Multigene Panels in Prostate Cancer Risk Assessment

Executive Summary

Background

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

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

Striking differences in incidence have been observed for different ethnic groups and populations. A high incidence has been observed in populations of African descent in several countries.[7] First-degree relatives of men with prostate cancer have a twofold to threefold increased risk for developing the disease,[6,8,9] and its estimated heritability is high.[10] Some patterns of familial aggregation have been observed that are consistent with an autosomal dominant mode of inheritance of a susceptibility gene, but this accounts for no more than 15 percent of cases.[11,12] Prostate cancer is currently considered to be a complex, multifactorial disease with the vast majority of familial clustering attributed to the interaction of multiple shared moderate to low penetrance

Evidence-based Practice Program

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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

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

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Evidence-Based Practice

susceptibility genes and shared environmental factors within these families. Many epidemiological studies have suggested a wide range of other risk factors for prostate cancer, but these have not been confirmed in controlled trials.

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

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

Single nucleotide polymorphisms (SNPs) are minute inherited variations in the DNA sequence. SNPs occur about once in every 800 base pairs[24] and are the most common type of genetic variation in humans. Since 2001, there have been about 1,000 published studies reporting associations between prostate cancer, SNPs, and other genetic variants. To date, genome-wide association (GWA) studies have identified replicated associations between prostate cancer and almost 40 specific SNPs.[25-34] The magnitude of the odds ratios (ORs) in these studies was in the range of 1.1 to 2.1, that is, of low penetrance. It is generally accepted that information on single low-penetrance alleles has no value in screening,[35-38] but a small to moderate number of common, low-penetrance variants, in combination, may account for a high proportion of a disease[36,39,40] and may be useful in predicting the risk for disease.[41] The aim of this review is to assess the evidence on the possible value of SNP panels in the detection of and prediction of risk for prostate cancer, and their value in predicting disease prognosis in affected men.

Scope and Purpose of the Systematic Review

This report addresses the evidence on the validity and utility of using SNP panels in the detection, diagnosis, and clinical management of prostate cancer. It is intended to

Table A. Elements and key components of evaluation framework for SNP-based panels in prostate cancer risk assessment[42]		
Element	**Strategies**	**Components**
Analytic validity	An indicator of how well a test or tool measures the property or characteristic (e.g., genomic variations) that it is intended to measure	Analytical sensitivity Analytical specificity Reliability (e.g., repeatability of test results) Assay robustness (e.g., resistance to small changes in pre-analytic or analytic variables)[43]
Clinical validity	A measurement of the accuracy with which a test or tool identifies or predicts a clinical condition	Clinical sensitivity Clinical specificity Positive predictive value Negative predictive value
Clinical utility	Degree to which benefits are provided by positive and negative test results	Availability and impact of effective interventions Health risks and benefits Economic assessment
Ethical, legal, and social implications	Issues affecting use of SNP-based panels that might negatively impact individuals, families, and society	Stigmatization Discrimination Psychological harms Risks to privacy and confidentiality

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

encompass all relevant areas of test evaluation as proposed by the ACCE framework (see Table A).

The specific Key Questions (KQs) are:

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

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

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

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

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

Methods

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

No evidence to address this question was identified.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Quality Assessment of Individual Studies

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

Rating the Body of Evidence

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

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

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

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

Discussion

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

Future research should focus on evaluating clinical validity more extensively and robustly in participants more representative of general clinical populations, and

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

Conclusion

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

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

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

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Canc. 2010;127(12):2893-917. PMID:21351269

2. American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society; 2010. www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-026238.pdf

3. Canadian Cancer Society. Canadian Cancer Statistics 2010. Toronto: Canadian Cancer Society; 2010 Apr.

4. 2008 National Population Projections. U.S. Census Bureau 2011. 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 Canc 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 Canc. 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 Canc. 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. Canc. 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 USA. 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 Canc. 2006;95(9):1186-94. PMID:17077805

14. Boyle P, Brawley OW. Prostate cancer: Current evidence weighs against population screening. CA Canc 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.FF 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 Base 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, 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 Dec 6;155(11):762-71. PMID:21984740

24. Feero WG, Guttmacher 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. Epidemiol. 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 Gen. 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. Wells, GA, Shea, B, O'Connel, D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses. 2009 Feb 1. www.ohri.ca/programs/clinical_epidemiology/oxford.htm

45. 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

46. 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

47. 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

48. 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

49. 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

50. Zheng SL, Sun J, Wiklund F, et al. Genetic variants and family history predict prostate cancer similar to prostate-specific antigen. Clin Canc Res. 2009;15(3):1105-11. PMID:19188186

51. 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

52. 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

53. Nam RK, Zhang WW, Trachtenberg J, et al. Utility of incorporating genetic variants for the early detection of prostate cancer. Clin Canc Res. 2009;15(5):1787-93. PMID:19223501

54. 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. Canc Epidemiol Biomarkers Prev. 2009;18(6):1869-80. PMID:19505920

55. Penney KL, Salinas CA, Pomerantz M, et al. Evaluation of 8q24 and 17q risk loci and prostate cancer mortality. Clin Canc Res. 2009;15(9):3223-30. PMID:19366828

56. Sun J, Kader AK, Hsu FC, et al. Inherited genetic markers discovered to date are able to identify a significant number of men at considerably elevated risk for prostate cancer. Prostate. 2011;71(4):421-30. PMID:20878950

57. Helfand BT, Kan D, Modi P, et al. Prostate cancer risk alleles significantly improve disease detection and are associated with aggressive features in patients with a "normal" prostate specific antigen and digital rectal examination. Prostate. 2011;71(4):394-402. PMID:20860009

58. Aly M, Wiklund F, Xu J, et al. Polygenic risk score improves prostate cancer risk prediction: Results from the Stockholm-1 cohort study. Eur Urol. 2011;60(1):21-8.

59. Wiklund FE, Adami HO, Zheng SL, et al. Established prostate cancer susceptibility variants are not associated with disease outcome. Canc Epidemiol Biomarkers Prev. 2009;18(5):1659-62. PMID:19423541

60. Eng J. Receiver operating characteristic analysis: a primer. Acad Radiol. 2005;12(7):909-16. PM:16039544

61. Fan J, Upandhye S, Worster A. Understanding receiver operating characteristic (ROC) curves: Pedagogical tools and methods. CJEM. 2006;8(1):19-20.

62. 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 Canc Inst. 2007;99(24):1836-44. PMID:18073375

63. Welcome to deCODE Health. deCODE Prostate Cancer. www.decodehealth.com/prostate-cancer. Accessed June 12, 2012.

Full Report

For More Copies