Validation of a genomic classifier that predicts metastatic disease progression in men with biochemical recurrence post radical prostatectomy.

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Background: The majority of the 29,000 men who die annually from prostate cancer present initially with localized disease and develop biochemical recurrence (BCR) following radical prostatectomy (RP). While the post-RP recurrence group of patients is highly enriched for those who will develop lethal disease, many of these patients will experience BCR without subsequent metastases. Thus, there is a clear need to improve patient risk stratification in this context. Here, we evaluate Decipher, a genomic classifier (GC) in men with BCR for its ability to predict metastasis. **Methods:** The 22-feature GC model was validated in a prospectively designed case-cohort study of a clinically high-risk population of 1,010 RP patients treated at Mayo Clinic between 2000-06. A random sample of 20% of this population was subjected to microarray analysis and GC scores were generated for 219 patients, including 110 who developed BCR post RP. The c-index for predicting metastatic disease progression (i.e., positive bone or CT scans), Cox modeling, decision curves and multivariable analyses were used to compare the performance of GC to Gleason score (GS), PSA doubling time (PSAdT) and time to BCR (ttBCR). **Results:** The c-index for predicting metastatic disease progression 3 years after BCR was 0.82 (95% CI, 0.80-0.90) for GC, which compared favorably to GS 0.65 (0.54-0.69), PSAdT 0.60 (0.62-0.78) and ttBCR 0.54 (0.64-0.81). Decision curve analysis showed that GC had a higher overall 'net benefit' compared to GS, PSAdT and ttBCR for risk of metastasis. Cumulative incidence of metastasis 3 years after BCR was 9% versus 43% ($p<0.001$) for patients with low and high GC scores, respectively. In multivariable modeling with clinicopathologic variables, GC ($p<0.001$) and GS ($p=0.02$) scores remained the only significant predictors of metastasis. **Conclusions:** When compared to clinicopathologic variables, GC better predicted metastatic progression among our cohort of men with BCR following RP. While confirmatory studies in additional patient populations are required, these results suggest that use of GC can allow for better selection of men

requiring additional treatment at the time of BCR.
