Title

Reply to Yuri Tolkach, Markus Kuczyk, Florian imkamp's letter to the editor re: Eric A. Klein, Matthew R. Cooperberg, Cristina Magi-Galluzzi, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of gleason grade heterogenei...

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Letter to the Editor

Reply to Yuri Tolkach, Markus Kuczyk, Florian Imkamp's Letter to the Editor re: Eric A. Klein, Matthew R. Cooperberg, Cristina Magi-Galluzzi, et al. A 17-gene Assay to Predict Prostate Cancer Aggressiveness in the Context of Gleason Grade Heterogeneity, Tumor Multifocality, and Biopsy Undersampling. Eur Urol 2014;66:550–60

We appreciate the interest in our article and have the following responses.

In regard to the selection of the prostatectomy cohort, as we describe in detail in the paper [1], we used an established stratified cohort sampling method (as described in references 23 and 24) in which all patients with clinical recurrence were selected, along with a 1:3 ratio of nonrecurrent patients. This does not mean that one-quarter of all patients in the total cohort failed but rather that the study cohort was enriched for failures to ensure that an adequate number of events were available for the analysis.

Next, with regard to the clinical utility of the Genomic Prostate Score (GPS), all of the analyses in the paper [1] (receiver operating characteristic curve, decision analysis, and net reclassification index) demonstrate unequivocally that adding GPS to standard clinical parameters more accurately classifies individual risk for clinical recurrence (prostatectomy study) or adverse pathology (biopsy and validation studies). The clinical utility of this information varies according to patient and clinician attitudes about surveillance and, it is important to note, adds to but does not replace the usual criteria that may lead to the decision that surveillance is a reasonable option.

In our experience, a major hurdle to the underuse of surveillance is patient and clinician uncertainty about the biologic potential of a given tumor. GPS and other tools like it are the first to address this issue based on the small amount of tumor material that is available on biopsy. The clinical utility of identifying a high risk of adverse pathology for a young patient with long life expectancy and clinically low-risk disease—for whom the decision may be made to forgo surveillance—is obvious. Less obvious, but still useful, are GPS scores that reaffirm a correct categorization of low-risk disease so that both patient and clinician can be reassured that more aggressive disease is not present at baseline and that an initial decision for surveillance is safe.

Beyond choosing an initial management strategy, potential benefits of using a biologic marker such as GPS to assess aggressiveness include (1) tailoring the intensity of follow-up evaluations with imaging or rebiopsy (less intense for patients with more favorable scores, and more intense for patients with higher scores) and (2) serial biologic monitoring to address another unmet need in surveillance, namely, helping to decide when curative intent intervention is necessary. Successful deployment of both these strategies will require a baseline assessment of biologic potential.

The way the authors phrase their question about what GPS dictates treatment suggests an impression that the GPS score has a threshold value above or below which adverse pathology is present. In fact, the GPS score is a continuous variable and should not be categorized for a *yes or no* prediction any more than prostate-specific antigen (PSA) should be used for screening with a threshold of 4 ng/ml. It is important to emphasize that any biologic marker should not by itself be used to make a decision on surveillance; the biological marker should always be interpreted in the context of grade, stage, extent of biopsy involvement, and PSA as well as individual clinical circumstances and, most important, the patient's preferences. Thus, the answer depends entirely on the details of an individual patient's desire, risk tolerance, comorbidities, and life expectancy. For a 70-yr-old with a life expectancy of 15 yr, a 20% risk of adverse pathology may be sufficiently low to make him comfortable with surveillance; this is not necessarily so for a 50-yr-old with a 35-yr life expectancy. In our clinical experience with this test (it has been available commercially in the United States since May 2013), the same score can—appropriately—result in different decisions for individual patients.

The question the authors raise about the issue of upgrading is not entirely clear from their letter. We believe that the microdissection experiments in the prostatectomy study demonstrate that there is a common underlying biology, as measured by gene expression, that is shared by both primary and secondary Gleason pattern tumors that

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coexist in the same prostate and that can be measured even if only the lowest-grade tumor is assessed. In fact, the emerging stories of multiple biomarkers based on prostate biopsy tissue that are able to predict final pathology or other clinical end points independent of clinical variables suggest that the genetic profile of aggressive tumors can be discerned even in areas of the tumor that appear less aggressive based solely on the venerable Gleason grading system.

The technical development of our assay, including RNA quality, is quite robust. We refer the authors and interested readers to our technical report on this issue [2].

The use of magnetic resonance imaging (MRI) was not assessed in this study [1], and we agree that multiparametric MRI may have clinical utility in patients deciding on active surveillance, as well as for monitoring. We also believe that MRI and biomarkers may have complementary, and not necessarily competing, roles in this clinical space.

The authors asked whether adverse pathology and clinical metastatic status have the same meaning. On a clinical level, the answer is *no* because many patients with adverse pathology as defined in our study are cured by prostatectomy and/or other local treatments. However, it is well established by long-term clinical experience and predictive modeling that patients with adverse pathology, as we defined it in the study (dominant pattern 4 disease and/or disease outside the prostate), are at the highest risk for disease recurrence, metastases, and death (see Eggener et al. [3] and Stephenson et al. [4]). In a biological sense, we have demonstrated that the same genes that predict for adverse pathology also are predictive for metastases and death, making their assay on biopsy specimens highly clinically relevant.

Biopsies in both the biopsy and validation studies were performed according to prevailing clinical standards at the times they were done, spanning many years and clinical sites. The results of this study are therefore likely to be robust to secular trends in biopsy and are likely to have meaning in the context of day-to-day urologic practice.

The authors state that "no really remarkable results identified clinically relevant genetic signatures in prostate cancer." We disagree with the authors on this point and have demonstrated clinical relevance by a variety of methods that show that adding GPS to standard clinical parameters more accurately classifies individual risk for clinical recurrence (prostatectomy study) or adverse pathology (biopsy and validation studies) [1]. We do not understand why the authors might think that more accurate classification of risk is of no clinical value.

Finally, we do not share the authors' nihilism regarding the robustness of gene expression as a marker for tumor aggressiveness; numerous published studies suggest that this approach is useful in prostate and other cancers. We note that in raising their objections to our findings, the authors provide no countermanding data and are simply expressing their own opinions.

Conflicts of interest: Matthew R. Cooperberg has an ongoing research agreement with Genomic Health.

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