Author's response to reviews

Title: A panel of kallikrein markers can predict outcome of prostate biopsy following clinical work-up: an independent validation study from the European Randomized Study of Prostate Cancer screening, France

Authors:

Amine Benchikh (alefgoun@hotmail.com)
Caroline Savage (savagec@mskcc.org)
Angel Cronin (serioa@mskcc.org)
Gilles Salama (labo@chic-castres-mazamet.com)
Arnauld Villers (arnauld.villers@wanadoo.fr)
Hans Lilja (liljah@mskcc.org)
Andrew Vickers (vickersa@mskcc.org)

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Author's response to reviews: see over
Editor

We hereby resubmit our paper on the kallikrein panel of markers when applied to participants in ERSPC France. Our rebuttal to the each reviewer’s comments, describing where we made changes to the paper, is given below.

We would respectfully like to point out that there was a large amount of time between the reviews being submitted (July 31st and August 4th) and a decision being sent to us. We are unclear why there was a seven week delay between obtaining the reviews, and the request for revision, especially given that the reviewers merely asked for clarifications on minor points. We do hope that this revision will be dealt with expeditiously.

Yours sincerely

Andrew Vickers
Reviewer: Kaushal

Comment: Good paper but needs more review of previously published screening studies so that a reader who is not familiar with prostate cancer screening can appreciate the difficulties involved with the process.

Response: We have added two paragraphs at the very beginning of the paper with additional details of prior screening studies. The new material reads:

Prostate specific antigen (PSA) is the only molecular marker routinely used for the early detection of a common cancer. Data from the US 2001 Behavioral Risk Factor Surveillance System are that 75% of men aged 50 years or older have had at least one PSA test and that, of men aged 50 to 69 years – the ages typically targeted in screening recommendations[ref] – 54% reported having had a PSA test within the past year [refs]. These numbers have remained fairly constant for data collected in 2002, 2004, and 2006[refs]. Racial disparities in PSA testing have been described. African-Americans below 50 have higher rates of screening that younger White men and Hispanic men[refs], likely due to explicit recommendations for an earlier start to screening in this population[NCCN]. Older African-Americans and Hispanics have lower rates of screening than comparably aged White men, an effect largely attributable to differences in socio-economic status[refs].

The recent results of two large, randomized trials give qualified support for the use of PSA screening. The value of PSA testing in men who would otherwise not be screened was assessed in the European Randomized Study of Prostate Cancer (ERSPC). A total of 182,000 men in seven European countries were randomized to PSA screening or control. The background rate of PSA testing in these countries was low. At a median follow-up of nine years, PSA screening was associated with a statistically significant 20% relative reduction in the risk of prostate cancer death. This difference is likely to increase over time. However, this benefit came at high cost, with an estimated 48 men needing to be treated for prostate cancer in order to prevent one death, or two cases of metastasis, at 9 years.[ref] The US-based PLCO trial, on the other hand, assessed a recommendation to screen in US men. As might be predicted from the population-based surveys described above, many of those accrued (~50%) had already had a PSA test. Moreover, many of the men randomized to the control group continued to have PSA tests irrespective of randomized assignment: 40% of men in the control group received a PSA test in the first year after randomization. At a median follow-up of 7 years, prostate cancer specific mortality was very low, with no difference between arms.[ref]

Reviewer: Den

Comment: in reviewing the literature, it appears that this model has been validated in other datasets already. This study did not advance this idea further.

Response: We were surprised by this comment. The introduction explicitly gives the rationale for the study. We state that in all our prior studies “all men with an elevated PSA were referred for biopsy” and that this is “distinct to usual clinical practice” because “men with elevated PSA are typically subject to clinical work-up before referral to biopsy”. We then explain how in the current cohort, the decision to biopsy was based on “clinical judgment” following additional work-up.
Comment: 1. The authors thoughtfully examine the details of further diagnostic workup of men with an elevated PSA in Table 1. I would like to see some analysis of either cost-function or QALY for undergoing additional tests. This may speak to the additional benefit that a more predictive assay would bring.
Response: The reviewer’s suggestion is not uninteresting. We respectfully submit however, that cost and QALY analyses of standard diagnostic tests are somewhat out of the remit of a paper evaluating a novel predictive model.

Comment: 2. Further, in the original ERSPC trial, overall survival and prostate cancer specific survival was reported. I would like to see how the kallikrein markers would impact on survival. Although, gleason score is a surrogate for aggressive disease, there is not a direct relationship to death from prostate cancer.
Response: We were somewhat confused by this comment. Prostate cancer mortality is not the endpoint of studies on the prediction of prostate biopsy, indeed, it is unclear as to how such a study could even be done. In particular, we would like to point out that ERSPC mortality data are not available to outside investigators.

Comment: 3. I would like to see the authors give more insight into how the base model and kallikrein model predict the AUC that they report. I understand that it is reported in a separate manuscript, but it would be beneficial to restate it in a few sentences within this manuscript.
Response: We have added details as to the development of the statistical models. We now say:

In brief, we created a “base” model using data routinely available in current clinical practice (age, PSA, DRE) and a “full” model also incorporating levels of total PSA, free PSA, intact PSA and hK2. In the original model, all markers were entered as restricted cubic splines with knots at the tertiles to allow a non-linear relationship with outcome. Multivariable logistic regression was used to fit all models.

Comment: 4. I think that it would be beneficial to comment on how this might be used prospectively in a trial
Response: We have added the following to the discussion section.

Our study involved frozen samples from a European population analyzed in a research laboratory. It is possible that results would vary were fresh samples to be analyzed in a clinical laboratory, as would the case in routine care. It is also possible that results may vary between Europe and the US, due to genetic differences between populations. In particular, aggressive prostate cancer is known to be more common in African-Americans[reference]. We intend to conduct a prospective study in the US, comparing the outcome of biopsy with the results of the predictive model when marker levels are analyzed in clinical laboratories using fresh bloods.