; Overall predictive performance of predictive models</p>	<p>Cases = 2,899 Controls = 1,722</p> <p>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)</p> <p>[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.)</p>	<p>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 &gt;0.05) (data not shown).</p> <p>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 &amp; 5 previously evaluated SNPs (Zheng 2008) = 0.63 (0.62 to 0.65)</p> <p>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.</p> <p>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.</p> <p>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</p>

**Table 6. Characteristics of included studies: analysis and results (cont'd)**

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  $\Delta$ AUC  Other Measure  Subgroup analysis of risk score, AUC, delta AUC or other measure
Zheng <sup>169</sup> 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 = 1231 Localized disease cases = 1619 Controls = 1781  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); $\geq$ 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;  $\Delta$ AUC = 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; PSA = prostate specific antigen; ROC = receiver operating characteristic; SAS = statistical analysis software; SD = standard deviation SNp = single nucleotide polymorphism; TNF = tumor necrosis factor

**Table 7. Summary of SNPs and other variables included in test panels**

SNP			9-SNP panel	11-SNP panel	14-SNP panel	3-SNPs in 8q24	4-SNP test	4-SNP test	3-SNP test	2-SNP test	6-SNP panel
Chromosome	rs number	Replicated in GWA studies <sup>s</sup>	Helfand <sup>172</sup>	Zheng <sup>173</sup>	Xu <sup>174</sup>	Sun <sup>175</sup>	Nam <sup>176</sup> model 2	Nam <sup>176</sup> model 3	Beuten <sup>177</sup>	Beuten <sup>177</sup>	Penney <sup>178</sup>
8q24 (region 1)	rs1447295	yes	x	x	x	x		x			x
	rs4242382	yes				(ass)					
	rs7017300					(ass)	x				
	rs10090154					(ass)					
	rs7837688	yes				(ass)	x				
	rs6470572					(ass)					
8q24 (region2)	rs16901979	yes	x	x	x (imputed in PLCO)	x					
	rs10086908					(ass)					
	rs13254738					(ass)					x
	rs6983561										x
8q24 (region3)	rs6983267	yes	x	x	x	x	x				x
	rs7000448					(ass)	x				x
8q24	rs7008482									x	
Region c-MYC	rs6470572					(ass)					
17q12	rs4430796	yes	x	x <sup>b</sup>	x		x				x
17q12	rs7501939	yes					x				
17q12	rs3760511						x				
17q24	rs1859962	yes	x	x <sup>b</sup>	x			x			x
19q13.2	rs8102476	yes									
19q13 (KLK2/KLK3)	rs2735839	yes		(ass)							
	rs5759167	yes									
1q25	rs1930293						x				
2p15	rs2710646		x								
	rs721048	yes		(ass)							

**Table 7. Summary of SNPs and other variables included in test panels (cont'd)**

SNP			9-SNP panel	11-SNP panel	14-SNP panel	3-SNPs in 8q24	4-SNP test	4-SNP test	3-SNP test	2-SNP test	6-SNP panel
Chromosome	rs number	Replicated in GWA studies <sup>§</sup>	Helfand <sup>172</sup>	Zheng <sup>173</sup>	Xu <sup>174</sup>	Sun <sup>175</sup>	Nam <sup>176</sup> model 2	Nam <sup>176</sup> model 3	Beuten <sup>177</sup>	Beuten <sup>177</sup>	Penney <sup>178</sup>
3p12	rs2660753	yes		x	x						
6q25	rs9364554	yes		x							
7p15	rs10486567	yes		x	x						
7q21	rs6465657	yes		x	x						
7p21	rs2348763						x	x			
9q33	rs1571801			x							
9p22	rs1552895						x				
10q26	rs4962416	yes		(ass)							
10q11	rs10993994	yes	x	x	x						
	rs7920517			(ass)							
11q13	rs10896450		x								
11q13(region2)	rs12418451										
11q13(region1)	rs10896449	yes		x							
11q13	rs7931342	yes		(ass)							
22q13					x						
Xp11	rs5945572	yes	x	(ass)							
	rs5945619	yes		x							
ERG	rs2836431						x				
ERG	rs8131855						x				
HOGG1-326	rs1052133						x				
KLK2	rs198972						x				
KLK2	rs2664155						x				
TNF	rs1800629						x	x			
4q22 PDLIM5	rs17021918										
<i>TERT</i>	rs401681	With serum PSA levels									
11p15	rs7127900	yes									
8p21	rs1512268	yes									

**Table 7. Summary of SNPs and other variables included in test panels (cont'd)**

SNP			9-SNP panel	11-SNP panel	14-SNP panel	3-SNPs in 8q24	4-SNP test	4-SNP test	3-SNP test	2-SNP test	6-SNP panel
Chromosome	rs number	Replicated in GWA studies <sup>§</sup>	Helfand <sup>172</sup>	Zheng <sup>173</sup>	Xu <sup>174</sup>	Sun <sup>175</sup>	Nam <sup>176</sup> model 2	Nam <sup>176</sup> model 3	Beuten <sup>177</sup>	Beuten <sup>177</sup>	Penney <sup>178</sup>
4q24	rs7679673	yes									
2q31	rs10207654										
3q21.3	rs10934853	yes									
8q24.21	rs16902104										
2p21 <i>THADA</i>	rs1465618	yes									
8q24.21	rs445114	yes									
<i>HSD3B2</i>	rs1819698								x (nHW)		
<i>CYP19</i>	rs12439137								x (nHW)		
<i>CYP19</i>	rs2470152								x (nHW)		
<i>CYP19</i>	rs10459592									x (HW)	
<i>CYP24A11</i>	rs3787554									x (HW)	
Variables adjusted for			Age	In AUC analysis, age and family Hx				age, family Hx, ethnicity, urinary symptoms, PSA, free: total PSA ratio and DRE			
Variables added to model containing SNPs					Family Hx						

<sup>§</sup> based on information in Table 1

<sup>a</sup> substituted by rs6983561, with which it was perfectly correlated

<sup>b</sup> additive model, in contrast to other five studies in which 5-SNP panel assessed

<sup>c</sup> 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

**Table 8. Focus 5 test**

5-SNP Panel (Focus 5)								
Chromosome	rs number	Replicated in GWA studies	Zheng <sup>169</sup>	Salinas <sup>170</sup>	Sun <sup>171</sup>	Nam <sup>176</sup> model 1	Helfand <sup>172</sup>	Zheng <sup>173</sup>
8q24 (region 1)	rs1447295	Yes	x	x	x	x	x	x
8q24(region2)	rs16901979	Yes	x	x <sup>a</sup>	x (imputed in PLCO)	x	x <sup>b</sup>	x
8q24(region3)	rs6983267	Yes	x	x	x	x	x <sup>b</sup>	x
17q12	rs4430796	Yes	x	x	x	x	x <sup>c</sup>	x
17q24	rs1859962	yes	x	x <sup>c</sup>	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			

<sup>a</sup> substituted by rs6983561, with which it was perfectly correlated

<sup>b</sup> additive model, in contrast to other five studies in which 5-SNP panel assessed

<sup>c</sup> 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 9. Genetic variants tested for by deCODE ProstateCancer**

<b>Chromosome</b>	<b>rs number</b>
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
<i>TERT</i>	Rs401681
11p15	Rs7127900
8p21	Rs1512268
4q24	Rs7679673
2q31	Rs10207654
3q21.3	Rs10934853
8q24.21	Rs16902104
2p21 <i>THADA</i>	Rs1465618
8q24.21	Rs445114

Table 10a. Newcastle-Ottawa Scale:<sup>166</sup> Case-control Studies

Question	Study											
	Zheng <sup>169</sup>	Salinas <sup>170</sup>	Sun <sup>171</sup>	Sun <sup>171</sup> JHH	Helfand <sup>172</sup>	Zheng <sup>173</sup>	Xu <sup>174</sup>	Sun <sup>175</sup>	Nam <sup>176</sup>	Beuten <sup>177</sup>	Penney <sup>178</sup> PHS and FHCRC	Penney <sup>178</sup> Gelb Center companion <sup>20</sup> <sub>0</sub>
<b>Is the case definition adequate?</b> 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>Representativeness of the cases</b> 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>Selection of Controls</b> A* = community controls B = hospital controls C = no description	A*	A*	A*	B	C	A*	PR	B	B	A*	A*	C
<b>Definition of Controls</b> A* = no history of disease (endpoint) B = no description of source	B	A*	B	B	B	B	PR	B	A*	A*	A*	B
<b>Comparability of cases and controls on the basis of the design of analysis</b> 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*

Table 10a. Newcastle-Ottawa Scale:<sup>166</sup> Case-control Studies (cont'd)

Question	Study											
	Zheng <sup>169</sup>	Salinas <sup>170</sup>	Sun <sup>171</sup>	Sun <sup>171</sup> JHH	Helfand <sup>172</sup>	Zheng <sup>173</sup>	Xu <sup>174</sup>	Sun <sup>175</sup>	Nam <sup>176</sup>	Beuten <sup>177</sup>	Penney <sup>178</sup> PHS and FHCRC	Penney <sup>178</sup> Gelb Center companion <sup>200</sup>
<b>Ascertainment of exposure: quality control &amp; blinding</b> 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*
<b>Same method of ascertainment for cases &amp; controls</b> A* = yes B = no	B	B	A*	A*	B	B	PR	B	A*	A*	A*	A*
<b>Non-Response rate</b> 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
<b>NOS Star Rating (out of 9)</b>	5	7	5	3	3	5	NA	4	6	6	7	3

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

**Table 10b. Selected items from QUADAS<sup>167</sup>**

Question	Zheng <sup>169</sup>	Salinas <sup>170</sup>	Sun <sup>171</sup>	Helfand <sup>172</sup>	Zheng <sup>173</sup>	Xu <sup>174</sup>	Sun <sup>175</sup>	Nam <sup>176</sup>	Beuten <sup>177</sup>	Penney <sup>178</sup>	Penney <sup>178</sup>	Penney <sup>178</sup>
<b>Spectrum of participants representative of the patients who would receive the test in practice</b>	yes	yes	yes	no	yes		no	no	yes	no (PHS)	yes (FHCRC)	Unclear (Gelb Center)
<b>Selection criteria clearly described</b>	yes	yes	yes	no	yes		unclear	yes	yes	yes	yes	yes
<b>Reporting of uninterpretable, indeterminate, or intermediate test results</b>	yes	yes	no	no	yes		no	unclear	no	No	No	no

\*yes, if look at companion

Abbreviations: FHCRC = Fred Hutchinson Cancer Research Center; PHS = Physician's Health Study

## Discussion

The purpose of this review was to establish the evidence base around using SNP-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.

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-based 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, none of the analyses showed any substantial increment in AUC when the SNPs were added to other risk factors in the model. The AUCs with the inclusion of SNPs ranged between 63 percent and 73 percent, and would not in themselves be considered useful for individual risk prediction. All of the studies were done in participants of European origin in Sweden and the United States, or in a population predominantly of European origin in Canada, limiting the generalizability of these findings to men of other than European origin. In the two studies that investigated associations with mortality or Gleason score, or differences between aggressive and non-aggressive disease, no differences were found between these subgroups.

There were single studies only 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 65 to 73 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.

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. This is unsurprising, given the early stages of development of this field.<sup>201,202</sup> 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).<sup>84,98,99</sup> Improving on this 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.<sup>203-208</sup> 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 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 from studies based on other forms of risk stratification (family history or genetic testing) that this actually occurs.<sup>209,210</sup>

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,<sup>69,70,80</sup> and a review of observational evidence was unable to reliably estimate the relative effectiveness because of differences in outcome reporting, lack of controls or risk adjustment, and possible overlap between studies.<sup>211</sup>

Taken together, therefore, benefits from improvements in prostate cancer risk prediction and screening will depend to a large extent on the 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.

## Future Research

We identified a number of evaluations of SNP panels which varied in their composition. We could not draw robust conclusions regarding their analytic validity. Clinical validity analyses showed statistically significant associations between the panels and prostate cancer diagnosis. However, when assessed using AUC analyses, the SNP components of the models only marginally improved on the nongenomic components in their ability to distinguish cases from noncases, and in distinguishing clinically meaningful from latent or asymptomatic cancer. 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 comparing SNP-based panels directly with the existing standard of care. There is also a need to identify and validate further genetic markers to enable larger SNP panels to be developed. 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.



## References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-917. PMID:21351269
2. American Cancer Society. *Cancer Facts & Figures 2010*. Atlanta: American Cancer Society; 2010.  
<http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-026238.pdf>
3. Canadian Cancer Society. *Canadian Cancer Statistics 2010*. Toronto: Canadian Cancer Society; 2010 Apr.  
<http://www.cancer.ca/~media/CCS/Canada%20wide/Files%20List/English%20files%20heading/pdf%20not%20in%20publications%20section/Canadian%20Cancer%20Statistics%202010%20-%20English.ashx>
4. National Cancer Institute. SEER (Surveillance, Epidemiology, and End Results Program of the National Cancer Institute) SEER Stat Fact Sheets: Prostate. 2011 May 9. 2011 May 9.  
<http://www.seer.cancer.gov/statfacts/html/prost.html>
5. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst*. 2009;101(18):1280-3. PMID:19713548
6. Gronberg H. Prostate cancer epidemiology. *Lancet*. 2003;361(9360):859-64. PMID:12642065
7. Evans S, Metcalfe C, Ibrahim F, et al. Investigating Black-White differences in prostate cancer prognosis: A systematic review and meta-analysis. *Int J Cancer*. 2008;123(2):430-5. PMID:18452170
8. Parkin DM, Sitas F, Chirenje M, et al. Part I: Cancer in Indigenous Africans--burden, distribution, and trends. *Lancet Oncol*. 2008;9(7):683-92. PMID:18598933
9. Delongchamps NB, Singh A, Haas GP. Epidemiology of prostate cancer in Africa: another step in the understanding of the disease? *Curr Probl Cancer*. 2007;31(3):226-36. PMID:17543950
10. Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. *Int J Cancer*. 2003;107(5):797-803. PMID:14566830
11. Zeegers MP, Jellema A, Ostrer H. Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis. *Cancer*. 2003;97(8):1894-903. PMID:12673715
12. Bratt O. Hereditary prostate cancer: clinical aspects. *J Urol*. 2002;168(3):906-13. PMID:12187189
13. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343(2):78-85. PMID:10891514
14. Carter BS, Beaty TH, Steinberg GD, et al. Mendelian inheritance of familial prostate cancer. *Proc Natl Acad Sci U S A*. 1992;89(8):3367-71. PMID:1565627
15. Carter BS, Bova GS, Beaty TH, et al. Hereditary prostate cancer: epidemiologic and clinical features. *J Urol*. 1993;150(3):797-802. PMID:8345587
16. Roddam AW, Allen NE, Appleby P, et al. Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. *Ann Intern Med*. 2008;149(7):461-8. PMID:18838726
17. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia*. 2004;47(6):1071-8. PMID:15164171

18. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2006;15(11):2056-62. PMID:17119028
19. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst.* 1998;90(6):440-6. PMID:9521168
20. Alkhenizan A, Hafez K. The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials. *Ann Saudi Med.* 2007;27(6):409-14. PMID:18059122
21. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA.* 2009;301(1):52-62. PMID:19066368
22. Klein EA, Thompson IM, Jr., Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA.* 2011;306(14):1549-56. PMID:21990298
23. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA.* 2009;301(1):39-51. PMID:19066370
24. Dagnelie PC, Schuurman AG, Goldbohm RA, et al. Diet, anthropometric measures and prostate cancer risk: a review of prospective cohort and intervention studies. *BJU Int.* 2004;93(8):1139-50. PMID:15142129
25. Etminan M, Takkouche B, Caamano-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. *Cancer Epidemiol Biomarkers Prev.* 2004;13(3):340-5. PMID:15006906
26. Hwang YW, Kim SY, Jee SH, et al. Soy food consumption and risk of prostate cancer: a meta-analysis of observational studies. *Nutr Cancer.* 2009;61(5):598-606. PMID:19838933
27. Yan L, Spitznagel EL. Soy consumption and prostate cancer risk in men: a revisit of a meta-analysis. *Am J Clin Nutr.* 2009;89(4):1155-63. PMID:19211820
28. Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. *J Natl Cancer Inst.* 2005;97(23):1768-77. PMID:16333032
29. Qin LQ, Xu JY, Wang PY, et al. Milk consumption is a risk factor for prostate cancer in Western countries: evidence from cohort studies. *Asia Pac J Clin Nutr.* 2007;16(3):467-76. PMID:17704029
30. Dennis LK. Meta-analysis for combining relative risks of alcohol consumption and prostate cancer. *Prostate.* 2000;42(1):56-66. PMID:10579799
31. Park CH, Myung SK, Kim TY, et al. Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies. *BJU Int.* 2010;106(6):762-9. PMID:20590551
32. Suzuki R, Allen NE, Key TJ, et al. A prospective analysis of the association between dietary fiber intake and prostate cancer risk in EPIC. *Int J Cancer.* 2009;124(1):245-9. PMID:18814263
33. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. *Am J Clin Nutr.* 2010;92(5):1223-33. PMID:20844069
34. Druesne-Pecollo N, Latino-Martel P, Norat T, et al. Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. *Int J Cancer.* 2010;127(1):172-84. PMID:19876916
35. Patel AR, Klein EA. Risk factors for prostate cancer. *Nat Clin Pract Urol.* 2009;6(2):87-95. PMID:19198622

36. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. *Cancer Causes Control*. 2006;17(8):989-1003. PMID:16933050
37. Dennis LK, Dawson DV. Meta-analysis of measures of sexual activity and prostate cancer. *Epidemiology*. 2002;13(1):72-9. PMID:11805589
38. Dennis LK, Coughlin JA, McKinnon BC, et al. Sexually transmitted infections and prostate cancer among men in the U.S. military. *Cancer Epidemiol Biomarkers Prev*. 2009;18(10):2665-71. PMID:19755645
39. Rusmevichientong A, Chow SA. Biology and pathophysiology of the new human retrovirus XMRV and its association with human disease. *Immunol Res*. 2010;48(1-3):27-39. PMID:20717743
40. Dennis LK, Dawson DV, Resnick MI. Vasectomy and the risk of prostate cancer: a meta-analysis examining vasectomy status, age at vasectomy, and time since vasectomy. *Prostate Cancer Prostatic Dis*. 2002;5(3):193-203. PMID:12496981
41. Tang LF, Jiang H, Shang XJ, et al. Vasectomy not associated with prostate cancer: a meta-analysis. *Zhonghua Nan Ke Xue*. 2009;15(6):545-50. PMID:19593998
42. Ballard T, Lagorio S, De AG, et al. Cancer incidence and mortality among flight personnel: a meta-analysis. *Aviat Space Environ Med*. 2000;71(3):216-24. PMID:10716165
43. Buja A, Lange JH, Perissinotto E, et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. *Toxicol Ind Health*. 2005;21(10):273-82. PMID:16463960
44. Van Maele-Fabry G, Willems JL. Prostate cancer among pesticide applicators: a meta-analysis. *Int Arch Occup Environ Health*. 2004;77(8):559-70. PMID:15688248
45. Mahmud SM, Franco EL, Aprikian AG. Use of nonsteroidal anti-inflammatory drugs and prostate cancer risk: a meta-analysis. *Int J Cancer*. 2010;127(7):1680-91. PMID:20091856
46. Browning DR, Martin RM. Statins and risk of cancer: a systematic review and meta-analysis. *Int J Cancer*. 2007;120(4):833-43. PMID:17131313
47. Bonovas S, Filioussi K, Sitaras NM. Statin use and the risk of prostate cancer: A meta-analysis of 6 randomized clinical trials and 13 observational studies. *Int J Cancer*. 2008;123(4):899-904. PMID:18491405
48. Huncharek M, Haddock KS, Reid R, et al. Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *Am J Public Health*. 2010;100(4):693-701. PMID:19608952
49. Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med*. 2009;7:36. PMID:19638245
50. Gilbert R, Metcalfe C, Oliver SE, et al. Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis. *Int J Cancer*. 2009;125(6):1414-23. PMID:19444909
51. Yin L, Raum E, Haug U, et al. Meta-analysis of longitudinal studies: Serum vitamin D and prostate cancer risk. *Cancer Epidemiol*. 2009;33(6):435-45. PMID:19939760
52. Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. *Int J Cancer*. 2011;128(6):1414-24. PMID:20473927
53. Cuzick J, Fisher G, Kattan MW, et al. Long-term outcome among men with conservatively treated localised prostate cancer. *Br J Cancer*. 2006;95(9):1186-94. PMID:17077805

54. Breslow N, Chan CW, Dhom G, et al. Latent carcinoma of prostate at autopsy in seven areas. The International Agency for Research on Cancer, Lyons, France. *Int J Cancer*. 1977;20(5):680-8. PMID:924691
55. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *In Vivo*. 1994;8(3):439-43. PMID:7803731
56. Sanchez-Chapado M, Olmedilla G, Cabeza M, et al. Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study. *Prostate*. 2003;54(3):238-47. PMID:12518329
57. Soos G, Tsakiris I, Szanto J, et al. The prevalence of prostate carcinoma and its precursor in Hungary: an autopsy study. *Eur Urol*. 2005;48(5):739-44. PMID:16203079
58. Stamatou K, Alevizos A, Agapitos E, et al. Incidence of impalpable carcinoma of the prostate and of non-malignant and precarcinomatous lesions in Greek male population: an autopsy study. *Prostate*. 2006;66(12):1319-28. PMID:16688747
59. Orde MM, Whitaker NJ, Lawson JS. High prevalence of prostatic neoplasia in Australian men. *Pathology*. 2009;41(5):433-5. PMID:19900081
60. Oon SF, Pennington SR, Fitzpatrick JM, et al. Biomarker research in prostate cancer-towards utility, not futility. *Nat Rev Urol*. 2011;8(3):131-8. PMID:21394176
61. Epstein JI, Allsbrook WC, Jr., Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol*. 2005;29(9):1228-42. PMID:16096414
62. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med*. 1994;330(4):242-8. PMID:8272085
63. Albertsen PC, Fryback DG, Storer BE, et al. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA*. 1995;274(8):626-31. PMID:7637143
64. Albertsen PC, Hanley JA, Gleason DF, et al. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA*. 1998;280(11):975-80. PMID:9749479
65. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005;293(17):2095-101. PMID:15870412
66. Adolfsson J, Steineck G, Hedlund PO. Deferred treatment of clinically localized low-grade prostate cancer: actual 10-year and projected 15-year follow-up of the Karolinska series. *Urology*. 1997;50(5):722-6. PMID:9372882
67. Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. *JAMA*. 1997;277(6):467-71. PMID:9020270
68. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA*. 2004;291(22):2713-9. PMID:15187052
69. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med*. 2002;347(11):781-9. PMID:12226148
70. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352(19):1977-84. PMID:15888698
71. Stattin P, Holmberg E, Johansson JE, et al. Outcomes in localized prostate cancer: National Prostate Cancer Register of Sweden follow-up study. *J Natl Cancer Inst*. 2010;102(13):950-8. PMID:20562373

72. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst.* 2002;94(13):981-90. PMID:12096083
73. Draisma G, Boer R, Otto SJ, et al. Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst.* 2003;95(12):868-78. PMID:12813170
74. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst.* 2009;101(6):374-83. PMID:19276453
75. Pashayan N, Powles J, Brown C, et al. Excess cases of prostate cancer and estimated overdiagnosis associated with PSA testing in East Anglia. *Br J Cancer.* 2006;95(3):401-5. PMID:16832417
76. Bangma CH, Roemeling S, Schroder FH. Overdiagnosis and overtreatment of early detected prostate cancer. *World J Urol.* 2007;25(1):3-9. PMID:17364211
77. Telesca D, Etzioni R, Gulati R. Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends. *Biometrics.* 2008;64(1):10-9. PMID:17501937
78. Gann PH, Han M. The natural history of clinically localized prostate cancer. *JAMA.* 2005;293(17):2149-51. PMID:15870419
79. Gulati R, Wever EM, Tsodikov A, et al. What if i don't treat my PSA-detected prostate cancer? Answers from three natural history models. *Cancer Epidemiol Biomarkers Prev.* 2011;20(5):740-50. PMID:21546365
80. Iversen P, Madsen PO, Corle DK. Radical prostatectomy versus expectant treatment for early carcinoma of the prostate. Twenty-three year follow-up of a prospective randomized study. *Scand J Urol Nephrol Suppl.* 1995;172:65-72. PMID:8578259
81. Rao AR, Motiwala HG, Karim OM. The discovery of prostate-specific antigen. *BJU Int.* 2008;101(1):5-10. PMID:17760888
82. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med.* 1987;317(15):909-16. PMID:2442609
83. Boyle P, Brawley OW. Prostate cancer: current evidence weighs against population screening. *CA Cancer J Clin.* 2009;59(4):220-4. PMID:19564244
84. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. *J Natl Cancer Inst.* 2009;101(19):1325-9. PMID:19720969
85. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA.* 2009;302(15):1685-92. PMID:19843904
86. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials.* 2000;21(6 Suppl):273S-309S. PMID:11189684
87. Andriole GL, Crawford ED, Grubb RL, III, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360(13):1310-9. PMID:19297565
88. Labrie F, Candas B, Dupont A, et al. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate.* 1999;38(2):83-91. PMID:9973093
89. Labrie F, Cusan L, Gomez L, et al. Screening and treatment of localized prostate cancer decreases mortality: first analysis of the first prospectiven and randomized study on prostate cancer screening. *Aging Male.* 1999;2:33-43.

90. Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate*. 2004;59(3):311-8. PMID:15042607
91. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*. 2010;11(8):725-32. PMID:20598634
92. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360(13):1320-8. PMID:19297566
93. Varenhorst E, Carlsson P, Capik E, et al. Repeated screening for carcinoma of the prostate by digital rectal examination in a randomly selected population. *Acta Oncol*. 1992;31(8):815-21. PMID:1290631
94. Sandblom G, Varenhorst E, Lofman O, et al. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. *Eur Urol*. 2004;46(6):717-23. PMID:15548438
95. Kjellman A, Akre O, Norming U, et al. Dihydrotestosterone levels and survival in screening-detected prostate cancer: a 15-yr follow-up study. *Eur Urol*. 2008;53(1):106-11. PMID:17482753
96. Kjellman A, Akre O, Norming U, et al. 15-year followup of a population based prostate cancer screening study. *J Urol*. 2009;181(4):1615-21. PMID:19233435
97. Jegu J, Tretarre B, Grosclaude P, et al. Results and participation factors to the European Randomized study of Screening for Prostate Cancer (ERSPC) with Prostate Specific Antigen: French departments of Tarn and Herault. *Prog Urol*. 2009;19(7):487-98. PMID:19559380
98. Djulbegovic M, Beyth RJ, Neuberger MM, et al. Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2010;341:c4543 PMID:20843937
99. Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer: an updated Cochrane systematic review. *BJU Int*. 2011;107(6):882-91. PMID:21392207
100. Barry MJ. Screening for prostate cancer--the controversy that refuses to die. *N Engl J Med*. 2009;360(13):1351-4. PMID:19297564
101. Neal DE, Donovan JL, Martin RM, et al. Screening for prostate cancer remains controversial. *Lancet*. 2009;374(9700):1482-3. PMID:19664817
102. Stark JR, Mucci L, Rothman KJ, et al. Screening for prostate cancer remains controversial. *BMJ*. 2009;339:b3601 PMID:19778971
103. Roobol MJ, Carlsson S, Hugosson J. Meta-analysis finds screening for prostate cancer with PSA does not reduce prostate cancer-related or all-cause mortality but results likely due to heterogeneity - the two highest quality studies identified do find prostate cancer-related mortality reductions. *Evid Based Med*. 2011;16(1):20-1. PMID:21228057
104. Pinsky PF, Blacka A, Kramer BS, et al. Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. *Clin Trials*. 2010;7(4):303-11. PMID:20571134
105. Lunn RM, Bell DA, Mohler JL, et al. Prostate cancer risk and polymorphism in 17 hydroxylase (CYP17) and steroid reductase (SRD5A2). *Carcinogenesis*. 1999;20(9):1727-31. PMID:10469617
106. Chou R, Croswell JM, Dana T, et al. Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011; PMID:21984740
107. Cavalli-Sforza LL and Bodmer WF. *The Genetics of Human Populations*, San Francisco: WH Freeman and Company; 1971. p. 118.

108. Feero WG, Gutmacher AE, Collins FS. Genomic medicine--an updated primer. *N Engl J Med.* 2010;362(21):2001-11. PMID:20505179
109. Qiu LX, Li RT, Zhang JB, et al. The E-cadherin (CDH1)--160 C/A polymorphism and prostate cancer risk: a meta-analysis. *Eur J Hum Genet.* 2009;17(2):244-9. PMID:18781193
110. Zeegers MP, Kiemeny LA, Nieder AM, et al. How strong is the association between CAG and GGN repeat length polymorphisms in the androgen receptor gene and prostate cancer risk? *Cancer Epidemiol Biomarkers Prev.* 2004;13(11 Pt 1):1765-71. PMID:15533905
111. Chen YC, Kraft P, Bretsky P, et al. Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiol Biomarkers Prev.* 2007;16(10):1973-81. PMID:17932344
112. Li J, Coates RJ, Gwinn M, et al. Steroid 5-{alpha}-reductase Type 2 (SRD5a2) gene polymorphisms and risk of prostate cancer: a HuGE review. *Am J Epidemiol.* 2010;171(1):1-13. PMID:19914946
113. Li X, Huang Y, Fu X, et al. Meta-analysis of three polymorphisms in the steroid-5-alpha-reductase, alpha polypeptide 2 gene (SRD5A2) and risk of prostate cancer. *Mutagenesis.* 2011;26(3):371-83. PMID:21177315
114. Ruiters R, Visser LE, Van Duijn CM, et al. The ACE Insertion/Deletion Polymorphism and Risk of Cancer, a Review and Meta-Analysis of the Literature. *Curr Cancer Drug Targets.* 2011;11(4):421-30. PMID:21395549
115. Geng J, Zhang Q, Zhu C, et al. XRCC1 genetic polymorphism Arg399Gln and prostate cancer risk: a meta-analysis. *Urology.* 2009;74(3):648-53. PMID:19428062
116. Zou YF, Wang F, Feng XL, et al. Lack of association of IL-10 gene polymorphisms with prostate cancer: evidence from 11,581 subjects. *Eur J Cancer.* 2011;47(7):1072-9. PMID:21211963
117. Shao N, Xu B, Mi YY, et al. IL-10 polymorphisms and prostate cancer risk: a meta-analysis. *Prostate Cancer Prostatic Dis.* 2011;14(2):129-35. PMID:21339768
118. Sun J, Hsu FC, Turner AR, et al. Meta-analysis of association of rare mutations and common sequence variants in the MSR1 gene and prostate cancer risk. *Prostate.* 2006;66(7):728-37. PMID:16425212
119. Murad A, Lewis SJ, Smith GD, et al. PTGS2-899G>C and prostate cancer risk: a population-based nested case-control study (Protect) and a systematic review with meta-analysis. *Prostate Cancer Prostatic Dis.* 2009;12(3):296-300. PMID:19488068
120. Danforth KN, Rodriguez C, Hayes RB, et al. TNF polymorphisms and prostate cancer risk. *Prostate.* 2008;68(4):400-7. PMID:18196539
121. Xu B, Tong N, Chen SQ, et al. FGFR4 Gly388Arg polymorphism contributes to prostate cancer development and progression: a meta-analysis of 2618 cases and 2305 controls. *BMC Cancer.* 2011;11:84 PMID:21349172
122. Liwei L, Chunyu L, Jie L, et al. Association between Fibroblast Growth Factor Receptor-4 Gene Polymorphism and Risk of Prostate Cancer: A Meta-Analysis. *Urol Int.* 2011;[Epub ahead of print] PMID:21625079
123. Wei BB, Xi B, Wang R, et al. TGFbeta1 T29C polymorphism and cancer risk: a meta-analysis based on 40 case-control studies. *Cancer Genet Cytogenet.* 2010;196(1):68-75.
124. Liao RY, Mao C, Qiu LX, et al. TGFBR1\*6A/9A polymorphism and cancer risk: a meta-analysis of 13,662 cases and 14,147 controls. *Mol Biol Rep.* 2010;37(7):3227-32. PMID:19882361

125. Chen X, Guan J, Song Y, et al. IGF-I (CA) repeat polymorphisms and risk of cancer: a meta-analysis. *J Hum Genet.* 2008;53(3):227-38. PMID:18188667
126. Li L, Huang X, Huo K. IGFBP3 polymorphisms and risk of cancer: a meta-analysis. *Mol Biol Rep.* 2010;37(1):127-40. PMID:19449212
127. Bai JL, Zheng MH, Xia X, et al. MTHFR C677T polymorphism contributes to prostate cancer risk among Caucasians: A meta-analysis of 3511 cases and 2762 controls. *Eur J Cancer.* 2009;45(8):1443-9. PMID:19223177
128. Collin SM, Metcalfe C, Zuccolo L, et al. Association of folate-pathway gene polymorphisms with the risk of prostate cancer: A population-based nested case-control study, systematic review, and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2009;18(9):2528-39.
129. Mao C, Qiu LX, Zhan P, et al. MnSOD Val16Ala polymorphism and prostate cancer susceptibility: a meta-analysis involving 8,962 subjects. *Journal of Cancer Research & Clinical Oncology.* 2010;136(7):975-9. PMID:20012093
130. Shaik AP, Jamil K, Das P. CYP1A1 polymorphisms and risk of prostate cancer. A meta-analysis. *Urology Journal.* 2009;6(2):78-86.
131. Keshava C, McCanlies EC, Weston A. CYP3A4 polymorphisms--potential risk factors for breast and prostate cancer: a HuGE review. *Am J Epidemiol.* 2004;160(9):825-41. PMID:15496535
132. Wang F, Zou YF, Feng XL, et al. CYP17 gene polymorphisms and prostate cancer risk: A meta-analysis based on 38 independent studies. *Prostate.* 2011;71(11):1167-77. PMID:21656827
133. Mo Z, Gao Y, Cao Y, et al. An updating meta-analysis of the GSTM1, GSTT1, and GSTP1 polymorphisms and prostate cancer: a HuGE review. *Prostate.* 2009;69(6):662-88. PMID:19143011
134. Raimondi S, Johansson H, Maisonneuve P, et al. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. *Carcinogenesis.* 2009;30(7):1170-80. PMID:19403841
135. Xu B, Tong N, Li JM, et al. ELAC2 polymorphisms and prostate cancer risk: a meta-analysis based on 18 case-control studies. *Prostate Cancer Prostatic Dis.* 2010;13(3):270-7. PMID:20231859
136. Li H, Tai BC. RNASEL gene polymorphisms and the risk of prostate cancer: a meta-analysis. *Clin Cancer Res.* 2006;12(19):5713-9. PMID:17020975
137. Zhu Y, Wang J, He Q, et al. Association of p53 codon 72 polymorphism with prostate cancer: a meta-analysis. *Mol Biol Rep.* 2011;38(3):1603-7. PMID:20842446
138. Ioannidis JP, Ntzani EE, Trikalinos TA, et al. Replication validity of genetic association studies. *Nat Genet.* 2001;29(3):306-9. PMID:11600885
139. Hirschhorn JN, Lohmueller K, Byrne E, et al. A comprehensive review of genetic association studies. *Genet Med.* 2002;4(2):45-61. PMID:11882781
140. Lohmueller KE, Pearce CL, Pike M, et al. Meta-analysis of genetic association studies supports a contribution of common variants to susceptibility to common disease. *Nat Genet.* 2003;33(2):177-82. PMID:12524541
141. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet.* 2008;9(5):356-69. PMID:18398418
142. Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nat Genet.* 2007;39(5):645-9. PMID:17401363
143. Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nat Genet.* 2007;39(5):631-7. PMID:17401366

144. Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nat Genet.* 2007;39(8):977-83. PMID:17603485
145. Thomas G, Jacobs KB, Yeager M, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet.* 2008;40(3):310-5. PMID:18264096
146. Gudmundsson J, Sulem P, Rafnar T, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nat Genet.* 2008;40(3):281-3. PMID:18264098
147. Eeles RA, Kote-Jarai Z, Giles GG, et al. Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet.* 2008;40(3):316-21. PMID:18264097
148. Sun J, Zheng SL, Wiklund F, et al. Sequence variants at 22q13 are associated with prostate cancer risk. *Cancer Res.* 2009;69(1):10-5. PMID:19117981
149. Gudmundsson J, Sulem P, Gudbjartsson DF, et al. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. *Nat Genet.* 2009;41(10):1122-6. PMID:19767754
150. Takata R, Akamatsu S, Kubo M, et al. Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population. *Nat Genet.* 2010;42(9):751-4. PMID:20676098
151. Haiman CA, Chen GK, Blot WJ, et al. Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. *Nat Genet.* 2011;43(6):570-3. PMID:21602798
152. Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nat Genet.* 2009;41(10):1116-21. PMID:19767753
153. Vineis P, Schulte P, McMichael AJ. Misconceptions about the use of genetic tests in populations. *Lancet.* 2001;357(9257):709-12. PMID:11247571
154. Khoury MJ, Yang Q, Gwinn M, et al. An epidemiologic assessment of genomic profiling for measuring susceptibility to common diseases and targeting interventions. *Genet Med.* 2004;6(1):38-47. PMID:14726808
155. Madlensky L, McLaughlin JR, Carroll JC, et al. Risks and benefits of population-based genetic testing for Mendelian subsets of common diseases were examined using the example of colorectal cancer risk. *J Clin Epidemiol.* 2005;58(9):934-41. PMID:16085197
156. Janssens AC, Gwinn M, Bradley LA, et al. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. *Am J Hum Genet.* 2008;82(3):593-9. PMID:18319070
157. Yang Q, Khoury MJ, Friedman JM, et al. On the use of population attributable fraction to determine sample size for case-control studies of gene-environment interaction. *Epidemiology.* 2003;14(2):161-7. PMID:12606881
158. Yang Q, Khoury MJ, Friedman J, et al. How many genes underlie the occurrence of common complex diseases in the population? *Int J Epidemiol.* 2005;34(5):1129-37. PMID:16043441
159. Yang Q, Khoury MJ, Botto L, et al. Improving the prediction of complex diseases by testing for multiple disease-susceptibility genes. *Am J Hum Genet.* 2003;72(3):636-49. PMID:12592605
160. Hawken SJ, Greenwood CM, Hudson TJ, et al. The utility and predictive value of combinations of low penetrance genes for screening and risk prediction of colorectal cancer. *Hum Genet.* 2010;128(1):89-101. PMID:20437058

161. Janssens AC, Ioannidis JP, Van Duijn CM, et al. Strengthening the reporting of genetic risk prediction studies: The GRIPS Statement. *Ann Intern Med.* 2011;154(6):421-5. PMID:21403077
162. Lu X, Zhang K, Van SC, et al. An algorithm for classifying tumors based on genomic aberrations and selecting representative tumor models. *BMC Medical Genomics [Electronic Resource].* 2010;3:23 PMID:20569491
163. Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. *Am J Prev Med.* 2003;24(2):128-35. PMID:12568818
164. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med.* 2009;11(1):3-14. PMID:18813139
165. A Catalog of Published Genome-Wide Association Studies. Hindorff L, MacArthur J (European Bioinformatics Institute), Wise A et al. 2011;
166. Wells, G. A, Shea, B., O'Connell, D. et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) 2009 Feb 1.
167. 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 PMID:14606960
168. GRADE Working Group. Grading the quality of evidence and strength of recommendations. *bmj com.* 2004;328(7454):1490 [www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)
169. Zheng SL, Sun J, Wiklund F, et al. Cumulative association of five genetic variants with prostate cancer. *N Engl J Med.* 2008;358(9):910-9. PMID:18199855
170. Salinas CA, Koopmeiners JS, Kwon EM, et al. Clinical utility of five genetic variants for predicting prostate cancer risk and mortality. *Prostate.* 2009;69(4):363-72. PMID:19058137
171. Sun J, Chang BL, Isaacs SD, et al. Cumulative effect of five genetic variants on prostate cancer risk in multiple study populations. *Prostate.* 2008;68(12):1257-62. PMID:18491292
172. Helfand BT, Fought AJ, Loeb S, et al. Genetic prostate cancer risk assessment: common variants in 9 genomic regions are associated with cumulative risk. *J Urol.* 2010;184(2):501-5. PMID:20620408
173. Zheng SL, Sun J, Wiklund F, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen. *Clin Cancer Res.* 2009;15(3):1105-11. PMID:19188186
174. Xu J, Sun J, Kader AK, et al. Estimation of absolute risk for prostate cancer using genetic markers and family history. *Prostate.* 2009;69(14):1565-72. PMID:19562736
175. Sun J, Lange EM, Isaacs SD, et al. Chromosome 8q24 risk variants in hereditary and non-hereditary prostate cancer patients. *Prostate.* 2008;68(5):489-97. PMID:18213635
176. Nam RK, Zhang WW, Trachtenberg J, et al. Utility of incorporating genetic variants for the early detection of prostate cancer. *Clin Cancer Res.* 2009;15(5):1787-93. PMID:19223501
177. Beuten J, Gelfond JA, Franke JL, et al. Single and multigenic analysis of the association between variants in 12 steroid hormone metabolism genes and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1869-80. PMID:19505920
178. Penney KL, Salinas CA, Pomerantz M, et al. Evaluation of 8q24 and 17q risk loci and prostate cancer mortality. *Clin Cancer Res.* 2009;15(9):3223-30. PMID:19366828

179. Zheng SL, Stevens VL, Wiklund F, et al. Two independent prostate cancer risk-associated Loci at 11q13. *Cancer Epidemiol Biomarkers Prev.* 2009;18(6):1815-20. PMID:19505914
180. Ekhart C, Rodenhuis S, Smits PH, et al. Relations between polymorphisms in drug-metabolising enzymes and toxicity of chemotherapy with cyclophosphamide, thiotepa and carboplatin. *Pharmacogenetics & Genomics.* 2008;18(11):1009-15. PMID:18854779
181. Helfand BT, Loeb S, Meeks JJ, et al. Pathological Outcomes Associated With the 17q Prostate Cancer Risk Variants. *J Urol.* 2009;181(6):2502-7.
182. Methods and compositions for correlating genetic markers with prostate cancer risk. Xu J, Zheng L, Gronberg H, and Isaac W. United States Patent Application Publication: 2009; 18/07/2011.
183. Proactive Genomics. Zheng L, Xu J, Trent J, Bleecker E, and Turner A. 2008.
184. deCODEhealth <http://www.decodehealth.com/prostate-cancer>. 2011.
185. deCODEme <http://www.decode.me.com/complete-genetic-scan>. 2011.
186. Genetic variants contributing to risk of prostate cancer <http://www.freepatentsonline.com/20110020320.pdf>. Gudmundsson J and Sulem P. United States Patent Application Publication: 2011; 18/07/2011.
187. 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
188. 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
189. Hernandez J, Balic I, Johnson-Pais TL, et al. Association between an estrogen receptor alpha gene polymorphism and the risk of prostate cancer in black men. *J Urol.* 2006;175(2):523-7. PMID:16406987
190. Torkko KC, van BA, Mai P, et al. VDR and SRD5A2 polymorphisms combine to increase risk for prostate cancer in both non-Hispanic White and Hispanic White men. *Clin Cancer Res.* 2008;14(10):3223-9.
191. Duggan D, Zheng SL, Knowlton M, et al. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. *J Natl Cancer Inst.* 2007;99(24):1836-44. PMID:18073375
192. Wacholder S, Rothman N, Caporaso N. Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. *J Natl Cancer Inst.* 2000;92(14):1151-8. PMID:10904088
193. Ardlie KG, Lunetta KL, Seielstad M. Testing for population subdivision and association in four case-control studies. *Am J Hum Genet.* 2002;71(2):304-11. PMID:12096349
194. Millikan RC. Re: Population stratification in epidemiologic studies of common genetic variants and cancer: quantification of bias. *J Natl Cancer Inst.* 2001;93(2):156-8. PMID:11208892
195. Ioannidis JP, Ntzani EE, Trikalinos TA. 'Racial' differences in genetic effects for complex diseases. *Nat Genet.* 2004;36(12):1312-8. PMID:15543147
196. Xu J, Zheng SL, Carpten JD, et al. Evaluation of linkage and association of HPC2/ELAC2 in patients with familial or sporadic prostate cancer. *Am J Hum Genet.* 2001;68(4):901-11. PMID:11254448
197. Nam RK, Zhang WW, Loblaw DA, et al. A genome-wide association screen identifies regions on chromosomes 1q25 and 7p21 as risk loci for sporadic prostate cancer. *Prostate Cancer Prostatic Dis.* 2008;11(3):241-6. PMID:17876339

198. Nam RK, Zhang WW, Jewett MA, et al. The use of genetic markers to determine risk for prostate cancer at prostate biopsy. *Clin Cancer Res.* 2005;11(23):8391-7. PMID:16322300
199. Nam RK, Zhang WW, Klotz LH, et al. Variants of the hK2 protein gene (KLK2) are associated with serum hK2 levels and predict the presence of prostate cancer at biopsy. *Clin Cancer Res.* 2006;12(21):6452-8. PMID:17085659
200. Oh WK, Hayes J, Evan C, et al. Development of an integrated prostate cancer research information system. *Clin Genitourin Cancer.* 2006;5(1):61-6. PMID:16859581
201. Khoury MJ, Gwinn M, Yoon PW, et al. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med.* 2007;9(10):665-74. PMID:18073579
202. Burke W, Burton H, Hall AE, et al. Extending the reach of public health genomics: what should be the agenda for public health in an era of genome-based and "personalized" medicine? *Genet Med.* 2010;12(12):785-91. PMID:21189494
203. Miesfeldt S, Jones SM, Cohn W, et al. Men's attitudes regarding genetic testing for hereditary prostate cancer risk. *Urology.* 2000;55(1):46-50. PMID:10654893
204. Myers RE, Hyslop T, Jennings-Dozier K, et al. Intention to be tested for prostate cancer risk among African-American men. *Cancer Epidemiol Biomarkers Prev.* 2000;9(12):1323-8. PMID:11142417
205. Doukas DJ, Li Y. Men's values-based factors on prostate cancer risk genetic testing: a telephone survey. *BMC Med Genet.* 2004;5:28 PMID:15588314
206. Schwartz LM, Woloshin S, Fowler FJ, Jr., et al. Enthusiasm for cancer screening in the United States. *JAMA.* 2004;291(1):71-8. PMID:14709578
207. Cowan R, Meiser B, Giles GG, et al. The beliefs, and reported and intended behaviors of unaffected men in response to their family history of prostate cancer. *Genet Med.* 2008;10(6):430-8. PMID:18496220
208. Goodwin JS, Singh A, Reddy N, et al. Overuse of Screening Colonoscopy in the Medicare Population. *Arch Intern Med.* 2011;doi:10.1001/archinternmed.2011.212: PMID:21555653
209. Wilson BJ, Qureshi N, Santaguida P, et al. Systematic review: family history in risk assessment for common diseases. *Ann Intern Med.* 2009;151(12):878-85. PMID:19884616
210. Palomaki GE, Melillo S, Neveux L, et al. Use of genomic profiling to assess risk for cardiovascular disease and identify individualized prevention strategies--a targeted evidence-based review. *Genet Med.* 2010;12(12):772-84. PMID:21045709
211. Wilt TJ, MacDonald R, Rutks I, et al. Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Intern Med.* 2008;148(6):435-48. PMID:18252677

**Use of Multi-Gene Panels Involving Single Nucleotide  
Polymorphisms (SNPs) for Prostate Cancer Risk  
Assessment**

**APPENDIXES**



**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

### Level 1 Title and Abstract Screening Form

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

YES/Can't tell

NO (STOP)

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

**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 (STOP)

### Level 2 Screening Form

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

YES

NO (exclude)

2. **Does this study include some proportion of HUMAN subjects who are free of prostate cancer at the baseline start of the study?**

YES

NO – 100% have PrCA (exclude)

3. **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...)

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

**Yes = Affymetrix, Illumina, Seqneme 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)

5. **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? \_\_\_\_\_

**Level 3 Screening 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-characterisation containing SNPs associated with Prostate Cancer in previous studies (Continue)
- UNSURE, Not sure (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)

**SNP Data Abstraction Form**

Name: \_\_\_\_\_ Date: \_\_\_\_\_

Please answer the following questions in regards 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])

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2. Setting (in which participants recruited):

- Hospitals
- Outpatient clinics
- Screening centres
- Registries
- Other (Specify) \_\_\_\_\_

3. Location (country, region, cities):

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---

4. Dates of data collection: \_\_\_\_\_ to \_\_\_\_\_

Study Participants

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

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2. Sources and methods of selection:

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3. Number assessed for eligibility:

--	--	--	--	--

SNPs

1. Number genotyped and considered for inclusion in panel:

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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])

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6. Concordance rate for duplicate samples:

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7. Any other quality control checks (Specify):

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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)

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

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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: \_\_\_\_\_

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b. Proportion of cases with aggressive disease: \_\_\_\_\_%

9. Risk Score: \_\_\_\_\_

10. AUC: \_\_\_\_\_

11.  $\Delta$ AUC: \_\_\_\_\_

12. Other measure: \_\_\_\_\_

13. Subgroup analysis of risk score, AUC,  $\Delta$ AUC or other measure:

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14. Results of validation (if relevant):

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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

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

## Excluded Studies

Adeyemo A, Rotimi C. Genetic variants associated with complex human diseases show wide variation across multiple populations. *Public Health Genomics* 2010;13(2):72-9. PMID:19439916 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Agalliu I, Karlins E, Kwon EM, et al. Rare germline mutations in the BRCA2 gene are associated with early-onset prostate cancer. *British Journal of Cancer* 2007;97(6):826-31. PMID:17700570 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

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. *Cancer Causes & Control* 2010;21(2):289-300. PMID:19902366 OVID-Medline.  
Exclude: Did not use SNP assembled panel

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

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). *Human Molecular Genetics* 2009;18(19):3749-57. PMID:19574343 OVID-Medline.  
Exclude: Test not commercially available

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 Olama AA, Kote-Jarai Z, Giles GG, et al. Multiple loci on 8q24 associated with prostate cancer susceptibility. *Nature Genetics* 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. *Urologia Internationalis* 2007;79(4):312-5. PMID:18025848 OVID-Medline.  
Exclude: Test not commercially available

Allin KH, Nordestgaard BG, Zacho J, et al. C-reactive protein and the risk of cancer: a mendelian randomization study. *Journal of the National Cancer Institute* 2010;102(3):202-6. PMID:20056955 OVID-Medline.  
Exclude: Study not about prostate cancer

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

Andreassen CN, Alsner J. Genetic variants and normal tissue toxicity after radiotherapy: A systematic review. *Radiotherapy and Oncology* 2009;92(3):299-309. OVID-Embase.  
Exclude: Study not about prostate cancer

Angele S, Falconer A, Edwards SM, et al. ATM polymorphisms as risk factors for prostate cancer development. *British Journal of Cancer* 2004;91(4):783-7. OVID-Embase.  
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 Biochemistry and Function* 2008;26(7):771-7. OVID-Embase.  
Exclude: Test not commercially available

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: Doesn't include test panel

Azria D, Ozsahin M, Kramar A, et al. Single nucleotide polymorphisms, apoptosis, and the development of severe late adverse effects after radiotherapy. *Clinical Cancer Research* 2008;14(19):6284-8. PMID:18829510 OVID-Medline.  
Exclude: Study 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. *Human Genetics* 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. *Current Pharmaceutical Design* 2010;16(6):718-24. OVID-Embase. 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 Cancer & Prostatic Diseases* 2006;9(1):50-5. PMID:16247489 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. *International Journal of Cancer* 2008;122(12):2876-9. PMID:18360876 OVID-Medline. Exclude: Test not commercially available

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

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. *Journal of Urology* 2009;182(4):1614-20. PMID:19683737 OVID-Medline. Exclude: Test not commercially available

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 approach

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. *Cancer Epidemiology, Biomarkers & Prevention* 2010;19(2):588-99. PMID:20086112 OVID-Medline. Exclude: Candidate gene approach

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. *Human Genetics* 2009;126(5):637-42. PMID:19568772 OVID-Medline. Exclude: Genome wide association study GWA

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

Brand TC, Bermejo C, Canby-Hagino E, et al. Association of polymorphisms in TGFBI and prostate cancer prognosis. *Journal of Urology* 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. *Cancer Epidemiology, Biomarkers & Prevention* 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. Gudmundsson J, Sulem P, Rafnar T, Bergthorsson JT, Manolescu A, Gudbjartsson D, Agnarsson BA, Sigurdsson A, Benediksdottir KR, Blondal T, Jakobsdottir M, Stacey SN, Kostic J, Kristinsson KT, Birgisdottir B, Ghosh S, Magnusdottir DN, Thorlacius S, Thorleifsson G, Zheng SL, Sun J, Chang BL, Elmore JB, Breyer JP. *Urologic Oncology: Seminars and Original Investigations* 2008;26(5):569-70. OVID-Embase. Exclude: Study design

Brooks J. Multiple loci identified in a genome-wide association study of prostate cancer. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E. *Urologic Oncology: Seminars and Original Investigations* 2008;26(5):571 OVID-Embase. Exclude: Study design

Brooks J. Multiple newly identified loci associated with prostate cancer susceptibility. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Arden-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM. *Urologic Oncology: Seminars and Original Investigations* 2008;26(5):570 OVID-Embase. Exclude: Study design

Burmester JK, Suarez BK, Lin JH, et al. Analysis of candidate genes for prostate cancer. *Human Heredity* 2004;57(4):172-8. PMID:15583422 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. *American Journal of Human Genetics* 2002;71(6):1475-8. PMID:12515253 OVID-Medline. Exclude: Test not commercially available

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. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(4):1290-4. PMID:19336566 OVID-Medline.  
Exclude: Did not use SNP assembled panel

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. *European Journal of Human Genetics* 2001;9(2):135-42. PMID:11313747 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

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

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 [Electronic Resource]* 2009;4(8):e6523 PMID:19654868 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. *Cancer Research* 2002;62(6):1784-9. PMID:11912155 OVID-Medline.  
Exclude: Test not commercially available

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, Zheng SL, Isaacs SD, et al. Polymorphisms in the CYP1A1 gene are associated with prostate cancer risk. *International Journal of Cancer* 2003;106(3):375-8. PMID:12845676 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

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

Chang BL, Zheng SL, Isaacs SD, et al. A polymorphism in the CDKN1B gene is associated with increased risk of hereditary prostate cancer. *Cancer Research* 2004;64(6):1997-9. PMID:15026335 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

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. *Cancer Research* 2007;67(9):4098-103. PMID:17483320 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

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. *Human Molecular Genetics* 2009;18(7):1368-75. PMID:19153072 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

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. *Molecular Medicine Reports* 2008;1(4):525-30. OVID-Embase.  
Exclude: Test not commercially available

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

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

Chen YC, Giovannucci E, Lazarus R, et al. Sequence variants of Toll-like receptor 4 and susceptibility to prostate cancer. *Cancer Research* 2005;65(24):11771-8. PMID:16357190 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Chen YC, Kraft P, Bretsky P, et al. Sequence variants of estrogen receptor beta and risk of prostate cancer in the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(10):1973-81. PMID:17932344 OVID-Medline.  
Exclude: Test not commercially available

Chen YC, Giovannucci E, Kraft P, et al. Association between Toll-like receptor gene cluster (TLR6, TLR1, and TLR10) and prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(10):1982-9. PMID:17932345 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Chen YC, Giovannucci E, Kraft P, et al. Sequence variants of *elaC* homolog 2 (*Escherichia coli*) (ELAC2) gene and susceptibility to prostate cancer in the Health Professionals Follow-Up Study. *Carcinogenesis* 2008;29(5):999-1004. PMID:18375959 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Cheng I, Stram DO, Penney KL, et al. Common genetic variation in IGF1 and prostate cancer risk in the Multiethnic Cohort. *Journal of the National Cancer Institute* 2006;98(2):123-34. PMID:16418515 OVID-Medline.  
Exclude: Test not commercially available

Cheng I, Penney KL, Stram DO, et al. Haplotype-based association studies of IGFBP1 and IGFBP3 with prostate and breast cancer risk: the multiethnic cohort. *Cancer Epidemiology, Biomarkers & Prevention* 2006;15(10):1993-7. PMID:17035411 OVID-Medline.  
Exclude: Test not commercially available

Cheng I, Liu X, Plummer SJ, et al. COX2 genetic variation, NSAIDs, and advanced prostate cancer risk. *British Journal of Cancer* 2007;97(4):557-61. PMID:17609663 OVID-Medline.  
Exclude: Test not commercially available

Cheng I, Krumroy LM, Plummer SJ, et al. MIC1 and IL1RN genetic variation and advanced prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(6):1309-11. PMID:17548705 OVID-Medline.  
Exclude: Test not commercially available

Cheng I, Plummer SJ, Casey G, et al. Toll-like receptor 4 genetic variation and advanced prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(2):352-5. PMID:17301271 OVID-Medline.  
Exclude: Test not commercially available

Cheng I, Plummer SJ, Jorgenson E, et al. 8q24 and prostate cancer: association with advanced disease and meta-analysis. *European Journal of Human Genetics* 2008;16(4):496-505. PMID:18231127 OVID-Medline.  
Exclude: Test not commercially available

Cheng Y, Kim JW, Liu W, et al. Genetic and epigenetic inactivation of TNFRSF10C in human prostate cancer. *Prostate* 2009;69(3):327-35. PMID:19035483 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Chiang C-H, Chen K-K, Chang LS, et al. The impact of polymorphism on prostate specific antigen gene on the risk, tumor volume and pathological stage of prostate cancer. *Journal of Urology* 2004;171(4):1529-32. OVID-Embase.  
Exclude: Test not commercially available

Chu LW, Zhu Y, Yu K, et al. Variants in circadian genes and prostate cancer risk: a population-based study in China. *Prostate Cancer & Prostatic Diseases* 2008;11(4):342-8. PMID:17984998 OVID-Medline.  
Exclude: Test not commercially available

Cicek MS, Liu X, Casey G, et al. Role of androgen metabolism genes CYP1B1, PSA/KLK3, and CYP11alpha in prostate cancer risk and aggressiveness. *Cancer Epidemiology Biomarkers and Prevention* 2005;14(9):2173-7. OVID-Embase.  
Exclude: Test not commercially available

Collin SM, Metcalfe C, Zuccolo L, et al. Association of folate-pathway gene polymorphisms with the risk of prostate cancer: A population-based nested case-control study, systematic review, and meta-analysis. *Cancer Epidemiology Biomarkers and Prevention* 2009;18(9):2528-39. OVID-Embase.  
Exclude: Test not commercially available

Cooper ML, Adami HO, Gronberg H, et al. Interaction between single nucleotide polymorphisms in selenoprotein P and mitochondrial superoxide dismutase determines prostate cancer risk. *Cancer Research* 2008;68(24):10171-7. PMID:19074884 OVID-Medline.  
Exclude: Test not commercially available

Costa S, Pinto D, Morais A, et al. Acetylation genotype and the genetic susceptibility to prostate cancer in a Southern European population. *Prostate* 2005;64(3):246-52. OVID-Embase.  
Exclude: Test not commercially available

Cunningham JM, Hebring SJ, McDonnell SK, et al. Evaluation of genetic variations in the androgen and estrogen metabolic pathways as risk factors for sporadic and familial prostate cancer. *Cancer Epidemiology Biomarkers and Prevention* 2007;16(5):969-78. OVID-Embase.  
Exclude: Test not commercially available

Cussenot O, Azzouzi AR, Bantsimba-Malanda G, et al. Effect of genetic variability within 8q24 on aggressiveness patterns at diagnosis and familial status of prostate cancer. *Clinical Cancer Research* 2008;14(17):5635-9. PMID:18765558 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Cybulski C, Gorski B, Huzarski T, et al. CHEK2 is a multiorgan cancer susceptibility gene. *American Journal of Human Genetics* 2004;75(6):1131-5. PMID:15492928 OVID-Medline.  
Exclude: Test not commercially available

Cybulski C, Gorski B, Debnick T, et al. NBS1 Is a Prostate Cancer Susceptibility Gene. *Cancer Research* 2004;64(4):1215-9. OVID-Embase.  
Exclude: Test not commercially available

Danforth KN, Hayes RB, Rodriguez C, et al. Polymorphic variants in PTGS2 and prostate cancer risk: results from two large nested case-control studies. *Carcinogenesis* 2008;29(3):568-72. PMID:17999989 OVID-Medline.  
Exclude: Test not commercially available

Danforth KN, Rodriguez C, Hayes RB, et al. TNF polymorphisms and prostate cancer risk. *Prostate* 2008;68(4):400-7. PMID:18196539 OVID-Medline.  
Exclude: Test not commercially available

Daugherty SE, Shugart YY, Platz EA, et al. Polymorphic variants in alpha-methylacyl-CoA racemase and prostate cancer. *Prostate* 2007;67(14):1487-97. PMID:17680641 OVID-Medline.  
Exclude: Test not commercially available

- Ding Y, Larson G, Rivas G, et al. Strong signature of natural selection within an FHIT intron implicated in prostate cancer risk. *PLoS ONE [Electronic Resource]* 2008;3(10):e3533 PMID:18953408 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Dong LM, Potter JD, White E, et al. Genetic susceptibility to cancer: The role of polymorphisms in candidate genes. *JAMA - Journal of the American Medical Association* 2008;299(20):2423-36. OVID-Embase.  
Exclude: Study not about prostate cancer
- Dos Reis ST, Villanova FE, De Andrade PM, et al. Polymorphisms of the matrix metalloproteinases associated with prostate cancer. *Molecular Medicine Reports* 2008;1(4):517-20. OVID-Embase.  
Exclude: Test not commercially available
- Dos Santos RM, De Jesus CMN, Trindade Filho JCS, et al. PSA and androgen-related gene (AR, CYP17, and CYP19) polymorphisms and the risk of adenocarcinoma at prostate biopsy. *DNA and Cell Biology* 2008;27(9):497-503. OVID-Embase.  
Exclude: Test not commercially available
- dos SA, Ribeiro ML, Mesquita JC, et al. No association of the 5' promoter region polymorphism of CYP17 gene with prostate cancer risk. *Prostate cancer and prostatic diseases* 2002;5(1):28-31. OVID-Embase.  
Exclude: Test not commercially available
- Dossus L, Kaaks R, Canzian F, et al. PTGS2 and IL6 genetic variation and risk of breast and prostate cancer: results from the Breast and Prostate Cancer Cohort Consortium (BPC3). *Carcinogenesis* 2010;31(3):455-61. PMID:19965896 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Douglas JA, Zuhlke KA, Beebe-Dimmer J, et al. Identifying susceptibility genes for prostate cancer--a family-based association study of polymorphisms in CYP17, CYP19, CYP11A1, and LH-beta. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14(8):2035-9. PMID:16103457 OVID-Medline.  
Exclude: Test not commercially available
- Douglas JA, Levin AM, Zuhlke KA, et al. Common variation in the BRCA1 gene and prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(7):1510-6. PMID:17585057 OVID-Medline.  
Exclude: Test not commercially available
- Duggan D, Zheng SL, Knowlton M, et al. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. *Journal of the National Cancer Institute* 2007;99(24):1836-44. PMID:18073375 OVID-Medline.  
Exclude: Genome wide association study GWA
- Eder T, Mayer R, Langsenlehner U, et al. Interleukin-10 [ATA] promoter haplotype and prostate cancer risk: A population-based study. *European Journal of Cancer* 2007;43(3):472-5. OVID-Embase.  
Exclude: Test not commercially available
- Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. *Nature Genetics* 2009;41(10):1116-21. PMID:19767753 OVID-Medline.  
Exclude: Genome wide association study GWA
- Eklund CM, Tammela TL, Schleutker J, et al. C-reactive protein haplotype is associated with high PSA as a marker of metastatic prostate cancer but not with overall cancer risk. *British Journal of Cancer* 2009;100(12):1846-51. PMID:19436291 OVID-Medline.  
Exclude: Test not commercially available
- Eriksson AL, Lorentzon M, Vandenput L, et al. Genetic variations in sex steroid-related genes as predictors of serum estrogen levels in men. *Journal of Clinical Endocrinology & Metabolism* 2009;94(3):1033-41. PMID:19116238 OVID-Medline.  
Exclude: Study not about prostate cancer
- Eroglu A, Ulu A, Cam R, et al. Plasminogen activator inhibitor-1 gene 4G/5G polymorphism in cancer patients. *Journal of B* 2007;12(1):135-6. PMID:17436417 OVID-Medline.  
Exclude: Study not about prostate cancer
- Eroglu A, Gulec S, Akar N. Vascular endothelial growth factor C936T polymorphism in cancer patients with thrombosis. *American Journal of Hematology* 2007;82(2):174 PMID:16917915 OVID-Medline.  
Exclude: Study not about prostate cancer
- Eroglu A, Ozturk A, Cam R, et al. Intron F G79A polymorphism of the protein Z gene in cancer patients with and without thrombosis. *Journal of Thrombosis & Thrombolysis* 2009;27(2):204-6. PMID:18246466 OVID-Medline.  
Exclude: Study not about prostate cancer
- Fall K, Stark JR, Mucci LA, et al. No association between a polymorphic variant of the IRS-1 gene and prostate cancer risk. *Prostate* 2008;68(13):1416-20. PMID:18615538 OVID-Medline.  
Exclude: Doesn't include test panel
- Fang S, Krahe R, Lozano G, et al. Effects of MDM2, MDM4 and TP53 codon 72 polymorphisms on cancer risk in a cohort study of carriers of TP53 germline mutations. *PLoS ONE [Electronic Resource]* 2010;5(5):e10813 PMID:20520810 OVID-Medline.  
Exclude: Study not about prostate cancer
- Faupel-Badger JM, Kidd LC, Albanes D, et al. Association of IL-10 polymorphisms with prostate cancer risk and grade of disease. *Cancer Causes & Control* 2008;19(2):119-24. PMID:17999153 OVID-Medline.  
Exclude: Test not commercially available

- Feik E, Baierl A, Madersbacher S, et al. Common genetic polymorphisms of AURKA and prostate cancer risk. *Cancer Causes & Control* 2009;20(2):147-52. PMID:18802780 OVID-Medline.  
Exclude: Test not commercially available
- Fernandez P, de Beer PM, van der Merwe L, et al. COX-2 promoter polymorphisms and the association with prostate cancer risk in South African men. *Carcinogenesis* 2008;29(12):2347-50. PMID:18974063 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Fitzgerald LM, Agalliu I, Johnson K, et al. Association of TMPRSS2-ERG gene fusion with clinical characteristics and outcomes: results from a population-based study of prostate cancer. *BMC Cancer* 2008;8:230 PMID:18694509 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline
- Fitzgerald LM, Thomson R, Polanowski A, et al. Sequence variants of alpha-methylacyl-CoA racemase are associated with prostate cancer risk: a replication study in an ethnically homogeneous population. *Prostate* 2008;68(13):1373-9. PMID:18537123 OVID-Medline.  
Exclude: Test not commercially available
- Fitzgerald LM, Patterson B, Thomson R, et al. Identification of a prostate cancer susceptibility gene on chromosome 5p13q12 associated with risk of both familial and sporadic disease. *European Journal of Human Genetics* 2009;17(3):368-77. PMID:18830231 OVID-Medline.  
Exclude: Genome wide association study GWA
- Fitzgerald LM, Karlins E, Karyadi DM, et al. Association of FGFR4 genetic polymorphisms with prostate cancer risk and prognosis. *Prostate Cancer & Prostatic Diseases* 2009;12(2):192-7. PMID:18762813 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Fitzgerald LM, Kwon EM, Koopmeiners JS, et al. Analysis of recently identified prostate cancer susceptibility loci in a population-based study: associations with family history and clinical features. *Clinical Cancer Research* 2009;15(9):3231-7. PMID:19366831 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Foley R, Marignol L, Thomas AZ, et al. The HIF-1alpha C1772T polymorphism may be associated with susceptibility to clinically localised prostate cancer but not with elevated expression of hypoxic biomarkers. *Cancer Biology and Therapy* 2009;8(2):118-24. OVID-Embase.  
Exclude: Test not commercially available
- Folsom AR, Pankow JS, Peacock JM, et al. Variation in TCF7L2 and increased risk of colon cancer: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 2008;31(5):905-9. PMID:18268068 OVID-Medline.  
Exclude: Test not commercially available
- Forszt P, Pilecka A, Malodobra M, et al. Single-nucleotide polymorphism association study of VDR and CDH1 genes and the risk of prostate cancer. *Advances in Clinical and Experimental Medicine* 2009;18(3):215-20. OVID-Embase.  
Exclude: Candidate gene approach
- Fradet V, Cheng I, Casey G, et al. Dietary omega-3 fatty acids, cyclooxygenase-2 genetic variation, and aggressive prostate cancer risk. *Clinical Cancer Research* 2009;15(7):2559-66. PMID:19318492 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Fredriksson H, Ikonen T, Autio V, et al. Identification of germline MLH1 alterations in familial prostate cancer. *European Journal of Cancer* 2006;42(16):2802-6. PMID:16963262 OVID-Medline.  
Exclude: Test not commercially available
- Freedman ML, Pearce CL, Penney KL, et al. Systematic evaluation of genetic variation at the androgen receptor locus and risk of prostate cancer in a multiethnic cohort study. *American Journal of Human Genetics* 2005;76(1):82-90. PMID:15570555 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Friedrichsen DM, Stanford JL, Isaacs SD, et al. Identification of a prostate cancer susceptibility locus on chromosome 7q11-21 in Jewish families. *Proceedings of the National Academy of Sciences of the United States of America* 2004;101(7):1939-44. PMID:14769943 OVID-Medline.  
Exclude: Test not commercially available
- Gao R, Price DK, Dahut WL, et al. Genetic polymorphisms in XRCC1 associated with radiation therapy in prostate cancer. *Cancer Biology and Therapy* 2010;10(1):13-8. OVID-Embase.  
Exclude: Test not commercially available
- Gardner ER, Ahlers CM, Shukla S, et al. Association of the ABCG2 C421A polymorphism with prostate cancer risk and survival. *BJU International* 2008;102(11):1694-9. PMID:18710444 OVID-Medline.  
Exclude: Test not commercially available
- Gelmann EP, Steadman DJ, Ma J, et al. Occurrence of NKX3.1 C154T polymorphism in men with and without prostate cancer and studies of its effect on protein function. *Cancer Research* 2002;62(9):2654-9. OVID-Embase.  
Exclude: Test not commercially available
- Ghousaini M, Song H, Koessler T, et al. Multiple loci with different cancer specificities within the 8q24 gene desert. *Journal of the National Cancer Institute* 2008;100(13):962-6. PMID:18577746 OVID-Medline.  
Exclude: Test not commercially available
- Grindedal EM, Moller P, Eeles R, et al. Germ-line mutations in mismatch repair genes associated with prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(9):2460-7. PMID:19723918 OVID-Medline.  
Exclude: Doesn't include test panel

Gudmundsson J, Sulem P, Manolescu A, et al. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. *Nature Genetics* 2007;39(5):631-7. PMID:17401366 OVID-Medline.  
Exclude: Genome wide association study GWA

Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. *Nature Genetics* 2007;39(8):977-83. PMID:17603485 OVID-Medline.  
Exclude: Genome wide association study GWA

Gudmundsson J, Sulem P, Rafnar T, et al. Common sequence variants on 2p15 and Xp11.22 confer susceptibility to prostate cancer. *Nature Genetics* 2008;40(3):281-3. PMID:18264098 OVID-Medline.  
Exclude: Genome wide association study GWA

Gudmundsson J, Sulem P, Gudbjartsson DF, et al. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. *Nature Genetics* 2009;41(10):1122-6. PMID:19767754 OVID-Medline.  
Exclude: Genome wide association study GWA

Gunes S, Bagci H, Sarikaya S, et al. Prostate-specific antigen and 17-hydroxylase polymorphic genotypes in patients with prostate cancer and benign prostatic hyperplasia. *DNA and Cell Biology* 2007;26(12):873-8. OVID-Embase.  
Exclude: Test not commercially available

Habuchi T, Liqing Z, Suzuki T, et al. Increased risk of prostate cancer and benign prostatic hyperplasia associated with a CYP17 gene polymorphism with a gene dosage effect. *Cancer Research* 2000;60(20):5710-3. PMID:11059764 OVID-Medline.  
Exclude: Test not commercially available

Haiman CA, Stram DO, Cheng I, et al. Common genetic variation at PTEN and risk of sporadic breast and prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2006;15(5):1021-5. PMID:16702386 OVID-Medline.  
Exclude: Test not commercially available

Haiman CA, Patterson N, Freedman ML, et al. Multiple regions within 8q24 independently affect risk for prostate cancer. *Nature Genetics* 2007;39(5):638-44. PMID:17401364 OVID-Medline.  
Exclude: Candidate gene approach

Hajdinjak T, Toplak N. E-Cadherin Polymorphism - 160 C/A and Prostate Cancer. *International Journal of Cancer* 2004;109(3):480-1. OVID-Embase.  
Exclude: Doesn't include test panel

Hajdinjak T, Zagradisnik B. Prostate cancer and polymorphism D85Y in gene for dihydrotestosterone degrading enzyme UGT2B15: Frequency of DD homozygotes increases with Gleason score. *Prostate* 2004;59(4):436-9. OVID-Embase.  
Exclude: Test not commercially available

Hamada A, Sissung T, Price DK, et al. Effect of SLC01B3 haplotype on testosterone transport and clinical outcome in caucasian patients with androgen-Independent prostatic cancer. *Clinical Cancer Research* 2008;14(11):3312-8. OVID-Embase.  
Exclude: Test not commercially available

Hamano T, Matsui H, Sekine Y, et al. Association of SNPs rs1447295 and microsatellite marker DG8S737 with familial prostate cancer and high grade disease. *Journal of Urology* 2010;184(2):738-42. PMID:20639049 OVID-Medline.  
Exclude: Test not commercially available

Hampel H, Sweet K, Westman JA, et al. Referral for cancer genetics consultation: a review and compilation of risk assessment criteria. *Journal of Medical Genetics* 2004;41(2):81-91. PMID:14757853 OVID-Medline.  
Exclude: Test not commercially available

Hawkins GA, Mychaleckyj JC, Zheng SL, et al. Germline sequence variants of the LZTS1 gene are associated with prostate cancer risk. *Cancer Genetics & Cytogenetics* 2002;137(1):1-7. PMID:12377406 OVID-Medline.  
Exclude: Test not commercially available

Hawkins GA, Cramer SD, Zheng SL, et al. Sequence variants in the human 25-hydroxyvitamin D3 1-alpha-hydroxylase (CYP27B1) gene are not associated with prostate cancer risk. *Prostate* 2002;53(3):175-8. PMID:12386916 OVID-Medline.  
Exclude: Test not commercially available

Hayashi T, Imai K, Morishita Y, et al. Identification of the NKG2D haplotypes associated with natural cytotoxic activity of peripheral blood lymphocytes and cancer immunosurveillance. *Cancer Research* 2006;66(1):563-70. PMID:16397273 OVID-Medline.  
Exclude: Study not about prostate cancer

Hayes VM, Severi G, Eggleton SA, et al. The E211 G>A androgen receptor polymorphism is associated with a decreased risk of metastatic prostate cancer and androgenetic alopecia. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14(4):993-6. PMID:15824176 OVID-Medline.  
Exclude: Test not commercially available

Hayes VM, Severi G, Padilla EJ, et al. 5alpha-Reductase type 2 gene variant associations with prostate cancer risk, circulating hormone levels and androgenetic alopecia. *International Journal of Cancer* 2007;Journal international du cancer. 120(4):776-80. OVID-Embase.  
Exclude: SNP(s) assessment in single gene only

Hedelin M, Balter KA, Chang ET, et al. Dietary intake of phytoestrogens, estrogen receptor-beta polymorphisms and the risk of prostate cancer. *Prostate* 2006;66(14):1512-20. PMID:16921512 OVID-Medline.  
Exclude: Test not commercially available

Hedelin M, Chang ET, Wiklund F, et al. Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. *International Journal of Cancer* 2007;120(2):398-405. PMID:17066444 OVID-Medline.

Exclude: SNP(s) assessment in single gene only

Hein DW, Leff MA, Ishibe N, et al. Association of prostate cancer with rapid N-acetyltransferase 1 (NAT1\*10) in combination with slow N-acetyltransferase 2 acetylator genotypes in a pilot case-control study. *Environmental & Molecular Mutagenesis* 2002;40(3):161-7. PMID:12355549 OVID-Medline.

Exclude: Test not commercially available

Helfand BT, Loeb S, Meeks JJ, et al. Pathological Outcomes Associated With the 17q Prostate Cancer Risk Variants. *Journal of Urology* 2009;181(6):2502-7. OVID-Embase.

Exclude: Did not use SNP assembled panel

Hernandez-Saavedra D, McCord JM. Association of a new intronic polymorphism of the SOD2 gene (G1677T) with cancer. *Cell Biochemistry & Function* 2009;27(4):223-7. PMID:19405048 OVID-Medline.

Exclude: Test not commercially available

Hernandez J, Balic I, Johnson-Pais TL, et al. Association between an estrogen receptor alpha gene polymorphism and the risk of prostate cancer in black men. *Journal of Urology* 2006;175(2):523-7. PMID:16406987 OVID-Medline.

Exclude: Test not commercially available

Hernandez W, Grenade C, Santos ER, et al. IGF-1 and IGFBP-3 gene variants influence on serum levels and prostate cancer risk in African-Americans. *Carcinogenesis* 2007;28(10):2154-9. PMID:17724372 OVID-Medline.

Exclude: Test not commercially available

Hirata H, Hinoda Y, Kikuno N, et al. CXCL12 G801A polymorphism is a risk factor for sporadic prostate cancer susceptibility. *Clinical Cancer Research* 2007;13(17):5056-62. PMID:17785557 OVID-Medline.

Exclude: Test not commercially available

Hirata H, Hinoda Y, Kawamoto K, et al. Mismatch Repair Gene MSH3 Polymorphism is Associated With the Risk of Sporadic Prostate Cancer. *Journal of Urology* 2008;179(5):2020-4. OVID-Embase.

Exclude: Test not commercially available

Hirata H, Hinoda Y, Kikuno N, et al. Bcl2 -938C/A Polymorphism Carries Increased Risk of Biochemical Recurrence After Radical Prostatectomy. *Journal of Urology* 2009;181(4):1907-12. OVID-Embase.

Exclude: Test not commercially available

Ho CK, Anwar S, Nanda J, et al. FGFR4 Gly388Arg polymorphism and prostate cancer risk in Scottish men. *Prostate Cancer & Prostatic Diseases* 2010;13(1):94-6. PMID:19918264 OVID-Medline.

Exclude: Test not commercially available

Holick CN, Stanford JL, Kwon EM, et al. Comprehensive association analysis of the vitamin D pathway genes, VDR, CYP27B1, and CYP24A1, in prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(10):1990-9. PMID:17932346 OVID-Medline.

Exclude: Did not use SNP assembled panel

Holt SK, Karyadi DM, Kwon EM, et al. Association of megalin genetic polymorphisms with prostate cancer risk and prognosis. *Clinical Cancer Research* 2008;14(12):3823-31. PMID:18559602 OVID-Medline.

Exclude: Candidate gene approach

Holt SK, Kwon EM, Lin DW, et al. Association of hepsin gene variants with prostate cancer risk and prognosis. *Prostate* 2010;70(9):1012-9. PMID:20166135 OVID-Medline.

Exclude: Candidate gene approach

Hooker S, Bonilla C, Akereyeni F, et al. NAT2 and NER genetic variants and sporadic prostate cancer susceptibility in African-Americans. *Prostate Cancer & Prostatic Diseases* 2008;11(4):349-56. PMID:18026184 OVID-Medline.

Exclude: Did not use SNP assembled panel

Hooker S, Hernandez W, Chen H, et al. Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African-Americans. *Prostate* 2010;70(3):270-5. PMID:19902474 OVID-Medline.

Exclude: Did not use SNP assembled panel

Hsu FC, Sun J, Wiklund F, et al. A novel prostate cancer susceptibility locus at 19q13. *Cancer Research* 2009;69(7):2720-3. PMID:19318570 OVID-Medline.

Exclude: Genome wide association study GWA

Huang SP, Huang LC, Ting WC, et al. Prognostic significance of prostate cancer susceptibility variants on prostate-specific antigen recurrence after radical prostatectomy. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(11):3068-74. PMID:19900942 OVID-Medline.

Exclude: Doesn't include any patients without PC at baseline

Huang SP, Ting WC, Chen LM, et al. Association analysis of Wnt pathway genes on prostate-specific antigen recurrence after radical prostatectomy. *Annals of Surgical Oncology* 2010;17(1):312-22. PMID:19777185 OVID-Medline.

Exclude: Did not use SNP assembled panel

Huse K, Taudien S, Groth M, et al. Genetic variants of the copy number polymorphic beta-defensin locus are associated with sporadic prostate cancer. *Tumour Biology* 2008;29(2):83-92. PMID:18515986 OVID-Medline.

Exclude: Doesn't include any patients without PC at baseline

Ikonen T, Matikainen MP, Syrjakoski K, et al. BRCA1 and BRCA2 mutations have no major role in predisposition to prostate cancer in Finland. *Journal of Medical Genetics* 2003;40(8):e98 PMID:12920090 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Iughetti P, Suzuki O, Godoi PHC, et al. A polymorphism in endostatin, an angiogenesis inhibitor, predisposes for the development of prostatic adenocarcinoma. *Cancer Research* 2001;61(20):7375-8. OVID-Embase.  
Exclude: Test not commercially available

Jacobs EJ, Hsing AW, Bain EB, et al. Polymorphisms in angiogenesis-related genes and prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2008;17(4):972-7. PMID:18398039 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Jakobsson J, Karypidis H, Johansson JE, et al. A functional C-G polymorphism in the CYP7B1 promoter region and its different distribution in Orientals and Caucasians. *Pharmacogenomics Journal* 2004;4(4):245-50. PMID:15007371 OVID-Medline.  
Exclude: Test not commercially available

Jakobsson J, Palonek E, Lorentzon M, et al. A novel polymorphism in the 17beta-hydroxysteroid dehydrogenase type 5 (aldo-keto reductase 1C3) gene is associated with lower serum testosterone levels in caucasian men. *Pharmacogenomics Journal* 2007;7(4):282-9. PMID:16983398 OVID-Medline.  
Exclude: Study not about prostate cancer

Jesser C, Mucci L, Farmer D, et al. Effects of G/A polymorphism, rs266882, in the androgen response element 1 of the PSA gene on prostate cancer risk, survival and circulating PSA levels. *British Journal of Cancer* 2008;99(10):1743-7. OVID-Embase.  
Exclude: Test not commercially available

Johansson M, McKay JD, Stattin P, et al. Comprehensive evaluation of genetic variation in the IGF1 gene and risk of prostate cancer. *International Journal of Cancer* 2007;120(3):539-42. PMID:17096324 OVID-Medline.  
Exclude: Test not commercially available

Johansson M, McKay JD, Wiklund F, et al. Implications for prostate cancer of insulin-like growth factor-I (IGF-I) genetic variation and circulating IGF-I levels. *Journal of Clinical Endocrinology & Metabolism* 2007;92(12):4820-6. PMID:17911177 OVID-Medline.  
Exclude: Test not commercially available

Johansson M, Van GB, Hultdin J, et al. The MTHFR 677C --> T polymorphism and risk of prostate cancer: results from the CAPS study. *Cancer Causes & Control* 2007;18(10):1169-74. PMID:17846906 OVID-Medline.  
Exclude: Test not commercially available

Johansson M, McKay JD, Wiklund F, et al. Genetic variation in the SST gene and its receptors in relation to circulating levels of insulin-like growth factor-I, IGFBP3, and prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(5):1644-50. PMID:19423539 OVID-Medline.  
Exclude: Test not commercially available

Johansson M, McKay JD, Rinaldi S, et al. Genetic and plasma variation of insulin-like growth factor binding proteins in relation to prostate cancer incidence and survival. *Prostate* 2009;69(12):1281-91. PMID:19455605 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Kaklamani V, Baddi L, Rosman D, et al. No major association between TGFBR1\*6A and prostate cancer. *BMC Genetics* 2004;5:28 PMID:15385056 OVID-Medline.  
Exclude: Test not commercially available

Kammerer S, Roth RB, Reneland R, et al. Large-scale association study identifies ICAM gene region as breast and prostate cancer susceptibility locus. *Cancer Research* 2004;64(24):8906-10. PMID:15604251 OVID-Medline.  
Exclude: Genome wide association study GWA

Kang D, Lee KM, Park SK, et al. Lack of association of transforming growth factor-beta1 polymorphisms and haplotypes with prostate cancer risk in the prostate, lung, colorectal, and ovarian trial. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(6):1303-5. PMID:17548703 OVID-Medline.  
Exclude: Test not commercially available

Kesarwani P, Mandhani A, Mittal RD. Polymorphisms in tumor necrosis factor-A gene and prostate cancer risk in North Indian cohort. *Journal of Urology* 2009;182(6):2938-43. PMID:19846139 OVID-Medline.  
Exclude: Test not commercially available

Kessler T, Wissenbach U, Grobholz R, et al. TRPV6 alleles do not influence prostate cancer progression. *BMC Cancer* 2009;9:380 PMID:19857260 OVID-Medline.  
Exclude: Test not commercially available

Kibel AS, Suarez BK, Belani J, et al. CDKN1A and CDKN1B polymorphisms and risk of advanced prostate carcinoma. *Cancer Research* 2003;63(9):2033-6. PMID:12727815 OVID-Medline.  
Exclude: Test not commercially available

Kibel AS. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Urologic Oncology: Seminars and Original Investigations* 2007;25(5):447-8. OVID-Embase.  
Exclude: Study not about prostate cancer

Kibel AS, Jin CH, Klim A, et al. Association between polymorphisms in cell cycle genes and advanced prostate carcinoma. *Prostate* 2008;68(11):1179-86. PMID:18459109 OVID-Medline.  
Exclude: Test not commercially available

- Kibel AS. Commentary on Cumulative association of five genetic variants with prostate cancer. *Urologic Oncology: Seminars and Original Investigations* 2009;27(4):462-3. OVID-Embase.  
Exclude: Study not about prostate cancer
- Kidd LC, Paltoo DN, Wang S, et al. Sequence variation within the 5' regulatory regions of the vitamin D binding protein and receptor genes and prostate cancer risk. *Prostate* 2005;64(3):272-82. PMID:15717311 OVID-Medline.  
Exclude: Test not commercially available
- Kiessling AA. Genetic variation in the COX-2 gene and the association with prostate cancer risk. *Chemtracts* 2007;19(3):122-3. OVID-Embase.  
Exclude: SNP(s) assessment in single gene only
- Kim SR, Sai K, Tanaka-Kagawa T, et al. Haplotypes and a novel defective allele of CES2 found in a Japanese population. *Drug Metabolism & Disposition* 2007;35(10):1865-72. PMID:17640957 OVID-Medline.  
Exclude: Study not about prostate cancer
- Kim W, Yoo TK, Kim SJ, et al. Lack of association between Y-chromosomal haplogroups and prostate cancer in the Korean population. *PLoS one* 2007;2(1):e172 OVID-Embase.  
Exclude: Doesn't include test panel
- Klein RJ, Hallden C, Cronin AM, et al. Blood biomarker levels to aid discovery of cancer-related single-nucleotide polymorphisms: kallikreins and prostate cancer. *Cancer Prevention Research* 2010;3(5):611-9. PMID:20424135 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Koike H, Suzuki K, Satoh T, et al. Cyclin D1 gene polymorphism and familial prostate cancer: the AA genotype of A870G polymorphism is associated with prostate cancer risk in men aged 70 years or older and metastatic stage. *Anticancer Research* 2003;23(6D):4947-51. PMID:14981950 OVID-Medline.  
Exclude: Test not commercially available
- Kote-Jarai Z, Jugurnauth S, Mulholland S, et al. A recurrent truncating germline mutation in the BRIP1/FANCD1 gene and susceptibility to prostate cancer. *British Journal of Cancer* 2009;100(2):426-30. PMID:19127258 OVID-Medline.  
Exclude: Test not commercially available
- Koutros S, Berndt SI, Sinha R, et al. Xenobiotic metabolizing gene variants, dietary heterocyclic amine intake, and risk of prostate cancer. *Cancer Research* 2009;69(5):1877-84. PMID:19223546 OVID-Medline.  
Exclude: Candidate gene approach
- Koutros S, Schumacher FR, Hayes RB, et al. Pooled analysis of phosphatidylinositol 3-kinase pathway variants and risk of prostate cancer. *Cancer Research* 2010;70(6):2389-96. PMID:20197460 OVID-Medline.  
Exclude: Candidate gene approach
- Kraft P, Pharoah P, Chanock SJ, et al. Genetic variation in the HSD17B1 gene and risk of prostate cancer. *PLoS Genetics* 2005;1(5):e68 PMID:16311626 OVID-Medline.  
Exclude: Candidate gene approach
- Kumpf O, Hamann L, Schlag PM, et al. Pre- and postoperative cytokine release after in vitro whole blood lipopolysaccharide stimulation and frequent toll-like receptor 4 polymorphisms. *Shock* 2006;25(2):123-8. PMID:16525349 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline
- Kurosaki T, Suzuki M, Enomoto Y, et al. Polymorphism of cytochrome P450 2B6 and prostate cancer risk: a significant association in a Japanese population. *International Journal of Urology* 2009;16(4):364-8. PMID:19425200 OVID-Medline.  
Exclude: Test not commercially available
- Lai J, Kedda M-A, Hinze K, et al. PSA/CLK3 ARE1 promoter polymorphism alters androgen receptor binding and is associated with prostate cancer susceptibility. *Carcinogenesis* 2007;28(5):1032-9. OVID-Embase.  
Exclude: Test not commercially available
- Lange EM, Beebe-Dimmer JL, Ray AM, et al. Genome-wide linkage scan for prostate cancer susceptibility from the University of Michigan Prostate Cancer Genetics Project: suggestive evidence for linkage at 16q23. *Prostate* 2009;69(4):385-91. PMID:19035517 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline
- Langeberg WJ, Tahir SA, Feng Z, et al. Association of caveolin-1 and -2 genetic variants and post-treatment serum caveolin-1 with prostate cancer risk and outcomes. *Prostate* 2010;70(9):1020-35. PMID:20209490 OVID-Medline.  
Exclude: Candidate gene approach
- Langeberg WJ, Kwon EM, Koopmeiners JS, et al. Population-based study of the association of variants in mismatch repair genes with prostate cancer risk and outcomes. *Cancer Epidemiology, Biomarkers & Prevention* 2010;19(1):258-64. PMID:20056646 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Langsenlehner T, Kapp KS, Langsenlehner U. TGFB1 Single-Nucleotide Polymorphisms Are Associated With Adverse Quality of Life in Prostate Cancer Patients Treated With Radiotherapy. In Regard to Peters et al. *International Journal of Radiation Oncology Biology Physics* 2008;71(3):960 OVID-Embase.  
Exclude: Study not about prostate cancer
- Langsenlehner T, Langsenlehner U, Renner W, et al. The Glu228Ala polymorphism in the ligand binding domain of death receptor 4 is associated with increased risk for prostate cancer metastases. *Prostate* 2008;68(3):264-8. PMID:18163425 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

- Langsenlehner T, Langsenlehner U, Renner W, et al. Single nucleotide polymorphisms and haplotypes in the gene for vascular endothelial growth factor and risk of prostate cancer. *European Journal of Cancer* 2008;44(11):1572-6. PMID:18514506 OVID-Medline.  
Exclude: Test not commercially available
- Lavender NA, Benford ML, VanCleave TT, et al. Examination of polymorphic glutathione S-transferase (GST) genes, tobacco smoking and prostate cancer risk among men of African descent: a case-control study. *BMC Cancer* 2009;9:397 PMID:19917083 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Lavender NA, Komolafe OO, Benford M, et al. No association between variant DNA repair genes and prostate cancer risk among men of African descent. *Prostate* 2010;70(2):113-9. PMID:19760636 OVID-Medline.  
Exclude: Candidate gene approach
- Lee KM, Kang D, Park SK, et al. Nitric oxide synthase gene polymorphisms and prostate cancer risk. *Carcinogenesis* 2009;30(4):621-5. PMID:19168583 OVID-Medline.  
Exclude: Test not commercially available
- Levin AM, Ray AM, Zuhlke KA, et al. Association between germline variation in the FHIT gene and prostate cancer in Caucasians and African-Americans. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(6):1294-7. PMID:17548701 OVID-Medline.  
Exclude: Test not commercially available
- Levin AM, Zuhlke KA, Ray AM, et al. Sequence variation in alpha-methylacyl-CoA racemase and risk of early-onset and familial prostate cancer. *Prostate* 2007;67(14):1507-13. PMID:17683075 OVID-Medline.  
Exclude: Test not commercially available
- Levin AM, Machiela MJ, Zuhlke KA, et al. Chromosome 17q12 variants contribute to risk of early-onset prostate cancer. *Cancer Research* 2008;68(16):6492-5. PMID:18701471 OVID-Medline.  
Exclude: Test not commercially available
- Li H, Bublely GJ, Balk SP, et al. Hypoxia-inducible factor-1alpha (HIF-1alpha) gene polymorphisms, circulating insulin-like growth factor binding protein (IGFBP)-3 levels and prostate cancer. *Prostate* 2007;67(12):1354-61. PMID:17624927 OVID-Medline.  
Exclude: Test not commercially available
- Li M, Guan T-Y, Li Y, et al. Polymorphisms of GSTM1 and CYP1A1 genes and their genetic susceptibility to prostate cancer in Chinese men. *Chinese Medical Journal* 2008;121(4):305-8. OVID-Embase.  
Exclude: Did not use SNP assembled panel
- Licastro F, Bertaccini A, Porcellini E, et al. Alpha 1 antichymotrypsin genotype is associated with increased risk of prostate carcinoma and PSA levels. *Anticancer Research* 2008;28(1B):395-9. PMID:18383875 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Lieberfarb ME, Lin M, Lechpammer M, et al. Genome-wide loss of heterozygosity analysis from laser capture microdissected prostate cancer using single nucleotide polymorphic allele (SNP) arrays and a novel bioinformatics platform dChipSNP. *Cancer Research* 2003;63(16):4781-5. PMID:12941794 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline
- Lin HY, Wang W, Liu YH, et al. Comparison of multivariate adaptive regression splines and logistic regression in detecting SNP-SNP interactions and their application in prostate cancer. *Journal of Human Genetics* 2008;53(9):802-11. PMID:18607530 OVID-Medline.  
Exclude: Study design
- Lindmark F, Zheng SL, Wiklund F, et al. H6D polymorphism in macrophage-inhibitory cytokine-1 gene associated with prostate cancer. *Journal of the National Cancer Institute* 2004;96(16):1248-54. PMID:15316060 OVID-Medline.  
Exclude: Test not commercially available
- Lindmark F, Zheng SL, Wiklund F, et al. Interleukin-1 receptor antagonist haplotype associated with prostate cancer risk. *British Journal of Cancer* 2005;93(4):493-7. PMID:16106254 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only
- Lindstrom S, Wiklund F, Jonsson BA, et al. Comprehensive genetic evaluation of common E-cadherin sequence variants and prostate cancer risk: strong confirmation of functional promoter SNP. *Human Genetics* 2005;118(3-4):339-47. PMID:16189707 OVID-Medline.  
Exclude: Test not commercially available
- Lindstrom S, Wiklund F, Adami HO, et al. Germ-line genetic variation in the key androgen-regulating genes androgen receptor, cytochrome P450, and steroid-5-alpha-reductase type 2 is important for prostate cancer development. *Cancer Research* 2006;66(22):11077-83. PMID:17108148 OVID-Medline.  
Exclude: Candidate gene approach
- Lindstrom S, Zheng SL, Wiklund F, et al. Systematic replication study of reported genetic associations in prostate cancer: Strong support for genetic variation in the androgen pathway. *Prostate* 2006;66(16):1729-43. PMID:16998812 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Lindstrom S, Adami HO, Balter KA, et al. Inherited variation in hormone-regulating genes and prostate cancer survival. *Clinical Cancer Research* 2007;13(17):5156-61. PMID:17785571 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline
- Lindstrom S, Adami HO, Adolfsson J, et al. Y chromosome haplotypes and prostate cancer in Sweden. *Clinical Cancer Research* 2008;14(20):6712-6. PMID:18927315 OVID-Medline.  
Exclude: Candidate gene approach

Lindstrom S, Hunter DJ, Gronberg H, et al. Sequence variants in the TLR4 and TLR6-1-10 genes and prostate cancer risk. Results based on pooled analysis from three independent studies. *Cancer Epidemiology, Biomarkers & Prevention* 2010;19(3):873-6. PMID:20200442 OVID-Medline.

Exclude: Did not use SNP assembled panel

Lisitskaya KV, Krakhmaleva IN, Shishkin SS. Study of single-nucleotide polymorphism in seven genes (GHR, IGFBP3, IGFR1, IRS1, FMN1, ANXA2, TAGLN) in ethnic Russians and patients with prostate cancer. *Molecular Genetics, Microbiology and Virology* 2010;25(2):84-8. OVID-Embase.

Exclude: Test not commercially available

Liu J-H, Li H-W, Gu L, et al. Single nucleotide polymorphisms in the 3' region of vitamin D receptor gene and the genetic risk of prostate cancer in Chinese population. *Chinese Journal of Clinical Rehabilitation* 2004;8(17):3429-32. OVID-Embase.

Exclude: Test not commercially available

Liu M, Kurosaki T, Suzuki M, et al. Significance of common variants on human chromosome 8q24 in relation to the risk of prostate cancer in native Japanese men. *BMC Genetics* 2009;10:37 PMID:19602258 OVID-Medline.

Exclude: Test not commercially available

Liu W, Chang B, Sauvageot J, et al. Comprehensive assessment of DNA copy number alterations in human prostate cancers using Affymetrix 100K SNP mapping array. *Genes, Chromosomes & Cancer* 2006;45(11):1018-32. PMID:16897747 OVID-Medline.

Exclude: Doesn't include any patients without PC at baseline

Liu W, Chang BL, Cramer S, et al. Deletion of a small consensus region at 6q15, including the MAP3K7 gene, is significantly associated with high-grade prostate cancers. *Clinical Cancer Research* 2007;13(17):5028-33. PMID:17785553 OVID-Medline.

Exclude: Candidate gene approach

Liu W, Ewing CM, Chang BL, et al. Multiple genomic alterations on 21q22 predict various TMPRSS2/ERG fusion transcripts in human prostate cancers. *Genes, Chromosomes & Cancer* 2007;46(11):972-80. PMID:17654723 OVID-Medline.

Exclude: Did not use SNP assembled panel

Liu W, Xie CC, Zhu Y, et al. Homozygous deletions and recurrent amplifications implicate new genes involved in prostate cancer. *Neoplasia (New York)* 2008;10(8):897-907. PMID:18670647 OVID-Medline.

Exclude: Doesn't include any patients without PC at baseline

Liu W, Laitinen S, Khan S, et al. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. *Nature Medicine* 2009;15(5):559-65.

PMID:19363497 OVID-Medline.

Exclude: Doesn't include any patients without PC at baseline

Liu W, Sun J, Li G, et al. Association of a germ-line copy number variation at 2p24.3 and risk for aggressive prostate cancer. *Cancer Research* 2009;69(6):2176-9.

PMID:19258504 OVID-Medline.

Exclude: Genome wide association study GWA

Liu X, Plummer SJ, Nock NL, et al. Nonsteroidal antiinflammatory drugs and decreased risk of advanced prostate cancer: modification by lymphotoxin alpha. *American Journal of Epidemiology* 2006;164(10):984-9. PMID:16931544 OVID-Medline.

Exclude: Test not commercially available

Liu X, Cicek MS, Plummer SJ, et al. Association of testis derived transcript gene variants and prostate cancer risk. *Journal of Urology* 2007;177(3):894-8. PMID:17296370 OVID-Medline.

Exclude: Test not commercially available

Liu Y, Lin N, Huang L, et al. Genetic polymorphisms of the interleukin-18 gene and risk of prostate cancer. *DNA and Cell Biology* 2007;26(8):613-8. OVID-Embase.

Exclude: Test not commercially available

Loeb S, Carter HB, Walsh PC, et al. Single nucleotide polymorphisms and the likelihood of prostate cancer at a given prostate specific antigen level. *Journal of Urology* 2005;173(1):101-4. PMID:15450841 OVID-Medline.

Exclude: Did not use SNP assembled panel

Loh YH, Mitrou PN, Bowman R, et al. MGMT Ile143Val polymorphism, dietary factors and the risk of breast, colorectal and prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study. *DNA Repair* 2010;9(4):421-8. PMID:20096652 OVID-Medline.

Exclude: SNP(s) assessment in single gene only

Lou H, Yeager M, Li H, et al. Fine mapping and functional analysis of a common variant in MSMB on chromosome 10q11.2 associated with prostate cancer susceptibility. *Proceedings of the National Academy of Sciences of the United States of America* 2009;106(19):7933-8. PMID:19383797 OVID-Medline.

Exclude: Did not use SNP assembled panel

Low YL, Taylor JJ, Grace PB, et al. Phytoestrogen exposure, polymorphisms in COMT, CYP19, ESR1, and SHBG genes, and their associations with prostate cancer risk. *Nutrition & Cancer* 2006;56(1):31-9. PMID:17176215 OVID-Medline.

Exclude: Test not commercially available

- Lu L, Sun J, Isaacs SD, et al. Fine-mapping and family-based association analyses of prostate cancer risk variants at Xp11. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(7):2132-6. PMID:19549809 OVID-Medline. Exclude: Did not use SNP assembled panel
- Lubahn J, Berndt SI, Jin CH, et al. Association of CASP8 D302H polymorphism with reduced risk of aggressive prostate carcinoma. *Prostate* 2010;70(6):646-53. PMID:20033885 OVID-Medline. Exclude: Test not commercially available
- Lundin KB, Nordenskjold A, Giwercman A, et al. Frequent finding of the androgen receptor A645D variant in normal population. *Journal of Clinical Endocrinology & Metabolism* 2006;91(8):3228-31. PMID:16705072 OVID-Medline. Exclude: Test not commercially available
- Maier C, Rosch K, Herkommer K, et al. A candidate gene approach within the susceptibility region PCaP on 1q42.2-43 excludes deleterious mutations of the PCTA-1 gene to be responsible for hereditary prostate cancer. *European Urology* 2002;42(3):301-7. PMID:12234517 OVID-Medline. Exclude: Test not commercially available
- Maistro S, Snitcovsky I, Sarkis AS, et al. Vitamin D receptor polymorphisms and prostate cancer risk in Brazilian men. *International Journal of Biological Markers* 2004;19(3):245-9. PMID:15503828 OVID-Medline. Exclude: Test not commercially available
- Mandal RK, Gangwar R, Mandhani A, et al. DNA repair gene X-ray repair cross-complementing group 1 and xeroderma pigmentosum group D polymorphisms and risk of prostate cancer: a study from North India. *DNA & Cell Biology* 2010;29(4):183-90. PMID:20070155 OVID-Medline. Exclude: Test not commercially available
- Marangoni K, Araujo TG, Neves AF, et al. The -786T>C promoter polymorphism of the NOS3 gene is associated with prostate cancer progression. *BMC Cancer* 2008;8:273 PMID:18823560 OVID-Medline. Exclude: Doesn't include any patients without PC at baseline
- Marchesani M, Hakkarainen A, Tuomainen T-P, et al. New paraoxonase 1 polymorphism I102V and the risk of prostate cancer in Finnish men. *Journal of the National Cancer Institute* 2003;95(11):812-8. OVID-Embbase. Exclude: Test not commercially available
- Margiotti K, Kim E, Pearce CL, et al. Association of the G289S single nucleotide polymorphism in the HSD17B3 gene with prostate cancer in Italian men. *Prostate* 2002;53(1):65-8. PMID:12210481 OVID-Medline. Exclude: Test not commercially available
- Mason TE, Ricks-Santi L, Chen W, et al. Association of CD14 variant with prostate cancer in African-American men. *Prostate* 2010;70(3):262-9. PMID:19830784 OVID-Medline. Exclude: Test not commercially available
- McCarron SL, Edwards S, Evans PR, et al. Influence of cytokine gene polymorphisms on the development of prostate cancer. *Cancer Research* 2002;62(12):3369-72. PMID:12067976 OVID-Medline. Exclude: Test not commercially available
- McKay JD, Kaaks R, Johansson M, et al. Haplotype-based analysis of common variation in the growth hormone receptor gene and prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(1):169-73. PMID:17220348 OVID-Medline. Exclude: Test not commercially available
- Medeiros R, Morais A, Vasconcelos A, et al. Endothelial nitric oxide synthase gene polymorphisms and genetic susceptibility to prostate cancer. *European Journal of Cancer Prevention* 2002;11(4):343-50. OVID-Embbase. Exclude: Test not commercially available
- Medeiros R, Vasconcelos A, Costa S, et al. Metabolic susceptibility genes and prostate cancer risk in a southern European population: the role of glutathione S-transferases GSTM1, GSTM3, and GSTT1 genetic polymorphisms. *Prostate* 2004;58(4):414-20. PMID:14968442 OVID-Medline. Exclude: Test not commercially available
- Meenakshisundaram R, Piumelli N, Pierpaoli L, et al. CHOP 5'UTR-c.279T>C and +nt30C>T variants are not associated with overweight condition or with tumors/cancer in Italians - a case-control study. *Journal of Experimental & Clinical Cancer Research* 2009;28:90 PMID:19558691 OVID-Medline. Exclude: Study not about prostate cancer
- Meyer A, Schurmann P, Ghahremani M, et al. Association of chromosomal locus 8q24 and risk of prostate cancer: a hospital-based study of German patients treated with brachytherapy. *Urologic Oncology* 2009;27(4):373-6. PMID:18625567 OVID-Medline. Exclude: Did not use SNP assembled panel
- Meyer TE, Boerwinkle E, Morrison AC, et al. Diabetes genes and prostate cancer in the Atherosclerosis Risk in Communities study. *Cancer Epidemiology, Biomarkers & Prevention* 2010;19(2):558-65. PMID:20142250 OVID-Medline. Exclude: Test not commercially available
- Michaud DS, Daugherty SE, Berndt SI, et al. Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. *Cancer Research* 2006;66(8):4525-30. PMID:16618781 OVID-Medline. Exclude: Test not commercially available

- Mikhak B, Hunter DJ, Spiegelman D, et al. Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk. *Prostate* 2007;67(9):911-23. PMID:17440943 OVID-Medline. Exclude: Test not commercially available
- Mikhak B, Hunter DJ, Spiegelman D, et al. Manganese superoxide dismutase (MnSOD) gene polymorphism, interactions with carotenoid levels and prostate cancer risk. *Carcinogenesis* 2008;29(12):2335-40. PMID:18784358 OVID-Medline. Exclude: Test not commercially available
- Mino C, Witte T, Robles P, et al. Association among polymorphisms in the steroid 5alpha-reductase type II (SRD5A2) gene, prostate cancer risk, and pathologic characteristics of prostate tumors in an Ecuadorian population. *Cancer Genetics & Cytogenetics* 2009;189(2):71-6. PMID:19215786 OVID-Medline. Exclude: Test not commercially available
- Mononen N, Seppala EH, Duggal P, et al. Profiling genetic variation along the androgen biosynthesis and metabolism pathways implicates several single nucleotide polymorphisms and their combinations as prostate cancer risk factors. *Cancer Research* 2006;66(2):743-7. PMID:16424004 OVID-Medline. Exclude: Did not use SNP assembled panel
- Moon S, Holley S, Bodiwala D, et al. Associations between G/A1229, A/G3944, T/C30875, C/T48200 and C/T65013 genotypes and haplotypes in the vitamin D receptor gene, ultraviolet radiation and susceptibility to prostate cancer. *Annals of Human Genetics* 2006;70(Pt.2):2-36. PMID:16626332 OVID-Medline. Exclude: Doesn't include any patients without PC at baseline
- Moore SC, Leitzmann MF, Weinstein SJ, et al. Insulin resistance-related gene polymorphisms and risk of prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(6):1315-7. PMID:17548707 OVID-Medline. Exclude: Test not commercially available
- Moore SC, Leitzmann MF, Albanes D, et al. Adipokine genes and prostate cancer risk. *International Journal of Cancer* 2009;124(4):869-76. OVID-Embase. Exclude: Test not commercially available
- Murabito JM, Rosenberg CL, Finger D, et al. A genome-wide association study of breast and prostate cancer in the NHLBI's Framingham Heart Study. *BMC Medical Genetics* 2007;8:Suppl PMID:17903305 OVID-Medline. Exclude: Doesn't include any patients without PC at baseline
- Murad A, Lewis SJ, Smith GD, et al. PTGS2-899G>C and prostate cancer risk: a population-based nested case-control study ( ProtecT) and a systematic review with meta-analysis. *Prostate Cancer & Prostatic Diseases* 2009;12(3):296-300. PMID:19488068 OVID-Medline. Exclude: Test not commercially available
- Murad AS, Smith GD, Lewis SJ, et al. A polymorphism in the glucokinase gene that raises plasma fasting glucose, rs1799884, is associated with diabetes mellitus and prostate cancer: Findings from a population-based, case-control study (the ProtecT study). *International Journal of Molecular Epidemiology and Genetics* 2010;1(3):175-83. OVID-Embase. Exclude: Test not commercially available
- Nam RK, Zhang WW, Jewett MA, et al. The use of genetic markers to determine risk for prostate cancer at prostate biopsy. *Clinical Cancer Research* 2005;11(23):8391-7. PMID:16322300 OVID-Medline. Exclude: Doesn't include any patients without PC at baseline
- Nam RK, Zhang WW, Klotz LH, et al. Variants of the hK2 protein gene (KLK2) are associated with serum hK2 levels and predict the presence of prostate cancer at biopsy. *Clinical Cancer Research* 2006;12(21):6452-8. PMID:17085659 OVID-Medline. Exclude: SNP(s) assessment in single gene only
- Nam RK, Zhang WW, Loblaw DA, et al. A genome-wide association screen identifies regions on chromosomes 1q25 and 7p21 as risk loci for sporadic prostate cancer. *Prostate Cancer & Prostatic Diseases* 2008;11(3):241-6. PMID:17876339 OVID-Medline. Exclude: Study design
- Narita S, Tsuchiya N, Wang L, et al. Association of lipoprotein lipase gene polymorphism with risk of prostate cancer in a Japanese population. *International Journal of Cancer* 2004;112(5):872-6. PMID:15386377 OVID-Medline. Exclude: Test not commercially available
- Narla G, Difeo A, Yao S, et al. Targeted inhibition of the KLF6 splice variant, KLF6 SV1, suppresses prostate cancer cell growth and spread. *Cancer Research* 2005;65(13):5761-8. OVID-Embase. Exclude: Doesn't include any patients without PC at baseline
- Narla G, Difeo A, Reeves HL, et al. A germline DNA polymorphism enhances alternative splicing of the KLF6 tumor suppressor gene and is associated with increased prostate cancer risk. *Cancer Research* 2005;65(4):1213-22. PMID:15735005 OVID-Medline. Exclude: Test not commercially available
- Navratil V, Penel S, Delmotte S, et al. DigiPINS: a database for vertebrate exonic single nucleotide polymorphisms and its application to cancer association studies. *Biochimie* 2008;90(4):563-9. PMID:17988782 OVID-Medline. Exclude: Study not about prostate cancer
- Ning B, Wang C, Morel F, et al. Human glutathione S-transferase A2 polymorphisms: Variant expression, distribution in prostate cancer cases/controls and a novel form. *Pharmacogenetics* 2004;14(1):35-44. OVID-Embase. Exclude: Test not commercially available

Noonan-Wheeler FC, Wu W, Roehl KA, et al. Association of hereditary prostate cancer gene polymorphic variants with sporadic aggressive prostate carcinoma. *Prostate* 2006;66(1):49-56. PMID:16114055 OVID-Medline.  
Exclude: Test not commercially available

Oakley-Girvan I, Feldman D, Eccleshall TR, et al. Risk of early-onset prostate cancer in relation to germ line polymorphisms of the vitamin D receptor. *Cancer Epidemiology Biomarkers and Prevention* 2004;13(8):1325-30. OVID-Embase.  
Exclude: Test not commercially available

Okugi H, Nakazato H, Matsui H, et al. Association of the polymorphisms of genes involved in androgen metabolism and signaling pathways with familial prostate cancer risk in a Japanese population. *Cancer Detection and Prevention* 2006;30(3):262-8. OVID-Embase.  
Exclude: Test not commercially available

Omrani MD, Bazargani S, Bageri M. Interlukin-10, interferon- and tumor necrosis factor-alpha genes variation in prostate cancer and benign prostatic hyperplasia. *Current Urology* 2008;2(4):175-80. OVID-Embase.  
Exclude: Test not commercially available

Onen IH, Ekmekci A, Eroglu M, et al. The association of 5alpha-reductase II (SRD5A2) and 17 hydroxylase (CYP17) gene polymorphisms with prostate cancer patients in the Turkish population. *DNA & Cell Biology* 2007;26(2):100-7. PMID:17328668 OVID-Medline.  
Exclude: Test not commercially available

Onen IH, Ekmekci A, Eroglu M, et al. Association of genetic polymorphisms in vitamin D receptor gene and susceptibility to sporadic prostate cancer. *Experimental Biology & Medicine* 2008;233(12):1608-14. PMID:18849534 OVID-Medline.  
Exclude: Test not commercially available

Onsory K, Sobti RC, Al-Badran AI, et al. Hormone receptor-related gene polymorphisms and prostate cancer risk in North Indian population. *Molecular & Cellular Biochemistry* 2008;314(1-2):25-35. PMID:18483761 OVID-Medline.  
Exclude: Test not commercially available

Orr-Urtreger A, Bar-Shira A, Matzkin H, et al. The homozygous P582S mutation in the oxygen-dependent degradation domain of HIF-1 alpha is associated with increased risk for prostate cancer. *Prostate* 2007;67(1):8-13. PMID:16998808 OVID-Medline.  
Exclude: Test not commercially available

Osborne NJ, Gurrin LC, Allen KJ, et al. HFE c282y homozygotes are at increased risk of breast and colorectal cancer. *Hepatology* 2010;51(4):1311-8. OVID-Embase.  
Exclude: Doesn't include any patients without PC at baseline

Pal P, Xi H, Kaushal R, et al. Variants in the HEPSIN gene are associated with prostate cancer in men of European origin. *Human Genetics* 2006;120(2):187-92. PMID:16783571 OVID-Medline.  
Exclude: Test not commercially available

Pal P, Xi H, Sun G, et al. Tagging SNPs in the kallikrein genes 3 and 2 on 19q13 and their associations with prostate cancer in men of European origin. *Human Genetics* 2007;122(3-4):251-9. PMID:17593395 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Pal P, Xi H, Guha S, et al. Common variants in 8q24 are associated with risk for prostate cancer and tumor aggressiveness in men of European ancestry. *Prostate* 2009;69(14):1548-56. PMID:19562729 OVID-Medline.  
Exclude: Candidate gene approach

Paltoo D, Woodson K, Taylor P, et al. Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-gamma (PPAR-gamma) gene and risk of prostate cancer among men in a large cancer prevention study. *Cancer Letters* 2003;191(1):67-74. PMID:12609711 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Panguluri RC, Long LO, Chen W, et al. COX-2 gene promoter haplotypes and prostate cancer risk. *Carcinogenesis* 2004;25(6):961-6. PMID:14754878 OVID-Medline.  
Exclude: Test not commercially available

Papanikolopoulou A, Landt O, Reczko M, et al. Association Study of the Single Nucleotide Polymorphism (SNP), rs6983267, at region 3 of chromosome 8q24, with prostate cancer in the Greek population. *Review of Clinical Pharmacology and Pharmacokinetics, International Edition* 2010;24(2):187-9. OVID-Embase.  
Exclude: Test not commercially available

Parikh H, Deng Z, Yeager M, et al. A comprehensive resequence analysis of the KLK15-KLK3-KLK2 locus on chromosome 19q13.33. *Human Genetics* 2010;127(1):91-9. PMID:19823874 OVID-Medline.  
Exclude: Study not about prostate cancer

Park K, Kim JH, Jeon HG, et al. Influence of IGFBP3 gene polymorphisms on IGFBP3 serum levels and the risk of prostate cancer in low-risk Korean men. *Urology* 2010;75(6):1516-7. PMID:20350746 OVID-Medline.  
Exclude: Test not commercially available

Penney KL, Schumacher FR, Li H, et al. A large prospective study of SEP15 genetic variation, interaction with plasma selenium levels, and prostate cancer risk and survival. *Cancer Prevention Research* 2010;3(5):604-10. PMID:20424130 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Perner S, Demichelis F, Beroukhir R, et al. TMPRSS2:ERG fusion-associated deletions provide insight into the heterogeneity of prostate cancer. *Cancer Research* 2006;66(17):8337-41. PMID:16951139 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Pierce BL, Biggs ML, DeCambre M, et al. C-reactive protein, interleukin-6, and prostate cancer risk in men aged 65 years and older. *Cancer Causes & Control* 2009;20(7):1193-203. PMID:19267250 OVID-Medline.  
Exclude: Test not commercially available

Pierce BL, Ahsan H. Genetic susceptibility to type 2 diabetes is associated with reduced prostate cancer risk. *Human Heredity* 2010;69(3):193-201. PMID:20203524 OVID-Medline.  
Exclude: Candidate gene approach

Pomerantz MM, Beckwith CA, Regan MM, et al. Evaluation of the 8q24 prostate cancer risk locus and MYC expression. *Cancer Research* 2009;69(13):5568-74. PMID:19549893 OVID-Medline.  
Exclude: Candidate gene approach

Pookot D, Li LC, Tabatabai ZL, et al. The E-cadherin -160 C/A polymorphism and prostate cancer risk in white and black American men. *Journal of Urology* 2006;176(2):793-6. PMID:16813949 OVID-Medline.  
Exclude: Test not commercially available

Powell IJ, Zhou J, Sun Y, et al. CYP3A4 genetic variant and disease-free survival among white and black men after radical prostatectomy. *Journal of Urology* 2004;172(5 I):1848-52. OVID-Embase.  
Exclude: Doesn't include any patients without PC at baseline

Prokunina-Olsson L, Fu YP, Tang W, et al. Refining the prostate cancer genetic association within the JAZF1 gene on chromosome 7p15.2. *Cancer Epidemiology, Biomarkers & Prevention* 2010;19(5):1349-55. PMID:20406958 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Qiu L, Wang Z, Shi X, et al. Associations between XPC polymorphisms and risk of cancers: A meta-analysis. *European Journal of Cancer* 2008;44(15):2241-53. PMID:18771913 OVID-Medline.  
Exclude: Study not about prostate cancer

Rafnar T, Sulem P, Stacey SN, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. *Nature Genetics* 2009;41(2):221-7. PMID:19151717 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Ray AM, Zuhlke KA, Johnson GR, et al. Absence of truncating BRIP1 mutations in chromosome 17q-linked hereditary prostate cancer families. *British Journal of Cancer* 2009;101(12):2043-7. PMID:19935797 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Ray AM, Zuhlke KA, Levin AM, et al. Sequence variation in the mitochondrial gene cytochrome c oxidase subunit I and prostate cancer in African-American men. *Prostate* 2009;69(9):956-60. PMID:19267350 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Rebbeck TR, Walker AH, Zeigler-Johnson C, et al. Association of HPC2/ELAC2 genotypes and prostate cancer. *American Journal of Human Genetics* 2000;67(4):1014-9. PMID:10986046 OVID-Medline.  
Exclude: Test not commercially available

Reljic A, Simundic AM, Topic E, et al. The methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and cancer risk: the Croatian case-control study. *Clinical Biochemistry* 2007;40(13-14):981-5. PMID:17573062 OVID-Medline.  
Exclude: Test not commercially available

Rennert H, Zeigler-Johnson CM, Addya K, et al. Association of susceptibility alleles in ELAC2/HPC2, RNASEL/HPC1, and MSR1 with prostate cancer severity in European American and African-American men. *Cancer Epidemiology Biomarkers and Prevention* 2005;14(4):949-57. OVID-Embase.  
Exclude: Test not commercially available

Ritchey JD, Huang W-Y, Chokkalingam AP, et al. Genetic variants of DNA repair genes and prostate cancer: A population-based study. *Cancer Epidemiology Biomarkers and Prevention* 2005;14(7):1703-9. OVID-Embase.  
Exclude: Candidate gene approach

Robbins C, Torres JB, Hooker S, et al. Confirmation study of prostate cancer risk variants at 8q24 in African-Americans identifies a novel risk locus. *Genome Research* 2007;17(12):1717-22. OVID-Embase.  
Exclude: Candidate gene approach

Robbins CM, Hernandez W, Ahaghotu C, et al. Association of HPC2/ELAC2 and RNASEL non-synonymous variants with prostate cancer risk in African-American familial and sporadic cases. *Prostate* 2008;68(16):1790-7. PMID:18767027 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Ross PL, Cheng I, Liu X, et al. Carboxypeptidase 4 gene variants and early-onset intermediate-to-high risk prostate cancer. *BMC Cancer* 2009;9:69 PMID:19245716 OVID-Medline.  
Exclude: Test not commercially available

Rubin MA. Using molecular markers to predict outcome. *Journal of Urology* 172(5:Pt 2):t-21 PMID:15535437 OVID-Medline.  
Exclude: Study not about prostate cancer

Saenz-Lopez P, Carretero R, Cozar JM, et al. Genetic polymorphisms of RANTES, IL1-A, MCP-1 and TNF-A genes in patients with prostate cancer. *BMC Cancer* 2008;8, 2008. Article Number: 382. Date of Publication: 19 Dec 2008.: OVID-Embase.  
Exclude: Test not commercially available

Salinas CA, Kwon E, Carlson CS, et al. Multiple independent genetic variants in the 8q24 region are associated with prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2008;17(5):1203-13. PMID:18483343 OVID-Medline.  
Exclude: Candidate gene approach

Sarma AV, Dunn RL, Lange LA, et al. Genetic polymorphisms in CYP17, CYP3A4, CYP19A1, SRD5A2, IGF-1, and IGFBP-3 and prostate cancer risk in African-American men: the Flint Men's Health Study. *Prostate* 2008;68(3):296-305. PMID:18163429 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Schab M, Janiszewska H, Jarzowski P, et al. Frequency of CYP1B1 homozygous genotype 355T/T in prostate cancer families from Poland. *European Journal of Cancer Prevention* 2010;19(1):31-4. PMID:19820397 OVID-Medline.  
Exclude: Test not commercially available

Scheble VJ, Braun M, Beroukhim R, et al. ERG rearrangement is specific to prostate cancer and does not occur in any other common tumor. *Modern Pathology* 2010;23(8):1061-7. OVID-Embase.  
Exclude: Doesn't include any patients without PC at baseline

Seppala EH, Autio V, Duggal P, et al. KLF6 IVS1 -27G>A variant and the risk of prostate cancer in Finland. *European Urology* 2007;52(4):1076-81. PMID:17125911 OVID-Medline.  
Exclude: Test not commercially available

Setiawan VW, Schumacher FR, Haiman CA, et al. CYP17 genetic variation and risk of breast and prostate cancer from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(11):2237-46. PMID:18006912 OVID-Medline.  
Exclude: Test not commercially available

Setlur SR, Chen CX, Hossain RR, et al. Genetic variation of genes involved in dihydrotestosterone metabolism and the risk of prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2010;19(1):229-39. PMID:20056642 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Severi G, Hayes VM, Neufing P, et al. Variants in the prostate-specific antigen (PSA) gene and prostate cancer risk, survival, and circulating PSA. *Cancer Epidemiology Biomarkers and Prevention* 2006;15(6):1142-7. OVID-Embase.  
Exclude: SNP(s) assessment in single gene only

Sfar S, Hassen E, Saad H, et al. Association of VEGF genetic polymorphisms with prostate carcinoma risk and clinical outcome. *Cytokine* 2006;35(1-2):21-8. PMID:16908180 OVID-Medline.  
Exclude: Test not commercially available

Sfar S, Saad H, Mosbah F, et al. Association of HSP70-hom genetic variant with prostate cancer risk. *Molecular Biology Reports* 2008;35(3):459-64. PMID:17578680 OVID-Medline.  
Exclude: Doesn't include test panel

Sfar S, Saad H, Mosbah F, et al. Combined effects of the angiogenic genes polymorphisms on prostate cancer susceptibility and aggressiveness. *Molecular Biology Reports* 2009;36(1):37-45. PMID:17917789 OVID-Medline.  
Exclude: Test not commercially available

Sfar S, Saad H, Mosbah F, et al. Synergistic effect and VEGF/HSP70-hom haplotype analysis: relationship to prostate cancer risk and clinical outcome. *Human Immunology* 2010;71(4):377-82. PMID:20096741 OVID-Medline.  
Exclude: Test not commercially available

Shahedi K, Lindstrom S, Zheng SL, et al. Genetic variation in the COX-2 gene and the association with prostate cancer risk. *International Journal of Cancer* 2006;119(3):668-72. PMID:16506214 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Sharma S, Cao X, Wilkens LR, et al. Well-done meat consumption, NAT1 and NAT2 acetylator genotypes and prostate cancer risk: The multiethnic cohort study. *Cancer Epidemiology Biomarkers and Prevention* 2010;19(7):1866-70. OVID-Embase.  
Exclude: Test not commercially available

Shea PR, Ferrell RE, Patrick AL, et al. ELAC2 and prostate cancer risk in Afro-Caribbeans of Tobago. *Human Genetics* 2002;111(4-5):398-400. OVID-Embase.  
Exclude: Test not commercially available

Shea PR, Ishwad CS, Bunker CH, et al. RNASEL and RNASEL-inhibitor variation and prostate cancer risk in Afro-Caribbeans. *Prostate* 2008;68(4):354-9. PMID:18189233 OVID-Medline.  
Exclude: Test not commercially available

Shioji G, Ezura Y, Nakajima T, et al. Nucleotide variations in genes encoding plasminogen activator inhibitor-2 and serine proteinase inhibitor B10 associated with prostate cancer. *Journal of Human Genetics* 2005;50(10):507-15. PMID:16172807 OVID-Medline.  
Exclude: Test not commercially available

- Shook SJ, Beuten J, Torkko KC, et al. Association of RNASEL variants with prostate cancer risk in Hispanic Caucasians and African-Americans. *Clinical Cancer Research* 2007;13(19):5959-64. OVID-Embase.  
Exclude: Test not commercially available
- Sieh W, Edwards KL, Fitzpatrick AL, et al. Genetic Susceptibility to Prostate Cancer: Prostate-specific Antigen and its Interaction with the Androgen Receptor (United States). *Cancer Causes & Control* 2006;17(2):187-97. PMID:16425097 OVID-Medline.  
Exclude: Test not commercially available
- Siltanen S, Syrjakoski K, Fagerholm R, et al. ARLTS1 germline variants and the risk for breast, prostate, and colorectal cancer. *European Journal of Human Genetics* 2008;16(8):983-91. PMID:18337727 OVID-Medline.  
Exclude: Test not commercially available
- Singal R, Ferdinand L, Das PM, et al. Polymorphisms in the methylenetetrahydrofolate reductase gene and prostate cancer risk. *International Journal of Oncology* 2004;25(5):1465-71. OVID-Embase.  
Exclude: Test not commercially available
- Singal R, Das PM, Manoharan M, et al. Polymorphisms in the DNA methyltransferase 3b gene and prostate cancer risk. *Oncology Reports* 2005;14(2):569-73. PMID:16012746 OVID-Medline.  
Exclude: Test not commercially available
- Sobti RC, Onsory K, Al-Badran AI, et al. CYP17, SRD5A2, CYP1B1, and CYP2D6 gene polymorphisms with prostate cancer risk in North Indian population. *DNA and Cell Biology* 2006;25(5):287-94. OVID-Embase.  
Exclude: Test not commercially available
- Song J, Kim DY, Kim CS, et al. The association between Toll-like receptor 4 (TLR4) polymorphisms and the risk of prostate cancer in Korean men. *Cancer Genetics & Cytogenetics* 2009;190(2):88-92. PMID:19380025 OVID-Medline.  
Exclude: Test not commercially available
- Srivastava DS, Mandhani A, Mittal B, et al. Genetic polymorphism of glutathione S-transferase genes (GSTM1, GSTT1 and GSTP1) and susceptibility to prostate cancer in Northern India. *BJU International* 2005;95(1):170-3. PMID:15638917 OVID-Medline.  
Exclude: Test not commercially available
- Stevens VL, Rodriguez C, Sun J, et al. No association of single nucleotide polymorphisms in one-carbon metabolism genes with prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2008;17(12):3612-4. PMID:19064578 OVID-Medline.  
Exclude: Test not commercially available
- Stevens VL, Rodriguez C, Talbot JT, et al. Paraoxonase 1 (PON1) polymorphisms and prostate cancer in the CPS-II Nutrition Cohort. *Prostate* 2008;68(12):1336-40. PMID:18500687 OVID-Medline.  
Exclude: Test not commercially available
- Stevens VL, Hsing AW, Talbot JT, et al. Genetic variation in the toll-like receptor gene cluster (TLR10-TLR1-TLR6) and prostate cancer risk. *International Journal of Cancer* 2008;123(11):2644-50. PMID:18752252 OVID-Medline.  
Exclude: Candidate gene approach
- Stevens VL, Ahn J, Sun J, et al. HNF1B and JAZF1 genes, diabetes, and prostate cancer risk. *Prostate* 2010;70(6):601-7. PMID:19998368 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Stiblar-Martincic D, Hajdinjak T. Polymorphism L26V in the cathepsin B gene may be associated with a risk of prostate cancer and differentiation. *Journal of International Medical Research* 2009;37(5):1604-10. PMID:19930869 OVID-Medline.  
Exclude: Test not commercially available
- Stoehr R, Hitzenbichler F, Kneitz B, et al. Mdm2-SNP309 polymorphism in prostate cancer: no evidence for association with increased risk or histopathological tumour characteristics. *British Journal of Cancer* 2008;99(1):78-82. PMID:18577987 OVID-Medline.  
Exclude: Test not commercially available
- Strawbridge RJ, Nister M, Brismar K, et al. Influence of MUC1 genetic variation on prostate cancer risk and survival. *European Journal of Human Genetics* 2008;16(12):1521-5. OVID-Embase.  
Exclude: SNP(s) assessment in single gene only
- Suarez BK, Pal P, Jin CH, et al. TGFBR1\*6A is not associated with prostate cancer in men of European ancestry. *Prostate cancer and prostatic diseases* 2005;8(1):50-3. OVID-Embase.  
Exclude: Test not commercially available
- Suga T, Iwakawa M, Tsuji H, et al. Influence of multiple genetic polymorphisms on genitourinary morbidity after carbon ion radiotherapy for prostate cancer. *International Journal of Radiation Oncology, Biology, Physics* 2008;72(3):808-13. PMID:18374504 OVID-Medline.  
Exclude: Did not use SNP assembled panel
- Suikki HE, Kujala PM, Tammela TL, et al. Genetic alterations and changes in expression of histone demethylases in prostate cancer. *Prostate* 2010;70(8):889-98. PMID:20127736 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline
- Sun J, Hedelin M, Zheng SL, et al. Interleukin-6 sequence variants are not associated with prostate cancer risk. *Cancer Epidemiology Biomarkers and Prevention* 2004;13(10):1677-9. OVID-Embase.  
Exclude: SNP(s) assessment in single gene only
- Sun J, Wiklund F, Zheng SL, et al. Sequence variants in Toll-like receptor gene cluster (TLR6-TLR1-TLR10) and prostate cancer risk. *Journal of the National Cancer Institute* 2005;97(7):525-32. PMID:15812078 OVID-Medline.  
Exclude: Candidate gene approach

Sun J, Wiklund F, Hsu F-C, et al. Interactions of sequence variants in interleukin-1 receptor-associated kinase4 and the Toll-like receptor 6-1-10 gene cluster increase prostate cancer risk. *Cancer Epidemiology Biomarkers and Prevention* 2006;15(3):480-5. OVID-Embase.  
Exclude: Candidate gene approach

Sun J, Zheng SL, Wiklund F, et al. Evidence for two independent prostate cancer risk-associated loci in the HNF1B gene at 17q12. *Nature Genetics* 2008;40(10):1153-5. PMID:18758462 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Sun J, Purcell L, Gao Z, et al. Association between sequence variants at 17q12 and 17q24.3 and prostate cancer risk in European and African-Americans. *Prostate* 2008;68(7):691-7. PMID:18361410 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Sun J, Zheng SL, Wiklund F, et al. Sequence variants at 22q13 are associated with prostate cancer risk. *Cancer Research* 2009;69(1):10-5. PMID:19117981 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Sun T, Zhou Y, Yang M, et al. Functional genetic variations in cytotoxic T-lymphocyte antigen 4 and susceptibility to multiple types of cancer. *Cancer Research* 2008;68(17):7025-34. PMID:18757416 OVID-Medline.  
Exclude: Study not about prostate cancer

Suuriniemi M, Agalliu I, Schaid DJ, et al. Confirmation of a positive association between prostate cancer risk and a locus at chromosome 8q24. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(4):809-14. PMID:17416775 OVID-Medline.  
Exclude: Test not commercially available

Suzuki K, Matsui H, Nakazato H, et al. Association of the genetic polymorphism in cytochrome P450 (CYP) 1A1 with risk of familial prostate cancer in a Japanese population: a case-control study. *Cancer Letters* 2003;195(2):177-83. PMID:12767526 OVID-Medline.  
Exclude: Test not commercially available

Suzuki K, Nakazato H, Matsui H, et al. Genetic polymorphisms of estrogen receptor alpha, CYP19, catechol-O-methyltransferase are associated with familial prostate carcinoma risk in a Japanese population. *Cancer* 2003;98(7):1411-6. OVID-Embase.  
Exclude: Test not commercially available

Suzuki M, Muto S, Hara K, et al. Single-nucleotide polymorphisms in the 17beta-hydroxysteroid dehydrogenase genes might predict the risk of side-effects of estramustine phosphate sodium in prostate cancer patients. *International Journal of Urology* 2005;12(2):166-72. PMID:15733111 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Suzuki M, Kurosaki T, Arai T, et al. The Val158Met polymorphism of the catechol-O-methyltransferase gene is not associated with the risk of sporadic or latent prostate cancer in Japanese men. *International Journal of Urology* 2007;14(9):800-4. PMID:17760745 OVID-Medline.  
Exclude: Test not commercially available

Tajtakova M, Pidanicova A, Valansky L, et al. Serum level of IGFBP3 and IGF1/IGFBP3 molar ratio in addition to PSA and single nucleotide polymorphism in PSA and CYP17 gene may contribute to early diagnostics of prostate cancer. *Neoplasma* 2010;57(2):118-22. PMID:20099974 OVID-Medline.  
Exclude: Test not commercially available

Tan YC, Zeigler-Johnson C, Mittal RD, et al. Common 8q24 sequence variations are associated with Asian Indian advanced prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2008;17(9):2431-5. PMID:18768513 OVID-Medline.  
Exclude: Test not commercially available

Tayeb MT, Clark C, Haites NE, et al. CYP3A4 and VDR gene polymorphisms and the risk of prostate cancer in men with benign prostate hyperplasia. *British Journal of Cancer* 2003;88(6):928-32. PMID:12644831 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Teixeira AL, Ribeiro R, Cardoso D, et al. Genetic polymorphism in EGF is associated with prostate cancer aggressiveness and progression-free interval in androgen blockade-treated patients. *Clinical Cancer Research* 2008;14(11):3367-71. PMID:18519765 OVID-Medline.  
Exclude: Test not commercially available

Teixeira AL, Ribeiro R, Morais A, et al. Combined analysis of EGF+61G>A and TGFB1+869T>C functional polymorphisms in the time to androgen independence and prostate cancer susceptibility. *Pharmacogenomics Journal* 2009;9(5):341-6. PMID:19488063 OVID-Medline.  
Exclude: Test not commercially available

Terada N, Tsuchiya N, Ma Z, et al. Association of genetic polymorphisms at 8q24 with the risk of prostate cancer in a Japanese population. *Prostate* 2008;68(15):1689-95. PMID:18726982 OVID-Medline.  
Exclude: Test not commercially available

Thellenberg-Karlsson C, Lindstrom S, Malmer B, et al. Estrogen receptor beta polymorphism is associated with prostate cancer risk. *Clinical Cancer Research* 2006;12(6):1936-41. PMID:16551880 OVID-Medline.  
Exclude: Test not commercially available

Thomas G, Jacobs KB, Yeager M, et al. Multiple loci identified in a genome-wide association study of prostate cancer. *Nature Genetics* 2008;40(3):310-5. PMID:18264096 OVID-Medline.  
Exclude: Genome wide association study GWA

Tischkowitz MD, Yilmaz A, Chen LQ, et al. Identification and characterization of novel SNPs in CHEK2 in Ashkenazi Jewish men with prostate cancer. *Cancer Letters* 2008;270(1):173-80. PMID:18571837 OVID-Medline.  
Exclude: Test not commercially available

Torkko KC, van BA, Mai P, et al. VDR and SRD5A2 polymorphisms combine to increase risk for prostate cancer in both non-Hispanic White and Hispanic White men. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2008;14(10):3223-9. OVID-Embase.  
Exclude: Test not commercially available

Torniainen S, Hedelin M, Autio V, et al. Lactase persistence, dietary intake of milk, and the risk for prostate cancer in Sweden and Finland. *Cancer Epidemiology, Biomarkers & Prevention* 2007;16(5):956-61. PMID:17507622 OVID-Medline.  
Exclude: Doesn't include test panel

Torrington N, Borre M, Sorensen KD, et al. Genome-wide analysis of allelic imbalance in prostate cancer using the Affymetrix 50K SNP mapping array. *British Journal of Cancer* 2007;96(3):499-506. PMID:17245344 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Travis RC, Schumacher F, Hirschhorn JN, et al. CYP19A1 genetic variation in relation to prostate cancer risk and circulating sex hormone concentrations in men from the Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(10):2734-44. PMID:19789370 OVID-Medline.  
Exclude: Test not commercially available

Tsuchiya N, Wang L, Horikawa Y, et al. CA repeat polymorphism in the insulin-like growth factor-I gene is associated with increased risk of prostate cancer and benign prostatic hyperplasia. *International Journal of Oncology* 2005;26(1):225-31. OVID-Embase.  
Exclude: Test not commercially available

Tsuchiya N, Narita S, Kumazawa T, et al. Clinical significance of a single nucleotide polymorphism and allelic imbalance of matrix metalloproteinase-1 promoter region in prostate cancer. *Oncology Reports* 2009;22(3):493-9. PMID:19639194 OVID-Medline.  
Exclude: Test not commercially available

VanCleave TT, Moore JH, Benford ML, et al. Interaction among variant vascular endothelial growth factor (VEGF) and its receptor in relation to prostate cancer risk. *Prostate* 2010;70(4):341-52. PMID:19908237 OVID-Medline.  
Exclude: Doesn't include test panel

Vijayalakshmi K, Vettriselvi V, Krishnan M, et al. Cytochrome p4501A1 gene variants as susceptibility marker for prostate cancer. *Cancer biomarkers : section A of Disease markers* 2005;1(4-5):251-8. OVID-Embase.  
Exclude: Test not commercially available

Vijayalakshmi K, Vettriselvi V, Krishnan M, et al. Polymorphisms at GSTM1 and GSTP1 gene loci and risk of prostate cancer in a South Indian population. *Asian Pacific journal of cancer prevention : APJCP* 2005;6(3):309-14. OVID-Embase.  
Exclude: Test not commercially available

Wang L, McDonnell SK, Slusser JP, et al. Two common chromosome 8q24 variants are associated with increased risk for prostate cancer. *Cancer Research* 2007;67(7):2944-50. PMID:17409399 OVID-Medline.  
Exclude: Test not commercially available

Wang L, McDonnell SK, Hebring SJ, et al. Polymorphisms in mitochondrial genes and prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2008;17(12):3558-66. PMID:19064571 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Wang MH, Helzlsouer KJ, Smith MW, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. *Prostate* 2009;69(8):874-85. PMID:19267370 OVID-Medline.  
Exclude: Test not commercially available

Wang W, Yuasa T, Tsuchiya N, et al. The novel tumor-suppressor Mel-18 in prostate cancer: its functional polymorphism, expression and clinical significance. *International Journal of Cancer* 2009;125(12):2836-43. PMID:19585577 OVID-Medline.  
Exclude: Test not commercially available

Watanabe M, Hirokawa Y, Tsuji M, et al. Lack of involvement of the GNAS1 T393C polymorphism in prostate cancer risk in a Japanese population. *Anticancer Research* 2008;28(6A):3711-6. PMID:19189654 OVID-Medline.  
Exclude: Test not commercially available

Wiklund F, Jonsson BA, Brookes AJ, et al. Genetic analysis of the RNASEL gene in hereditary, familial, and sporadic prostate cancer. *Clinical Cancer Research* 2004;10(21):7150-6. PMID:15534086 OVID-Medline.  
Exclude: Test not commercially available

Wiklund F, Zheng SL, Sun J, et al. Association of reported prostate cancer risk alleles with PSA levels among men without a diagnosis of prostate cancer. *Prostate* 2009;69(4):419-27. PMID:19116992 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Wiklund FE, Adami HO, Zheng SL, et al. Established prostate cancer susceptibility variants are not associated with disease outcome. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(5):1659-62. PMID:19423541 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Wilborn TW, Lang NP, Smith M, et al. Association of SULT2A1 allelic variants with plasma adrenal androgens and prostate cancer in African-American men. *Journal of Steroid Biochemistry & Molecular Biology* 2006;99(4-5):209-14. PMID:16617014 OVID-Medline.  
Exclude: Test not commercially available

Wokolorczyk D, Gliniewicz B, Sikorski A, et al. A range of cancers is associated with the rs6983267 marker on chromosome 8. *Cancer Research* 2008;68(23):9982-6. PMID:19047180 OVID-Medline.  
Exclude: Test not commercially available

Wokolorczyk D, Gliniewicz B, Stojewski M, et al. The rs1447295 and DG8S737 markers on chromosome 8q24 and cancer risk in the Polish population. *European Journal of Cancer Prevention* 2010;19(2):167-71. PMID:19952762 OVID-Medline.  
Exclude: Test not commercially available

Wolf S, Mertens D, Pscherer A, et al. Ala228 variant of trail receptor 1 affecting the ligand binding site is associated with chronic lymphocytic leukemia, mantle cell lymphoma, prostate cancer, head and neck squamous cell carcinoma and bladder cancer. *International Journal of Cancer* 2006;118(7):1831-5. PMID:16217763 OVID-Medline.  
Exclude: Test not commercially available

Wright JL, Kwon EM, Lin DW, et al. CYP17 polymorphisms and prostate cancer outcomes. *Prostate* 2010;70(10):1094-101. PMID:20503394 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Wright ME, Peters U, Gunter MJ, et al. Association of variants in two vitamin e transport genes with circulating vitamin e concentrations and prostate cancer risk. *Cancer Research* 2009;69(4):1429-38. PMID:19190344 OVID-Medline.  
Exclude: Test not commercially available

Wu HC, Chang CH, Wan L, et al. IL-2 gene C/T polymorphism is associated with prostate cancer. *Journal of Clinical Laboratory Analysis* 2006;20(6):245-9. PMID:17115417 OVID-Medline.  
Exclude: Test not commercially available

Xu B, Wang J, Tong N, et al. A functional polymorphism in MSMB gene promoter is associated with prostate cancer risk and serum MSMB expression. *Prostate* 2010;70(10):1146-52. PMID:20333697 OVID-Medline.  
Exclude: Test not commercially available

Xu B, Feng NH, Li PC, et al. A functional polymorphism in Pre-miR-146a gene is associated with prostate cancer risk and mature miR-146a expression in vivo. *The Prostate* 2010;70(5):467-72. OVID-Embase.  
Exclude: Test not commercially available

Xu J, Zheng SL, Carpten JD, et al. Evaluation of linkage and association of HPC2/ELAC2 in patients with familial or sporadic prostate cancer. *American Journal of Human Genetics* 2001;68(4):901-11. PMID:11254448 OVID-Medline.  
Exclude: Test not commercially available

Xu J, Zheng SL, Hawkins GA, et al. Linkage and association studies of prostate cancer susceptibility: evidence for linkage at 8p22-23. *American Journal of Human Genetics* 2001;69(2):341-50. PMID:11443539 OVID-Medline.  
Exclude: Test not commercially available

Xu J, Zheng SL, Komiya A, et al. Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. *Nature Genetics* 2002;32(2):321-5. OVID-Embase.  
Exclude: Doesn't include any patients without PC at baseline

Xu J, Zheng SL, Turner A, et al. Associations between hOGG1 sequence variants and prostate cancer susceptibility. *Cancer Research* 2002;62(8):2253-7. PMID:11956079 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Xu J, Zheng SL, Komiya A, et al. Common sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. *American Journal of Human Genetics* 2003;72(1):208-12. PMID:12471593 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Xu J, Lowey J, Wiklund F, et al. The interaction of four genes in the inflammation pathway significantly predicts prostate cancer risk. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14(11:Pt 1):t-8 PMID:16284379 OVID-Medline.  
Exclude: Candidate gene approach

Xu J, Kibel AS, Hu JJ, et al. Prostate cancer risk associated loci in African-Americans. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(7):2145-9. PMID:19549807 OVID-Medline.  
Exclude: Did not use SNP assembled panel

Xu J, Zheng SL, Isaacs SD, et al. Inherited genetic variant predisposes to aggressive but not indolent prostate cancer. *Proceedings of the National Academy of Sciences of the United States of America* 2010;107(5):2136-40. PMID:20080650 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Yamada H, Penney KL, Takahashi H, et al. Replication of prostate cancer risk loci in a Japanese case-control association study. *Journal of the National Cancer Institute* 2009;101(19):1330-6. PMID:19726753 OVID-Medline.  
Exclude: Genome wide association study GWA

Yang HP, Woodson K, Taylor PR, et al. Genetic variation in interleukin 8 and its receptor genes and its influence on the risk and prognosis of prostate cancer among Finnish men in a large cancer prevention trial. *European Journal of Cancer Prevention* 2006;15(3):249-53. PMID:16679868 OVID-Medline.  
Exclude: Test not commercially available

Yang J, Wu H-F, Zhang W, et al. Polymorphisms of metabolic enzyme genes, living habits and prostate cancer susceptibility. *Frontiers in Bioscience* 2006;11(SUPPL. 1):2052-60. OVID-Embase.  
Exclude: Test not commercially available

Yaspan BL, McReynolds KM, Elmore JB, et al. A haplotype at chromosome Xq27.2 confers susceptibility to prostate cancer. *Human Genetics* 2008;123(4):379-86. PMID:18350320 OVID-Medline.  
Exclude: Test not commercially available

Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nature Genetics* 2007;39(5):645-9. PMID:17401363 OVID-Medline.  
Exclude: Genome wide association study GWA

Yeager M, Xiao N, Hayes RB, et al. Comprehensive resequence analysis of a 136 kb region of human chromosome 8q24 associated with prostate and colon cancers. *Human Genetics* 2008;124(2):161-70. PMID:18704501 OVID-Medline.  
Exclude: Test not commercially available

Yeager M, Deng Z, Boland J, et al. Comprehensive resequence analysis of a 97 kb region of chromosome 10q11.2 containing the MSMB gene associated with prostate cancer. *Human Genetics* 2009;126(6):743-50. OVID-Embase.  
Exclude: Doesn't include test panel

Yeager M, Chatterjee N, Ciampa J, et al. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. *Nature Genetics* 2009;41(10):1055-7. PMID:19767755 OVID-Medline.  
Exclude: Genome wide association study GWA

Yokomizo A, Koga H, Kinukawa N, et al. HPC2/ELAC2 polymorphism associated with Japanese sporadic prostate cancer. *Prostate* 2004;61(3):248-52. PMID:15368467 OVID-Medline.  
Exclude: Test not commercially available

Yokomizo A, Koga H, Kinukawa N, et al. Association of HER-2 polymorphism with Japanese sporadic prostate cancer susceptibility. *Prostate* 2005;62(1):49-53. PMID:15389808 OVID-Medline.  
Exclude: Doesn't include test panel

Yu Z, Li Z, Jolicoeur N, et al. Aberrant allele frequencies of the SNPs located in microRNA target sites are potentially associated with human cancers. *Nucleic Acids Research* 2007;35(13):4535-41. PMID:17584784 OVID-Medline.  
Exclude: Study not about prostate cancer

Zabaleta J, Lin HY, Sierra RA, et al. Interactions of cytokine gene polymorphisms in prostate cancer risk. *Carcinogenesis* 2008;29(3):573-8. PMID:18174250 OVID-Medline.  
Exclude: Test not commercially available

Zabaleta J, Su LJ, Lin HY, et al. Cytokine genetic polymorphisms and prostate cancer aggressiveness. *Carcinogenesis* 2009;30(8):1358-62. PMID:19474090 OVID-Medline.  
Exclude: Doesn't include any patients without PC at baseline

Zeigler-Johnson CM, Walker AH, Mancke B, et al. Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4. *Human Heredity* 2002;54(1):13-21. PMID:12446983 OVID-Medline.  
Exclude: Doesn't include test panel

Zheng SL, Chang B-L, Faith DA, et al. Sequence variants of alpha-methylacyl-CoA racemase are associated with prostate cancer risk. *Cancer Research* 2002;62(22):6485-8. OVID-Embase.  
Exclude: SNP(s) assessment in single gene only

Zheng SL, Mychaleckyj JC, Hawkins GA, et al. Evaluation of DLC1 as a prostate cancer susceptibility gene: mutation screen and association study. *Mutation Research* 2003;528(1-2):45-53. PMID:12873722 OVID-Medline.  
Exclude: Test not commercially available

Zheng SL, Augustsson-Balter K, Chang B, et al. Sequence variants of toll-like receptor 4 are associated with prostate cancer risk: results from the Cancer Prostate in Sweden Study. *Cancer Research* 2004;64(8):2918-22. PMID:15087412 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Zheng SL, Liu W, Wiklund F, et al. A comprehensive association study for genes in inflammation pathway provides support for their roles in prostate cancer risk in the CAPS study. *Prostate* 2006;66(14):1556-64. PMID:16921508 OVID-Medline.  
Exclude: Candidate gene approach

Zheng SL, Sun J, Cheng Y, et al. Association between two unlinked loci at 8q24 and prostate cancer risk among European Americans. *Journal of the National Cancer Institute* 2007;99(20):1525-33. PMID:17925536 OVID-Medline.  
Exclude: Candidate gene approach

Zheng SL, Stevens VL, Wiklund F, et al. Two independent prostate cancer risk-associated Loci at 11q13. *Cancer Epidemiology, Biomarkers & Prevention* 2009;18(6):1815-20. PMID:19505914 OVID-Medline.  
Exclude: SNP(s) assessment in single gene only

Zheng SL, Hsing AW, Sun J, et al. Association of 17 prostate cancer susceptibility loci with prostate cancer risk in Chinese men. *Prostate* 2010;70(4):425-32. PMID:19866473 OVID-Medline.  
Exclude: Genome wide association study GWA

Zhenhua L, Tsuchiya N, Narita S, et al. CYP3A5 gene polymorphism and risk of prostate cancer in a Japanese population. *Cancer Letters* 2005;225(2):237-43. PMID:15876487 OVID-Medline.  
Exclude: Test not commercially available

Zhu Y, Stevens RG, Hoffman AE, et al. Testing the circadian gene hypothesis in prostate cancer: a population-based case-control study. *Cancer Research* 2009;69(24):9315-22. PMID:19934327 OVID-Medline.  
Exclude: Did not use SNP assembled panel

