EDITORIAL

The evolving clinical use of prostate cancer biomarkers

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In men with elevated PSA, risk stratification can be refined by further diagnostic testing with multiparametric MRI and/or one of several commercially available biomarker assays. SelectMDx is one such test that combines urinary mRNA expression with DRE, age, and PSA density to predict the presence of Gleason score ≥7 prostate cancer on biopsy. Expert clinical guidelines currently offer that biomarker tests such as SelectMDx be considered for risk stratification prior to prostate biopsy [1]. However, which biomarkers to use and how exactly to incorporate them into the diagnostic pathway remains unclear. In the current report, Visser et al. [2] provide a descriptive analysis of 5 157 men who underwent SelectMDx testing across ten European countries. They further compared the clinical characteristics of this real-world testing population to the Haese et al. patient population (a 100% biopsy-naive cohort) used for the original validation of the test [3].

The authors report that the Netherlands and Spain account for the majority of SelectMDx testing, comprising 34.8% and 31.1% of the testing population, respectively. Thirty-seven percent of men tested with SelectMDx were 55–64 years old. Notably, 23% of the SelectMDx tests were performed in men with PSA <3 or >10 ng/ml. Comparing this real-world testing population to the original validation cohort ($n = 916$), the authors found no significant differences in age (median 65 vs. 65, $p = 0.465$) or PSA (6.6 vs. 6.4, $p = 0.067$), while the clinical testing population had higher prostate volume (50 vs. 42.5, $p < 0.001$), lower PSAD (0.126 vs. 0.140, $p < 0.001$), and fewer abnormal DRE results (17.8% vs. 22.3%, $p = 0.001$) [2, 3]. Relative to the validation cohort, significantly fewer men in the testing cohort had a positive test result (59.3% vs. 64.3%, $p = 0.004$) (Table 1). These findings begin to characterize the study population undergoing SelectMDx testing in current clinical practice in Europe. Notably, the report is limited by a lack of data regarding baseline biopsy status (i.e., biopsy-naive vs. previous negative biopsy), use and findings of MRI, and biopsy results.

While recent data have better characterized the potential role of biomarker testing, several critical questions remain. First, we need to understand how biomarker tests interface with mpMRI, a question currently being prospectively pursued [4]. In the meantime, retrospective data have sought to inform on this question [5, 6]. For example, Hendriks et al. [5] found that using MRI to guide the decision to biopsy could potentially reduce biopsies by 49% (compared to 38% for SelectMDx alone), while missing fewer clinically significant cancers (4.9% vs. 9.8%). However, if a biopsy is performed when either mpMRI or SelectMDx is abnormal, 27.5% of biopsies are potentially avoided, while missing only 1.6% of Grade Group (GG) ≥2 disease. Highlighting the imperfect negative predictive value of MRI, Maggi et al. [6] found that performing biopsy only in men with positive MRI (PIRADS 3–5) would have missed 16% of GG ≥2 cancers, while use of SelectMDx to select for biopsy in the MRI-negative population led to missing only 1.1% of GG ≥2 cancers. These data support the likelihood that prostate cancer diagnosis can be further refined with mpMRI and biomarkers, yet the optimal combined or sequential approach remains to be defined.

Second, there is a need to more clearly define use of biomarkers in disparate populations and consider practical testing implications. A body of data reflect that a previous negative biopsy is associated with a reduced risk of clinically significant cancer on subsequent biopsies and more favorable pathology when cancer is detected [7, 8]. Nonetheless, validation studies have in some

Table 1. Characteristics of contemporary European testing population and published validation cohorts.

	Clinical testing population [2]				Validation study populations	
	By PSA			Overall	Haese et al. [3]	Van Neste et al. [10]
Median (IQR) or %	<3 ($n = 275$)	3–10 ($n = 3953$)	>10 and ≤15 ($n = 579$)	$N = 5157$	$N = 916$	$N = 386$
Age, years	62 (54–68)	65 (59–70)	67 (62–72)	65 (60–71)	65 (60–70)	65 (60–70)
PSA, ng/mL	1.98 (1.22–2.50)	6.10 (4.88–7.66)	12.0 (11.0–13.1)	6.60 (4.90–9.06)	6.37 (4.50–9.20)	7.3 (5.2–10.9)
PV, cm^3	37.5 (30.0–49.3)	50 (38–66)	62.3 (47.0–88.1)	51 (38–70)	42.5 (30.9–60.0)	45 (35–62)
PSAD, ng/mL^2	0.05 (0.03–0.06)	0.12 (0.09–0.17)	0.19 (0.13–0.28)	0.13 (0.09–0.19)	0.14 (0.09–0.22)	0.15 (0.10–0.25)
Abnormal DRE	29.8%	15.8%	16.7%	17.8%	22.3%	31.3%
% Previous Bx	Not reported				0%	11%
% MRI	Not reported				15.1%[a]	Not reported
SelectMDx test positive	24.7%	55.3%	80.7%	59.3%	64.3%	N/A

IQR interquartile range, *PSA* prostate specific antigen, *PV* prostate volume, *PSAD* prostate specific antigen density.
[a]Includes men from the training and validation cohort.

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cases used an "all-comer" population, without regard for how previous biopsy status impacts present and future risk [9]. Thus, it is unclear how the current report should be interpreted relative to validation data in which the vast majority of patients were biopsy-naive [3, 10]. Indeed, biomarker tests that do not account for previous biopsy status in modeling should consider this distinction at the time of clinical application. Furthermore, there is a great need to validate the performance of biomarker tests across racially diverse populations.

In summary, the authors have nicely described the population of men undergoing SelectMDx testing in the contemporary European setting. More importantly, they compare this contemporary testing population to validation cohorts, raising the question of how current use compares to the proposed use. While the clinical impact of the report is somewhat limited by a lack of corollary information (e.g., MRI use, biopsy findings), the authors have made another important contribution to our evolving understanding of prostate cancer biomarkers. Better characterizing the "real-world" testing population is critical as we seek to more clearly define current testing applications, and, in parallel, develop a new generation of biomarkers ideally suited to the current clinical landscape.

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AUTHOR CONTRIBUTIONS

The authors drafted this comment in reference to a recently published study (Visser et al. [2]).

COMPETING INTERESTS

JJT is a co-founder of LynxDx, Inc. The other authors declare no competing interests.

ADDITIONAL INFORMATION

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