Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Multigene Panels in Prostate Cancer Risk Assessment

Draft review available for public comment from November 22, 2011 to December 20, 2011.

Research Review Citation: Little J, Wilson B, Carter R, Walker K, Santaguida P, Tomiak E, Beyene J, Raina P. Multigene Panels in Prostate Cancer Risk Assessment. Evidence Report/Technology Assessment No. 209 (Prepared by the McMaster University Evidence-based Practice Center under Contract No. 290-2007-10060-1.) AHRQ Publication No. 12-E020-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	Introduction	The introduction is appropriate. A summary of the genetics of prostate cancer as well as of its heritability would have been welcome, especially in the context of a report on genetic markers for prostate cancer risk assessment	This part of the introduction has been re-organized, to make information on genetics of prostate cancer more prominent.
Peer Reviewer 2	Introduction	Fine	Thank you.
Peer Reviewer 3	Introduction	Good overview	Thank you.
Peer Reviewer 4	Introduction	Well done and comprehensive	Thank you.
Peer Reviewer 1	Methods	The databases searched as well as the other sources are appropriate, as well as the search keywords. Exclusion and inclusion criteria seem appropriate and justifiable, but only English papers were included. The search strategies are clearly stated and logical. The tools to assess the studies (ACCE framework, partial-QUADAS and NOS) are appropriate. Definitions and diagnostic criteria were appropriate for prostate cancer and similar across studies. There was no need for statistical methods given the small number of manuscripts analyzed.	Thank you for your comment. The authors do not feel that any literature was missed by restricting the search to the English language. A citation has been added to support this statement.
Peer Reviewer 2	Methods	yes	Thank you.
Peer Reviewer 3	Methods	Yes, however, there is one small issue: In the executive summary and in the main article: 1a Calibration section is blank. I assume this is because it wasn't assessed in any study. I would suggest reporting that no information is available or removing completely. 2 a, to be consistent with section 1b, the title should be "discriminative accuracy" I am a bit confused about the difference between 1 and 2 for KQ2. In 1b it states "the incremental gain in AUC observed when the predictive model including the SNP data was compared against the best alternative non-SNPs model". What is the difference between that and section 2 titled, "2. How do available panels predict the risk of prostate cancer when substituted for, or added to, PSA based and other clinical risk assessment test."	Thank you for pointing this out. We reviewed the way in which the subquestions in KQ2 were expressed and revised them to be clearer and mutually exclusive. This addresses all of these comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Methods	There may be prediction models that are commercially available but with no peer-review literature associated. These should be listed and mentioned if they exist.	Thank you for your comment. On behalf of the authors, the Scientific Resource Center directly contacted 40 companies known to provide either test services or diagnostic reagents potentially relevant to the key questions, in an effort to elicit unpublished sources of information. By the deadline of September 1, 2011, no information had been received from the companies.
Peer Reviewer 1	Results	The result section present all the relevant details to support the conclusions. There are many tables describing the details of the studies analyzed. Key messages are explicit and applicable, to the extent that they point to a lack of evidence for clinical use of SNP-based prostate cancer risk assessment. Figures, Tables and appendices are adequate. There does not seem to be important studies that have been overlooked	Thank you.
Peer Reviewer 2	Results	Fine	Thank you.
Peer Reviewer 3	Results	See issue above (methods)	
Peer Reviewer 4	Results	The two separate paragraphs on steroid hormone pathways could probably be combined. (2 SNPs vs. 3 SNPs).	Thank you for your comment. The authors prefer to leave the text as currently written as we feel it is explicit.
Peer Reviewer 1	Discussion	The discussion covers very well the limitations of this work, essentially due to the paucity of data and eligible studies for full assessment. The implications of the major findings are clearly stated. Given the current state of the art, and the many GWAS performed, it is likely that the most "useful" (or strongly associated) SNPs have been identified. Given the conclusion of this report on the clinical validity of SNPs-panels to assess risk, a discussion of the glim future prospects of SNP-based (or DNA-based) prostate cancer risk assessment tools would have been welcome, as recent studies have pointed to the limited added value of DNA-based markers (even in combination) in risk prediction of several complex traits.	Thank you for your comment. A discussion of the future prospects of SNP-based prostate cancer risk assessment tools would push us into the realm of speculation. This review confirms that at the moment there is nothing.
Peer Reviewer 2	Discussion	Yes	Thank you.
Peer Reviewer 3	Discussion	good	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 4	Discussion	Need more discussion of publication bias and how that may affect results. But more importantly need a more in depth discussion of these prediction models and their potential use in clinical decision making vs. their use in population screening (which seems to be the focus of this review). Any prediction model must be examined in the context of an intervention where the benefits of the intervention can be weighed against the harm. This may be in a RCT, but can also be taken from population-based observational studies. I recommend a starting point for this discussion and article in JCO by Andrew Vickers titled "Prediction Models: Revolutionary in Principle, But Do They Do More Good Than Harm?"	Thank you for your comment. A more detailed discussion of publication bias has been added to the report. As mentioned in response to "General Comments", we have added consideration of this work in the Discussion and in the section on Future Research.
Peer Reviewer 1	General	The report is clinically meaningful as prostate cancer is an important public health problem, with challenges in diagnosis and detection, but also in treatment and follow-up. The target population and audience are clearly defined at the beginning of the report. The three key questions cover well the issues at stake and to be resolved, and they are clearly stated and defined.	Thank you.
Peer Reviewer 2	General	data/conclusions seem straightforward. Clear KQs. Clear results	Thank you.
Peer Reviewer 3	General	Very well written and the authors followed the review guide well	Thank you.
Peer Reviewer 4	General	The article is well written and organized. Key questions are explicitly stated and answered. The key consideration that the review does not discuss or examine is the clinical net benefit of these risk prediction models. While the c-statisitic may be useful for eligibility criteria for a prostate chemoprevention trial or to identify a high risk group to be screened (this needs an extremely high c-statistic, not yet see in risk prediction models of cancer incidence), what is really needed is a metric that seeks to quantify the net benefit to a patient for using a particular decision rule to opt for a prostate biopsy or perhaps PSA screening, specifically, by choosing a threshold risk and deciding to undergo biopsy or PSA screening only if risk predicted by the decision rule exceeds this value. Andrew Vickers has written extensively on decision curve analysis and decision analysis. All the reviewed studies need to address their usefulness in clinical decision making. Even with a low c-statistic their clinical usefulness could be high, even if the prediction model cannot discriminate a high risk group. I highly recommend reading some of Andrew Vickers methodology work and incorporating this into the discussion.	Thank you for these very thoughtful comments. We have added a reference to the Vickers paper in JCO to the summary of prostate cancer screening in the Introduction. We have also added a brief discussion of the limitations of discrimination and calibration for clinical decisionmaking to the Discussion, and of the potential value of decision-analysis methods to the section on Future Research.

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Peer Reviewer 1	Clarity and Usability	The structure and organization of the report is adequate. The main points are clear. Perhaps, if the format allows it, putting major concluding sentences in bold would have been helpful, especially in the detailed parts of the report. The conclusions should be helpful to inform policy and practice decisions, as well as help identify the areas of research that warrant more investments (or not).	Thank you for your comment. The report was written according to the style requirements of AHRQ, some concluding paragraphs have been added which we hope are helpful.
Peer Reviewer 2	Clarity and Usability	yes	Thank you.
Peer Reviewer 3	Clarity and Usability	Very good	Thank you.
Peer Reviewer 4	Clarity and Usability	The conclusions are informative for population screening but not for individual clinical decision making	Please see previous response to “General Comments”.
Thomas Sellers (public comment)		The report is nicely done. A few critical points that are not evident from this presentation: 1) "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." In my opinion, the report doesn't address the "possible" value but rather "the value of current SNP panels". This is important because the field is moving so quickly, that they authors really needed to look down the road a bit (if indeed the "possible" value is to determined). For example, there are now over 50 confirmed loci for PC. 2) The future directions conclusion totally misses the critical issue: "There is also a need to identify and validate further genetic markers to enable larger SNP panels to be developed." The problem is that the GWAS SNPs are the not the causal SNP - they've merely identified the region where the true risk SNP resides. The risk significance will certainly increase once the actual causal variant has been identified. In addition, the functional effect has to be determined before any possible risk reduction strategy can be envisioned. To simply call for "larger panels" is insufficient.	Thank you for these thoughtful comments. In response to the first comment, we are already looking at potential rather than actual panels. With regard to the second point, we agree, and have revised the Discussion section accordingly.