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Biomarkers for prostate cancer: who will benefit from local treatment, who harbors occult systemic disease and who needs treatment at all?

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Prostate cancer is one of the most common cancers in men. The disease is heterogeneous in presentation and prognosis. Prior to the 1980s, the vast majority of prostate cancer diagnoses in the developed world were at advanced stages, either locally advanced or metastatic. The development of PSA as a method to screen for prostate cancer in the 1980s led to a sudden and dramatic increase in the proportion of patients diagnosed with earlier stages of disease [1]. Simultaneously, the appreciation that many men die of other causes while harboring clinically insignificant prostate cancer led to consternation among clinicians regarding whether treatment is really indicated for the vast number of older prostate cancer patients or those harboring ‘low-risk’ localized disease. As increasing early diagnoses were made, it became clear that aggressive local treatment, although effective for the vast majority of patients, may also be overtreatment for many.

However, it remains certain that not all prostate cancer is insignificant and not all patients should be enrolled in surveillance protocols. An estimated 10% of prostate cancer patients will die of prostate cancer and many more will progress after local therapy and go on to receive long-term systemic therapy that can diminish their quality of life [2,3]. Treatment options for men with castration-resistant metastatic prostate cancer are expanding, and the

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disease is increasingly being treated as a chronic illness; however, a subset of these patients progress rapidly and are left with few effective treatments.

Although a number of clinical prognostic factors are known and are in clinical use, patients from both ends of the prostate cancer spectrum – those with highly aggressive or indolent tumors – would benefit from the development of accurate prognostic biomarkers. Perhaps most useful would be biomarkers that allow a clinician to determine prior to biopsy if a patient harbors clinically insignificant or high-grade, aggressive disease. Biomarkers are not only useful at diagnosis for purposes of prognostication, but as a marker of efficacy of treatment. These predictive biomarkers promise to revolutionize the method of treatment selection for patients with clinically significant cancers. Understanding which tumors are better treated with a specific local modality would allow treatment decisions based on efficacy and toxicity.

This issue of *Biomarkers in Medicine* describes the current state of the science in developing and validating biomarkers in prostate cancer. The intent of the issue is to describe biomarkers from the standpoint of disease stage and from the setting of biomarker type. Clearly, the future of the field will be enriched with the ability to accurately determine a patient's prognosis, need for treatment, optimal treatment and anticipated efficacy of treatment. Much work remains to determine which biomarkers, or panels of biomarkers, will provide the best prognostic and predictive information at each stage of disease.

In this issue, Schmid *et al.* review methods of stratification of men at risk for prostate cancer prior to biopsy, such as nomographs, PCA3 and human kallikrein panel [4]. Many patients with low-risk prostate cancer find recommendations for surveillance or observation challenging to accept and eventually undergo therapy. Accurate biomarkers and nomograms in this context could spare a tremendous number of patients the diagnosis of prostate cancer for which no treatment will be recommended.

Prostate tissue obtained at biopsy or surgery provides tumor samples for direct analysis, and frequently an opportunity for validation of circulating biomarkers. Prostate cancer is unique in the high prevalence of mutations or deletions in genes such as *PTEN* and *p53*, as well as fusions of *TMPRSS2* to members of the *ETS* family of transcription factors [5–8]. Furthermore, *TMPRSS2:ERG* fusions have been shown to correlate with prostate cancer aggressiveness and prognosis [9]. In this issue, Falzarano *et al.* present a comprehensive review of ERG protein expression as a biomarker of prostate cancer [10]. As highlighted in their article, ERG protein expression has both diagnostic utility and prognostic capabilities.

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Circulating cell-free nucleic acids as biomarkers for cancer have been an area of intense research in a number of cancer histologies in the recent past. Tumor cell turnover releases these nucleic acids into the circulation, which can provide an excellent opportunity for detection. In this issue, Sita-Lumsden *et al.* provide a thorough review of the promise and limitations of circulating nucleic acids as biomarkers in prostate cancer [11]. A variety of

circulating nucleic acids have been evaluated in this context, including DNA and RNA. Perhaps the greatest rationale for the use of DNA biomarkers is the known high prevalence of mutations with prognostic relevance, such as *TMPRSS2:ERG* fusions, in prostate cancer. Although mutations are an obvious choice, other nucleic acids or modifications preferentially observed in tumors can be detected in the circulation, such as hypermethylation of CpG islands, allelic imbalance, miRNA and mRNA. Certainly, the frequent multifocal nature of prostate cancer also makes these sorts of noninvasive sampling methods attractive, as areas not sampled with a biopsy may be sampled in surrogate via the circulation.

Prostate cancer is not simply a mass of tumor cells, requiring a robust supporting stroma that interacts with the host and tumor [12,13]. Similarly, angiogenesis has long been appreciated as a major requirement for tumor growth [14]. In this issue, Reeves *et al.* provide a unique insight into the opportunities that circulating endothelial cells, endothelial progenitors and platelets provide as biomarkers of prostate cancer progression and aggressiveness [15]. The limitations and confounding factors of assays to detect these markers are well described and the need for prospective validation championed.

Although tissue and circulating biomarkers have thus far been the most studied, urinary biomarkers are under ever increasing study in this setting. Urine is an attractive substrate for study given the ease of collection combined with the proximity of the prostate to the urinary tract. Studies of urine markers in the context of prostate cancer have included spot urine collection or collection following prostate examination or massage. Two articles in this issue describe novel prostate cancer biomarkers detected in urine. McGrath *et al.* review several urinary biomarkers, including PCA3, ANXA3 and *TMPRSS2:ERG* fusion transcripts [16]. They also describe *En-2*, a homeobox family gene, as a diagnostic marker and as a marker of tumor volume. Prager *et al.* present a panel of urinary markers, IGFBP-3, activated HGF and OPN, in an attempt to identify urinary markers to distinguish localized from metastatic disease [17].

Other surrogates, such as MRI, are being used alone or in combination with the sorts of biomarkers described here [18]. Combining bio-markers into panels and correlating imaging findings with biomarkers and clinical outcomes promises to redefine how we manage prostate cancer patients in the future. Although a single issue is insufficient to describe every horizon in the field of prostate cancer biomarkers, it is hoped that the reader will develop a greater understanding of unique areas of study and the diversity of biomarker source, biomarker type and the setting of use for these biomarkers.

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Biographies

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