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INVITED OPINION

Prostate Cancer

The Xu's chart for prostate biopsy: a visual presentation of the added value of biomarkers to prostate-specific antigen for estimating detection rates of prostate cancer

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Elevated serum prostate-specific antigen (PSA) level is the primary indication for prostate biopsy for detection of prostate cancer (PCa) in the modern era. The detection rate of PCa from biopsy is typically below 30%, especially among patients with PSA levels at 4–10 ng ml^{-1}. In the past several years, additional biomarkers, such as Prostate Health Index, PCA3 and genetic risk score (GRS) derived from multiple PCa risk-associated single nucleotide polymorphisms (SNPs) have been shown to provide added value to PSA in discriminating prostate biopsy outcomes. However, the adoption rate of these novel biomarkers in clinics is low, largely due to poor understanding of the added value of novel biomarkers. To address this matter, we developed a chart to visually present (i) expected detection rates of PCa from biopsy with respect to PSA levels, and more importantly, (ii) a range of PCa detection rates at the same PSA levels when novel biomarkers are considered. This chart, called the Xu's chart for prostate biopsy, is not a formal risk prediction model; rather, a simple visual tool for urologists to communicate with their patients an initial evaluation of PCa detection rate based on their PSA levels and a possible recommendation for additional biomarkers. A more comprehensive evaluation of PCa risk using existing risk assessment tools such as nomograms can be followed once additional biomarkers are measured. The current version of the chart is only a prototype and should be further developed to include the detection rate of aggressive PCa, and validated in larger studies.

PCa is the second most frequently diagnosed cancer and the sixth leading cause of cancer-related death in men, with an estimated 914 000 new cases and 258 000 deaths per year globally in 2008.[1,2] PCa incidence rate differs widely among countries and regions, possibly due to differences in the adoption rate of PSA screening for PCa, as well as inherited risk and environmental exposures such as diet. The trend of PCa incidence in the last several decades also differed considerably among various countries and regions. In the United States, the incidence rate increased sharply in the early to mid-1990s with the introduction of PSA screening for PCa, and declined since.[3] In Shanghai, China, the age-adjusted incidence rate of PCa increased from 2.3 per 100 000 during 1988–1992 to 6.9 per 100 000 during 1998 to 2002,[4] and reached 16.0 per 100 000 in 2007 (unpublished data). The sevenfold increase of PCa incidence in Shanghai coincided with the gradual introduction of PSA screening for PCa during that period of time.

ELEVATED PSA LEVELS, PROSTATE BIOPSY AND PCa DETECTION RATE

In developed countries and many developing countries where modern medical services are readily accessible, most PCa are diagnosed from prostate biopsy among asymptomatic men with elevated PSA levels through a systematic PSA screening or incidental PSA tests. While PCa detection rate is typically over 50% among patients with considerably elevated PSA levels (e.g., >10 ng ml^{-1}), its detection rate is generally low, especially among those with moderately elevated PSA levels (4–10 ng ml^{-1}). For example, the overall PCa detection rates were only 33.0% among 25 733 patients who underwent prostate biopsy in 10 biopsy cohorts from the Prostate Biopsy Collaborative Group,[5] and personal communication with Dr Donna *P* Ankerst (**Table 1**). The PCa detection rate was 25.2%, 33.8% and 56.3% among patients with PSA <4, 4–10 and >10 ng ml^{-1}, respectively. Similar results were found in Chinese men. In a hospital-based study of 667 consecutive patients who underwent prostate biopsy at two tertiary hospitals in Shanghai, China between 2011 and 2012, the PCa detection rate was 39.0% in the entire cohort, and was 17.7% and 52.3% in patients with PSA at 4–10 and >10 ng ml^{-1}, respectively.[6]

The overall low detection rate of PCa from biopsy may be attributed to the fact that PSA is prostate specific, but not PCa specific. Many noncancer factors such as enlarged prostate and inflammation in the prostate may also lead to elevated PSA levels. Therefore, a decision of prostate biopsy based on PSA levels alone may lead to many unnecessary biopsies. Prostate biopsy is an invasive procedure and is often associated with potential harms. It is estimated that one-third of men who have prostate biopsy experience pain, fever, bleeding, infection, transient

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Table 1: Detection rate of prostate cancer from biopsy in patients with various PSA levels

Study	No. of patients by PSA levels (ng ml^{-1})				Detection rate of PCa by PSA levels (ng ml^{-1}) (%)			
	All	<4	4–10	>10	All	<4	4–10	>10
Goeteborg round 1	740	254	397	89	25.9	16.5	24.9	57.3
Goeteborg rounds 2–6	1241	840	385	16	25.9	26.5	24.7	25.0
Rotterdam round 1	2895	769	1745	381	27.6	20.2	24.8	55.9
Rotterdam rounds 2–3	1494	1019	452	23	26.0	23.5	31.0	39.1
Tarn	298	117	161	20	32.2	24.8	34.8	55.0
SABOR	392	238	133	21	33.9	28.2	41.4	52.4
Cleveland clinic	3286	636	2059	591	39.3	33.6	40.3	42.1
Prorect T	7324	2967	3669	688	35.1	26.1	35.6	71.4
Tyrol	5644	2626	2294	724	27.7	20.3	30.4	45.9
Durham VA	2419	763	1182	474	47.5	39.6	43.4	70.3
Total	25 733	10 229	12 477	3027	33.0	25.2	33.8	56.3

PCa: prostate cancer; PSA: prostate-specific antigen

urinary difficulties or other issues requiring clinician follow-up, and approximately 1% require hospitalization.[7]

OTHER NOVEL BIOMARKERS FOR PCa

To overcome the low specificity of PSA for predicting PCa and reduce over-biopsy, extensive efforts have been devoted to develop other biomarkers. One such biomarker is serum free PSA (fPSA), the form of PSA that is unbounded by protein. It has been shown that men with PCa have a lower %fPSA (proportion of fPSA in total PSA (tPSA)) than those without PCa.[8] Several studies demonstrated that a cutoff of 14%–28% could reduce unnecessary biopsies by 19%–64%, while maintaining a sensitivity of 71%–100%.[9-11]

Another related biomarker is a truncated PSA isoform, [-2]proPSA (p2PSA).[12] A systematic review and meta-analysis demonstrated that serum p2PSA has greater accuracy than tPSA or fPSA in detecting PCa in men with a tPSA between 2 and 10 ng ml^{-1}.[13] Furthermore, a prostate health index (PHI), derived from a combination of p2PSA, tPSA and fPSA, has been shown to be a better predictor of PCa.[14] PHI test for men 50 years and older with a tPSA value between 4 and 10 ng ml^{-1} and a digital rectal exam (DRE) with no suspicion of cancer by Beckman Coulter Inc has been approved by the European Medicines Agency and the United States Food and Drug Administration.

Several urine biomarkers for PCa have also been developed. The prostate cancer antigen 3 (*PCA3*) gene is overexpressed in PCa tissue compared with adjacent benign prostate hyperplasia or normal prostate tissue.[15] In addition, *PCA3* expression is not detectable in non-prostatic normal tissues and tumors, suggesting that *PCA3* is PCa specific.[16] A quantitative urinary assay for *PCA3* messenger RNA (mRNA) has been developed, with an area under the receiver operating characteristic curve (AUC) of ~0.75 in discriminating prostate biopsy outcomes.[17] Its predictive performance was later confirmed in multiple studies, with an AUC from 0.69 to 0.75 for discriminating PCa and high-grade PCa.[18-21] A urine PCA3 test for considering a repeat biopsy in men 50 years of age or older who have had one or more previous negative prostate biopsies by Hologic Gen-Probe has been approved by the European Medicines Agency and Food and Drug Administration.

Similar to the PCA3 test, a urine biomarker of mRNA for the fusion gene *TMPRESS2-ERG* has also been developed. The fusion gene is commonly found in prostate tumors.[22] Its AUC for discriminating PCa from non-PCa in prostate biopsy was ~0.77.[23] Results from a multicenter study suggested that *TMPRSS2-ERG* had independent additional predictive value when compared to *PCA3* for biopsy outcomes.[24]

Another type of PCa biomarkers is inherited genetic markers. Genetic susceptibility to PCa is well-established from twin studies and family studies.[25,26] Specifically, more than 70 PCa risk-associated SNPs have been identified using genome-wide association studies in the last several years.[27] These SNPs have been consistently associated with PCa risk in multiple study populations. Several groups, including ours, have reported that a GRS derived from a combination of these risk-associated SNPs can be used to predict inherited risk for PCa.[28-33] In particular, we recently confirmed the predictive performance of GRS derived from the first 33 PCa risk-associated SNPs within the context of a clinical trial (REDUCE (REduction by DUtasteride of prostate Cancer Events)).[34] We demonstrated that they perform significantly better (AUC = 0.59) than many existing clinical parameters to predict positive biopsy during the 4-year trial, including tPSA (AUC = 0.53), %fPSA (AUC = 0.54) and family history (AUC = 0.52). The increased performance of GRS over family history, another commonly used measurement for inherited risk, was supported from multiple study populations.[35] In addition to subjects from European descent, the added value of GRS derived from multiple PCa risk-associated SNPs to PSA in discriminating biopsy outcomes was also demonstrated in the Chinese population, especially among patients with moderately elevated PSA levels.[6,36]

NOVEL BIOMARKERS ARE POORLY ADOPTED IN CLINICS

Despite extensive evidence for the added value of these novel biomarkers to PSA and that some of these biomarkers are approved by Food and Drug Administration, their adoption in clinics for assisting PSA in determining the need for biopsy is low. Many factors may contribute to this dilemma, including the fact that these biomarkers have not been adopted in various clinical guidelines and the costs for measuring these biomarkers. For example, no statement about *PCA3* and p2PSA is mentioned in the National Comprehensive Cancer Network and American Urological Association. In the European Union guidelines (2013), it states 'main current indication of the PCA3 urine test may be used to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome, but its cost-effectiveness remains to be shown'. Another major factor is a lack of appreciation of the added value of these biomarkers to the existing clinical predictors in a clinical and practical sense. This is in part because most statistical measurements in the literature for assessing the performance of biomarkers do not have direct clinical meaning. For example, AUC is an excellent and widely used statistical measurement for assessing discriminative performance of a test. However, it does not directly convey clinical information to urologists and patients regarding their biopsy outcomes. Therefore, other approaches are urgently needed to translate these biomarkers from research into clinics.

A PROTOTYPE OF THE XU'S CHART FOR PROSTATE BIOPSY

We propose to use a simple measurement, expected PCa detection rate, to improve appreciation of the added value of novel biomarkers to PSA in making a decision for prostate biopsy. We use a chart to visually present (i) expected detection rates of PCa

from biopsy with respect to PSA levels, and more importantly, (ii) a range of PCa detection rate at the same PSA levels when a biomarker is considered. This chart, called the Xu's chart for prostate biopsy, offers a simple and informative tool for urologists to discuss expected biopsy outcomes and the added value of additional biomarkers with their patients prior to biopsy. It provides more clinically meaningful information to urologists and patients than commonly used measurements such as AUC. In the following section, we describe a prototype of the chart, using GRS as an example, to demonstrate its effect in improving appreciation of the added value of biomarkers.

As described above, more than 70 PCa risk-associated SNPs have been consistently discovered from genome-wide association studies.[27] Although GRS derived from these risk-associated SNPs have been consistently shown to be a significant and independent predictor of PCa from biopsy,[6,28-36] few clinicians use GRS in clinics to assess their patients' genetic risk for PCa. In contrast, clinicians and patients rely greatly on family history to achieve this goal, even though family history is less objective and performs worse than GRS.[35] Better understanding of how GRS can add value to PSA in making a decision of prostate biopsy may promote its use in clinics.

We genotyped 33 of these PCa risk-associated SNPs in subjects from a population-based biopsy cohort from Sweden[32] and the placebo arm of REDUCE.[34] We then calculated GRS for each individual based on their genotypes at these 33 SNPs, the odds ratio of these SNPs derived from an external meta-analysis and the allele frequency of these SNPs in the CEU (Caucasian) population. Because GRS is relative to a general population, a GRS of 1.0 indicates an average inherited risk for PCa in the general population. Consequently, each subject can be classified as low-, intermediate- and high-inherited risk groups, if their GRS is < 0.5, 0.5–1.5 and > 1.5, respectively.

The average PCa detection rates from biopsy and their 95% confidence interval (CI) for men with different PSA levels (4–6.9, 7.0–9.9 and > 10 ng ml^{-1}) are presented in **Table 2**. In addition, in each of these PSA groups, the average PCa detection rates for subjects with low-, intermediate- and high-inherited risk for PCa are also presented. Finally, these PCa detection rates and the 95% CI are plotted in a chart for a visual presentation (**Figure 1**). Several messages are clearly noticeable from the chart. First, each patient can easily find out his expected PCa detection rate based on his PSA level prior to biopsy. For example, if a patient's PSA is at 4–6.9 ng ml^{-1}, he will find he has a 43.1% chance to be diagnosed with PCa from a biopsy. Based on the expected detection rate and other factors as well as considering potential benefits and harms, his urologist may or may not recommend a biopsy at this time. On the other hand, if a patient's PSA is ≥10 ng ml^{-1}, he will find he has a 75.1% chance to be diagnosed with PCa. Therefore, his urologist will most likely recommend a biopsy. Second, for patients whose PSA levels are in the grey zone (4–9.9 ng ml^{-1}), they will notice that they would have much more information regarding their expected PCa detection rate if they know their genetic risk for PCa. For example, for men whose PSA levels are between 4 and 6.9 ng ml^{-1}, the expected PCa detection rate would be as low as 27.9% if their GRS is <0.5 (12% of men in the group) or as high as 54.6% if their GRS is >1.5 (25% of men in the group). As a result, it is easier for urologists and patients to appreciate the added value of genetic risk and opt for measuring this biomarker. The additional information from GRS may offer a better assessment of biopsy outcomes and therefore reduce unnecessary biopsy for many patients, while improving the detection rate of PCa in a subset of patients.

We also developed the Xu's chart for biopsy for Chinese men (**Figure 2** and **Table 3**). The data were based on a biopsy cohort from two tertiary hospitals in Shanghai, China.[6] A GRS was calculated for each patient based on the 13 strongest PCa risk-associated SNPs in Chinese men. Again, two messages are clearly conveyed by the chart. First, each patient can easily find out his PCa detection rate based on his PSA level; 17.7%, 35.3% or 70.7% if his PSA level is at 4–9.9, 10–19.9 or ≥ 20 ng ml^{-1}, respectively. It is interesting to note that the detection rate of PCa in Chinese men is considerably lower than Caucasian men, and the PSA level grey zone in Chinese men is not 4–9.9, but 10–19.9 ng ml^{-1}. Second, the added value of GRS in estimating PCa detection is more prominent for patients in the grey zone PSA levels. The expected detection rate of PCa-based on PSA alone is moderate for this group (35.3%). However, the rate would be as low as 7.7% if they have a low genetic risk (GRS <0.5) or as high as 47.6% if they have a high genetic risk (GRS >1.5). In contrast, the added value of GRS is limited for patients with relatively low PSA (4–9.9 ng ml^{-1}) or very high PSA levels (>20 ng ml^{-1}). Although the PCa detection rate ranges from 7.1% to 24.6% between low- and high-GRS for patients with PSA at 4–9.9 ng ml^{-1}, they are all relatively

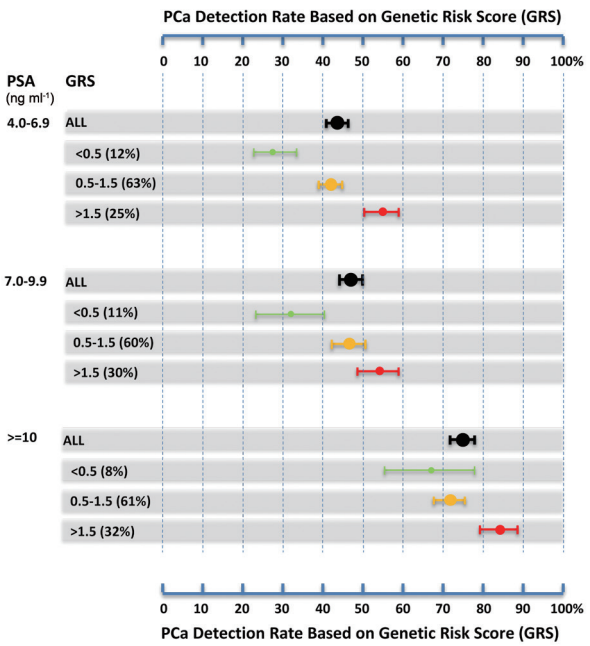

Figure 1: The Xu's chart for prostate biopsy (Caucasian). The average detection rates of prostate cancer (PCa) from biopsy (black dots) and 95% confidence intervals (black horizontal lines) are plotted for patients at different prostate-specific antigen (PSA) levels. In addition, within each PSA level group, the average PCa cancer detection rates and 95% confidence intervals are plotted for individuals with low genetic risk score (GRS) (<0.5, green), intermediate- GRS (0.5–1.5, yellow) and high GRS (>1.5, red). The percentage of patients with low-, intermediate- and high-GRS in each PSA level group is described in the parenthesis. Data were based on a total of 4499 biopsy patients from a population-based biopsy cohort from Sweden[32] and the placebo arm of REDUCE (reduction by dutasteride of prostate cancer events).[34]

Table 2: Detection rate of prostate cancer in Stockholm-1 and REDUCE study

Total PSA (ng ml^{-1})	*No. (%) of biopsy patients by GRS*				*Detection rate (95% CI) of PCa based on GRS*			
	All	*<0.5*	*0.5–1.5*	*>1.5*	*All*	*<0.5*	*0.5–1.5*	*>1.5*
4–6.9	2423	283 (11.7)	1535 (63.4)	605 (25)	43.1 (41.1–45.1)	27.9 (22.8–33.5)	41.3 (38.8–43.8)	54.6 (50.5–58.6)
7–9.9	1118	118 (10.6)	667 (59.7)	333 (29.8)	47.1 (44.2–50.1)	31.4 (23.1–40.5)	46.8 (42.9–50.7)	53.5 (47.9–58.9)
≥10	958	73 (7.6)	583 (60.9)	302 (31.5)	75.1 (72.2–77.8)	67.1 (55.1–77.7)	71.5 (67.7–75.2)	83.8 (79.1–87.8)

CI: confidence interval; GRS: genetic risk score; PCa: prostate cancer; PSA: prostate-specific antigen; REDUCE: Reduction by Dutasteride of prostate cancer events

Table 3: Detection rate of prostate cancer in Changhai and Huashan Hospitals, Shanghai, China

Total PSA (ng ml^{-1})	*No. (%) of biopsy patients by GRS*				*Detection rate (95% CI) of PCa based on GRS*			
	All	*<0.5*	*0.5–1.5*	*>1.5*	*All*	*<0.5*	*0.5–1.5*	*>1.5*
4–9.9	232	28 (12.1)	143 (61.6)	61 (26.3)	17.7 (13.0–23.2)	7.1 (0.9–23.5)	16.8 (11.1–23.9)	24.6 (14.5–37.3)
10–19.9	207	26 (12.6)	139 (67.1)	42 (20.3)	35.3 (28.8–42.2)	7.7 (1.0–25.1)	36.7 (28.7–44.7)	47.6 (32.0–63.6)
≥20	191	20 (10.5)	105 (55)	66 (34.6)	70.7 (63.7–77.0)	55.0 (31.5–76.9)	66.7 (56.8–75.6)	81.8 (70.4–90.2)

CI: confidence interval; GRS: genetic risk score; PCa: prostate cancer; PSA: prostate-specific antigen

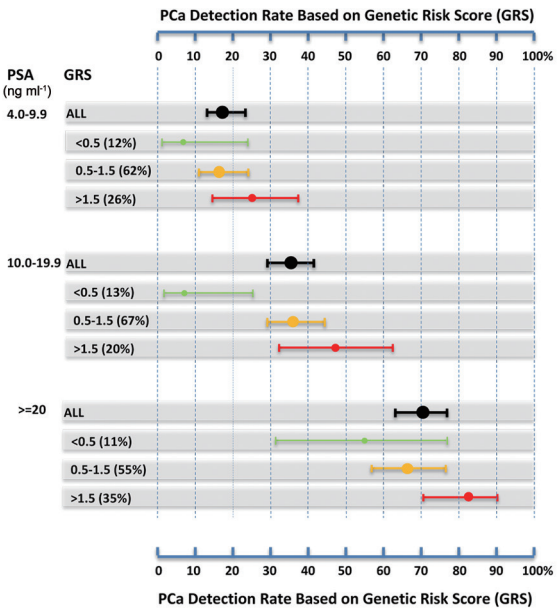

Figure 2: The Xu's chart for prostate biopsy (Chinese). The average detection rates of prostate cancer (PCa) from biopsy (black dots) and 95% confidence intervals (black horizontal lines) are plotted for patients at different prostate-specific antigen (PSA) levels. In addition, within each PSA level group, the average PCa cancer detection rates and 95% confidence intervals are plotted for individuals with low genetic risk score (GRS) (<0.5, green), intermediate- GRS (0.5–1.5, yellow) and high GRS (>1.5, red). The percentage of patients with low-, intermediate- and high-GRS in each PSA level group is described in the parenthesis. Data were based on a total of 630 biopsy patients from two tertiary hospitals in Shanghai, China.[6]

low to consider for a biopsy. Similarly, for patients with PSA >20 ng ml^{-1}, even though the detection rate ranges from 55.0% to 81.8% between low and high GRS, they are all high enough to warrant a biopsy.

UTILITY AND FUTURE IMPROVEMENTS

The primary purpose of the Xu's chart for prostate biopsy is to provide a simple and practical tool for urologists to discuss with their patients prior to biopsy. If this chart is available at each urological clinic, urologists can use it to explain to their patients what they can expect from biopsy based on PSA information alone or if additional information from other biomarkers are available. This would promote the uptake of novel biomarkers in clinics for a better assessment of PCa risk using more comprehensive risk assessment tools. Together with a discussion of potential benefits and harms of biopsy, urologists and patients can make an informed decision regarding the need for a prostate biopsy.

The key advantage of the chart is that the information it conveys (PCa detection rate) addresses a primary concern of patients and therefore can be easily understood. It is important to note that the chart is not a formal risk prediction model; rather, it is a simple tool for urologists to communicate initial evaluations and recommendations for additional biomarkers based on their individual PSA levels. It differs from other well-established statistical measurements for discriminating biopsy outcomes such as AUC, Integrated Discrimination Improvement,[37] Net Reclassification Index[37] and Decision Curve Analysis.[38] These measurements capture the overall discriminative performance of a test at a population level, but do not directly convey clinically meaningful information to individual patients. It is also important to note that the chart does not intend to compete with but complements sophisticated risk prediction tools such as such as nomograms,[39] the Prostate Cancer Prevention Trial risk calculator[40] and the Cancer of the Prostate Risk Assessment (CAPRA) score.[41] It serves as the first step to preliminarily assess patients' risk for PCa based on PSA levels and to encourage a subset of patients to obtain additional biomarkers for a comprehensive evaluation of PCa risk using these tools. This is a practical and important issue in a busy clinic, especially in China where urologists typically see several dozens of patients in a day.

The current chart is only a prototype and needs to be further developed and validated in large sample studies. Several improvements can be considered. First, with a larger sample size, the chart can include PSA levels at different age groups. Second, in addition to plotting the detection rate of any PCa, it is more important to plot PCa detection rate of high-grade PCa. Third, the chart should extend to other novel biomarkers such as PHI, *PCA3* and TMPRESS2-ERG. It is expected that the detection rate of PCa and high-grade PCa

could be further differentiated based on a combination of these biomarkers. Finally, because of the large differences in clinical presentations of PCa and high-grade PCa as well as the biomarkers between races, a chart specific for men of African descent is needed.

COMPETING INTERESTS

The author declares no competing interests.

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