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Diagnosis, staging, and risk stratification in prostate cancer: Utilizing diagnostic tools to avoid unnecessary therapies and side effects

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ABSTRACT

A lack of appropriate diagnostic tools for prostate cancer has led to overdiagnosis and over treatment. In a recent publication in the *New England Journal of Medicine*, Hamdy et al showed no difference in the outcomes of patients that had undergone either radical prostatectomy, radiotherapy, or active monitoring. In an effort to enhance clinical stratification, the development of improved, more accurate diagnostic tools is actively being pursued. Herein, we explore recent advances in prostate cancer screening, including biomarker assays, genetic testing, and specialized fields, such as mathematical oncology. These newly developed, highly sensitive diagnostic assays may potentially aid clinicians in selecting appropriate therapies for patients in the very near future.

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Since the early 1990s, the FDA approved prostate-specific antigen (PSA) testing in blood has been used as a method of screening for prostate cancer in asymptomatic men.[1] Consequently, the number of diagnoses and subsequent treatments dramatically increased[2,3] despite alternative forms of the PSA test that improved selectivity for prostate cancer, such as PSA velocity and PSA free-to-total ratio.[4,5] However, there is much controversy surrounding this initial screen. Not all men benefit from early intervention, and treatment often leads to urinary, bowel, or sexual dysfunction. It has been shown that up to 70% of men could avoid treatment after active monitoring of 15 years[6]; however, physicians and patients are often concerned about missing the window of opportunity to cure aggressive prostate cancer. In an effort to avoid early treatment and associated side effects, emphasis has been placed on the development of prognostic and predictive biomarker assays so that more appropriate treatments can be assigned to men with prostate cancer.

In a recent publication from the *New England Journal of Medicine*, Hamdy et al. explored the effectiveness of 3 common treatment methods - radical prostatectomy, radiotherapy, and active monitoring - in men who were diagnosed with PSA-detected, clinically localized prostate cancer.[7] With the relative effectiveness of these traditional treatment regimens still unknown, the authors examined differences in prostate cancer-specific mortality, all-cause mortality, and disease progression between cohorts.

The Prostate Testing for Cancer and Treatment (ProtecT) trial, which was supported by the National Institute for Health Research, screened 82,429 men between the years of 1999 and 2009 for prostate cancer. Of those men, 2,664 (3.2%) were diagnosed with localized prostate cancer after receiving a PSA test, and 1,643 of those (62%) were randomized into one of 3 treatment cohorts – 545 to active monitoring, 553 to radical prostatectomy, and 545 to radiotherapy. The men in the active monitoring group were used as a control to minimize the risk of overtreatment. If a change in PSA level was noticed, the men were considered for radical treatment. Men in the radiotherapy cohort received neoadjuvant androgen-deprivation therapy for 3 to 6 months before and during treatment with 3-dimensional conformal radiotherapy at a dose of 74 Gy in 37 fractions. Radiotherapy was considered for men assigned to prostatectomy if their disease progressed after surgery.

After 10 years, the rates of disease progression and metastatic disease in the prostatectomy and radiotherapy cohorts were less than half of those in the active monitoring group (2.4, 3.0, and 6.3 events per 1000 person-years, respectively). This suggested that early radical treatment is more effective in preventing prostate cancer progression than active monitoring. However, while over half of the men in the active monitoring cohort received radical treatment before the end of the study, 44% received no treatment and avoided potential negative side effects, emphasizing the need to weigh costs and benefits before radical treatment. In addition, no significant difference ($p = 0.48$) in prostate cancer-specific mortality was noted between groups (1.5, 0.9, and 0.7 deaths per 1000 person-years in active monitoring, surgery, and radiotherapy cohorts, respectively), suggesting a need for lengthened survival data and better methods to predict prostate cancer progression.

In an effort to reveal a more predictive biomarker, preferably earlier in the course of treatment, Alhasan et al. correlated the expression of circulating microRNAs (miRNAs) with very high-risk (VHR) prostate cancer.[8] With the use of a high-

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throughput, spherical nucleic acid-based miRNA (Scano-miR) expression profiling platform, the authors identified a molecular panel – miR-200c, miR-605, miR-153a*, miR-433, and miR-106a – specific to very high-risk, aggressive prostate cancer. To validate their findings, the researchers conducted correlation and blinded reverse qRT-PCR validation studies and found that the signature, but not all of the individual miRNAs, correlated with very high-risk prostate cancer. In addition, the receiver operating characteristic score, which designates the diagnostic capability of a binary classification system by comparing specificity and sensitivity, for each miRNA (1.0, 0.98, 0.98, 0.92, and 0.89 for miR-200c, miR-433, miR-135a*, miR-605, and miR-106a, respectively) were higher than that of a prostatic needle biopsy (0.81), suggesting that the molecular signature is more accurate than biopsy when distinguishing between low and very high-risk prostate cancers.

Additionally, the validated miRNA signature was shown to be correlated with cancer progression and phosphatidylinositol-4,5-bisphosphate 3-kinase-Akt serine/threonine kinase (PI3K-Akt) signaling. These findings suggest that the miRNAs may target genes in pathways involved in the progression of localized to metastatic prostate cancer. However, additional studies are needed to determine the specific role of the miRNAs in prostate cancer progression and to validate the efficacy of these biomarkers in a larger patient cohort. This procedure could allow physicians to distinguish between low- and high-grade prostate cancers and inform physicians of optimal treatment options to avoid unnecessary intervention.

The use of genetic testing has also been targeted for use as a predictive biomarker in prostate cancer. For the past decade, the role of intratumoral androgen synthesis has been a focus of resistance to androgen deprivation therapy (ADT). With testosterone depleted during ADT, the tumor continues to proliferate through the conversion of adrenal precursor steroids. Hearn et al. examined the clinical relevance of a mutation in *HSD3B1*, which encodes the enzyme 3β-hydroxysteroid dehydrogenase-1 (3βHSD1), in prostate cancer.[9] 3βHSD1 is involved in a key step in the conversion of adrenal androgen precursors to dihydrotestosterone,[10] and *HSD3B1* 1245A>C results in an increase in 3βHSD1 activity, and therefore intratumoral androgen synthesis.[11] Three cohorts were included: primary (n = 118), post-prostatectomy validation (n = 137), and metastatic validation (n = 188). The *HSD3B1* (1245C) allelic frequency in the primary, post-prostatectomy, and metastatic cohorts were 36%, 26%, and 27%, respectively, with a pooled allelic frequency of 29%. The distribution of homozygous wild-type, heterozygous, and homozygous variant genotypes were 49%, 43%, and 7%, respectively. The results showed a stepwise decrease in progression-free survival, distant metastasis-free survival, and overall survival between the homozygous wild-type, heterozygous, and homozygous variant cohorts, respectively. Supported by the group's earlier finding that 3βHSD1 levels increase as a result of *HSD3B1* 1245C SNP, the data suggest that screening for the *HSD3B1* genotype may be a valuable biomarker when considering a patient's resistance to ADT. Early, aggressive treatment options may be more appropriate for men either heterozygous or homozygous variant for the *HSD3B1* genotype.

While these biomarkers may be capable of distinguishing between indolent and aggressive cancers, they lack specificity toward a single treatment option. Zhao et al. recently validated the first treatment-specific predictive signature, Post-Surgical Radiation Therapy Outcomes Score (PORTOS), which included 24 genes involved in DNA damage and radiation response.[12] A patient's PORTOS was calculated using a ridge-penalized Cox model, which was validated in a training cohort (n = 196). Eligible men must have received a radical prostatectomy and a genetic analysis of their tumors. In the training cohort, men who received radiotherapy after surgery were matched with men who did not, but the men shared similar factors, such as surgical Gleason score, PSA concentration, seminal vesicle and lymph node invasion, and ADT. The difference between the prediction with and without radiotherapy was calculated from the model and converted to a binary score, with 0 as the cutoff. Patients above 0 would benefit from radiotherapy, while patients at or below 0 would not benefit from radiotherapy. A validation cohort (n = 330) was used to verify the signature. The primary end point was occurrence of distant metastasis.

PORTOS was successful in predicting outcome due to radiotherapy treatment. In the training cohort, men with a high PORTOS had a lower incidence of distant metastasis after receiving postsurgical radiotherapy than men who did not. Men with a low PORTOS had a higher incidence of distant metastasis after receiving postsurgical radiotherapy than men who did not; however, this finding was not confirmed in the validation cohort. The data suggest that men with high PORTOS could be good candidates for postsurgical radiotherapy.

Furthermore, predictive medicine in prostate cancer staging and treatment determination has recently spread into the field of mathematical oncology. In a recent publication from the *Proceedings of the National Academy of Science*, Lorenzo et al. developed a computer simulation to predict the growth of prostate cancer.[13] The progression of early to midlate prostate cancer was modeled using the phase-field method and diffusion-reaction equations, taking into account cellular transformation, nutrient utilization, and PSA production. The growth model matched well with experimental and clinical observations, showing a change in tumor shape from spheroidal to fingered geometry. This fingered geometry is believed to allow greater surface area and uptake of nutrients and may be responsible for false negatives due to missed 12-point needle biopsies. Paired with MRI, the use of this model could allow physicians to bypass invasive biopsy procedures and guide in the diagnosis and treatment of individual cases of prostate cancer. In fact, Lorenzo et al. used the model to predict the progression of a patient's cancer, using original images of the tumor and actual anatomy of the patient's prostate. Once optimized, this computer model could possibly be combined with patient parameters, including specific biomarkers, to predict response to specific treatment options.

In conclusion, the number of men diagnosed with prostate cancer, and the number of subsequent treatments, increased with the introduction of PSA testing. In an effort to avoid unnecessary intervention and its side effects, the development of prognostic and predictive biomarker assays have become the focus of current research. While many of these studies have yet to be validated in larger patient cohorts, it is evident that biomarker assays, genetic testing, and specialized approaches like mathematical oncology are becoming more prevalent, and

promising, in the field of prostate cancer diagnosis and treatment.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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