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Improving the evaluation and diagnosis of clinically significant prostate cancer in 2017

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Abstract

Purpose of review—To provide an overview of the current state of the evidence and highlight recent advances in the evaluation and diagnosis of clinically significant prostate cancer, focusing on biomarkers, risk calculators and mpMRI.

Recent findings—In 2017, there are numerous options to improve early detection as compared to a purely PSA-based approach. All have strengths and drawbacks. In addition to repeating the PSA and performing clinical work-up (DRE and estimation of prostate volume), additional tests investigated in the initial biopsy setting are: %free PSA, PHI, 4Kscore, SelectMDx and MiPS and in the repeat setting: %free PSA, PHI, 4Kscore, PCA3, and ConfirmMDx. Risk calculators are available for both biopsy settings and incorporate clinical data with, or without, biomarkers. mpMRI is an important diagnostic adjunct.

Summary—There are numerous tests available that can help increase the specificity of PSA, in the initial and repeat biopsy setting. All coincide with a small decrease in sensitivity of detecting high-grade cancer. Cost effectiveness is crucial. The way forward is a multivariable risk assessment on the basis of readily available clinical data, potentially with the addition of PSA subforms, preferably at low cost. MRI in the pre-diagnostic setting is promising, but is not ready for “prime time”.

Keywords

prostate cancer; screening; early detection; risk stratification; biopsy; overdiagnosis; biomarkers; MRI

Introduction

Population-based screening for prostate cancer (PC) with prostate-specific antigen (PSA) is controversial due to the imbalance between the magnitude of benefits, in terms of reduction

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Competing interests statement

None.

in the risk of metastasis[1] and death from the disease[2, 3], relative to the magnitude of harm in terms of overdiagnosis[4, 5] and risk of overtreatment with side-effects from surgery or radiation and deterioration of quality of life[6]. For these reasons, there is a call for a better screening test that can detect aggressive tumors that are destined to become lethal during the man's lifetime, while avoiding the detection of low grade tumors. There is an urgent need for biomarkers, or multivariable approaches, that can improve the specificity of PSA[7], while maintaining its sensitivity, in order to achieve a better balance between benefits and harms. This review focuses on recent advances in biomarker/risk-stratification approaches to the detection of clinically significant PC, particularly evaluating the effects on cancers detected versus cancers missed, and number of biopsies avoided.

Determining the need for screening

Before discussing which biomarkers and approaches for risk-stratified screening are available to improve the detection of clinically significant prostate cancer, it deserves mentioning that "smarter" screening and optimization of the balance between benefits and harms can also be achieved through "upstream" approaches, i.e. by carefully selecting only those men for screening who are believed to be at highest risk of aggressive or life-threatening prostate cancer. Doing so implies enriching the cohort of men who are more likely to be subjected to biopsy to those at highest risk of high-grade disease. Guideline groups differ regarding what defines "high risk" and includes risk factors for prostate cancer outcomes and fitness for curative therapy, such as: age, general health/life expectancy, race/ethnicity, family history, and the baseline PSA-level in midlife.[8–11] Many guideline groups recommend PSA screening, after shared-decision making, to start in the mid 40's to 50's and end in the early-mid 70's.[8] Re-screening intervals vary between guideline groups; few suggest annual testing, 2–4 years was utilized in the European screening trial (ERSPC) [2] and some groups suggest individualizing the re-screening interval, and when to cease screening, according to the man's PSA level for his age, his general health/life expectancy and DRE findings[8, 10, 11].

A recent 2016 microsimulation modeling study showed that the balance between benefits and harms of current screening and treatment practices could be improved four-fold if a few simple guidelines were followed: limited screening in older men, additional biomarkers added to PSA before proceeding to biopsy, recommending initial active surveillance to most men with low risk PC and curative treatment delivered by high-volume physicians or centers.[12] Interestingly, stopping screening at age 70 and increasing the utilization of active surveillance had substantial effects on quality-adjusted life years, compared to moderate effects of the addition of novel biomarkers before biopsy. This implies that the downstream negative consequences of PSA is perhaps not so much the poor test characteristics, but rather lack of adherence to guidelines emphasizing "smarter" approaches, e.g. overuse of the PSA-test when not indicated and suboptimal management of screen-detected tumors.

Determining the need for prostate biopsy

Once a man has been screened with PSA, several “reflex tests” are available to help the man and his physician determine the need for prostate biopsy. Avoiding unnecessary biopsy is critical to avoiding exposing men to an uncomfortable and risky invasive procedure, and to avoid labeling men with a cancer diagnosis with ensuing psychological stress. Because the purpose of this paper is to highlight studies from the past year, focus will be on the recent National Comprehensive Cancer Network (NCCN) v.2.2016 guideline.

Initial biopsy setting: Repeating the PSA and work-up for benign disease

In the initial biopsy setting, following an elevated PSA-level > 3 ng/mL, the NCCN first recommends to repeat the PSA after a few weeks to confirm an elevated value. This is because PSA tends to fluctuate from one measurement to another[13–15], as first shown by Eastham *et al.* in a landmark study from a dietary study to prevent colon polyps in which men had annual serial blood draws over a 5-year period; the probability that the PSA-level would return to normal, and remain normal, was high, >40% and >65%, respectively[13]. The commonality of PSA fluctuations was recently confirmed in a 2016 study by Nordström *et al.* from a screening study in Stockholm, Sweden, furthering the evidence that omitting prostate biopsy for men with PSA 3–10 ng/mL which subsequently returned to ≤ 3 ng/mL eight weeks later could save 17% of biopsies while missing only 5% of Gleason score 7 or higher[14]. Another recent 2016 study from Canada similarly showed that among men with referral PSA levels between 4–10 ng/mL, repeated PSA tests results in the same laboratory fell below 4 ng/mL in 25% of men.[15] In addition to repeating the PSA, NCCN 2016 also suggests following up an elevated PSA-value with clinical work-up for benign prostatic disease including digital rectal examination (DRE) and estimation of prostate volume.[10]

Initial biopsy setting: Blood biomarkers free-to-total PSA, PHI and 4Kscore

Next, the 2016 NCCN guideline recommends any of the following reflex tests (blood) to follow an elevated PSA > 3 ng/mL: free-to-total PSA (%fPSA), 4-kallikrein score (4KScore) or Prostate Health Index (PHI).[10]

Free PSA—Free PSA is a component of both PHI and 4Kscore and removing free PSA from the 4Kscore reduced the AUC from 0.82 to 0.70 in a recent U.S. validation study.[16] A lower %fPSA suggests greater risk of PC (any grade). The test is approved by the U.S. Food and Drug Administration (FDA) for men with normal DRE and total PSA between 4–10 ng/mL. In a study of men with PSA between 4–10 ng/mL and normal DRE, PC (any grade) was found in 56% of men with a %fPSA < 10%, in contrast to 8% cancer among men with %fPSA >25%.[17] NCCN 2016 thus recommends <10% as an informative cut-off in men who have never undergone biopsy (or after negative biopsy).[10] In addition, recently published data from the San Antonio Biomarkers of Risk of PC Study comprising 6,982 serial %free PSA and PSA measurements over 10 years showed that %free PSA as a reflex test to PSA could save 2/3 of unnecessary biopsies.[18] Using a cut-off of <25% free PSA provided the first cancer suspicion (before total PSA) 71% of the time (34% if using <15% as a cut-off). Like total PSA-levels, fluctuations of %free PSA are common, particularly

among men never diagnosed with PC. Some therefore suggest repeating a %free PSA for men with PSA <4 ng/mL so that a spurious value does not prompt unnecessary biopsy.[18]

PHI—The PHI is a test approved by the FDA in 2012 to be used in men over the age of 50, with a PSA in the range 2–10 ng/mL and negative DRE. It is based on a mathematical formula of the measured biomarkers (PHI = ([−2]proPSA/free PSA) × √total PSA). Similar to %fPSA, it is intended as a secondary aid to PSA to distinguish any PC from benign prostatic condition, as cancer releases more proPSA and freePSA than BPH.[19, 20] NCCN considers a PHI > 35 as potentially informative in men who have never undergone biopsy (or after negative biopsy)[10]. In a large, prospective, multi-center study in the U.S. of 892 men with a PSA 2–10 ng/mL, PHI improved the detection of any PC and Gleason score ≥4+3=7 compared to free PSA and total PSA (AUC 0.78–0.82). A PHI cut-off of ≥ 25 for biopsy could avoid 36–41% of unnecessary biopsies and 17–24% of overdiagnoses, while missing 5% of tumors with Gleason score 7 or higher.[21]

4Kscore—The 4Kscore is a combination of free, total, intact PSA and hK2 with age, DRE and prior biopsy information. The test predicts risk of aggressive PC (high-grade)[22] and it has recently been shown to be associated with long-term risk of metastasis among unscreened men with elevated PSA ≥ 3 ng/mL at age 60; among men with a “low” 4Kscore below 7.5% (38% of men) the 10-year risk of metastasis was 0.2%.[23] The test has been evaluated in several clinical studies[16, 20, 24, 25]. It is not FDA approved, but a CLIA-accredited Laboratory Developed Test. It is included in the 2016 NCCN guideline as a secondary testing option after PSA and prior to initial or repeat biopsy.[10] In the validation study, a large, prospective, multi-center study of 1,012 men in the U.S. scheduled for biopsy, regardless of PSA-level, the test decreased unnecessary biopsies by 30–58%, without delaying an undue number of high-grade cancers (1.3–4.7%).[16] In a recent “impact study” conducted in routine clinical care in 611 patients with abnormal PSA and/or DRE, 65% of men did not have a biopsy after the 4Kscore test result was received.[25] In a recent 2016 study conducted within a multiethnic cohort in the PLCO screening trial, the 4K-panel improved the prediction of high-grade PC over total PSA (AUC 0.80 vs. 0.67). Using a cut-off of 6% risk of high-grade disease to determine biopsy kept the detection of high-grade disease by 88% and reduced unnecessary biopsies by 42%.[26]

Next to serum based markers also urine based biomarkers are being investigated in the initial biopsy setting. Two novel urin markers are SelectMDx and Michigan Prostate Score *(MiPS).*

SelectMDx—SelectMDx is performed on post-DRE, first-void urine and measures the mRNA levels of the HOXC6 and DLX1 biomarkers, using KLK3 expression as internal reference. The first evaluation resulted in AUC of 0.86 for significant PC on multivariable analysis, and a 42% reduction in biopsies with 2% high-grade cancers missed. However, a clinical base model without SelectMDx (age, PSA, PSA density, family history, DRE and prior biopsy) had a high AUC by itself (0.87), mainly driven by PSA density.[27]

MiPS—The MiPS, as developed by the University of Michigan MLabs, is a multiplex urine analysis of PCA3 and TMPRSS2:ERG combined with serum PSA, designed to detect high-grade PC (Gleason score 7 or higher) on biopsy after initial PSA-testing. The test is not FDA

approved (as of 2016).[28] A first evaluation, using a 30% risk threshold for biopsy, showed a halving of the number of biopsies (16% of biopsies avoided with the PCPT risk calculator vs. 35% with PCPT-RC+MiPS) while missing, or delaying, 1% of high-grade cancers.[29]

Initial biopsy setting: Risk calculators

Risk calculators—Nomograms, or risk calculators (RC), have the advantage of incorporating easy to retrieve clinical variables such as age, family history, DRE, PSA density, with or without biomarkers.[30] In a recent meta-analysis of six nomograms predicting risk of any PC on biopsy (Prostaclass, Finne, Karakiewicz, PCPT, Chun, ERSPC-RC3), most RCs performed better than PSA alone in terms of discrimination (AUC)[31]. However, guidelines leave the decision which RC to use to the physician's discretion. It is important to utilize a RC in the clinical setting and the population in which it was developed. As an example of the clinical utility of using a RC, an ERSPC-RC combining PSA with DRE, TRUS and prostate volume with biopsy at a cut-off of 12.5% risk, could avoid 33% of biopsies while missing no lethal PC cases compared to PSA alone and biopsy at a cut-off of 3 ng/mL.[32] Biomarkers such as %free PSA, PHI and PCA3 can be integrated into RCs together with clinical information, e.g. the ERSPC-RC, the PCPT-RC and the Sunnybrook RC, with improvements in the AUC when adding these biomarkers to clinical information such as age, family history, DRE and prior biopsy.[19, 20, 33, 34] As an example, adding PHI to the PCPT-RC or ERSPC-RC improves the predictive accuracy of aggressive disease.[35]

Repeat biopsy setting: Biomarkers in blood, urine and biopsy tissue

Some men will have negative prostate biopsy and persistently elevated PSA-levels > 3 ng/mL. In this repeat biopsy setting, the most recent NCCN guideline v.2.2016 recommends utilization of free-to-total PSA (blood), 4Kscore (blood), PHI (blood), PCA3 (urine) and ConfirmMDx (prostate biopsy tissue).[10]

PCA3—PCA3 is a non-coding mRNA that is overexpressed in PC and can be measured in urine after DRE. Numerous studies show that PCA3 can better predict any PC on repeat biopsy compared to PSA and clinical models[36–38]. However, the reason the test is FDA approved only for men ≥ 50 years with previous negative biopsy and other indications for repeat biopsy, is because there is conflicting data regarding the relationship between PCA3 and PC aggressiveness[20, 39, 40] and a risk of 13% high-grade PC missed among men with low PCA3 scores <20 in the initial setting in the U.S. validation study (compared to 3% in the repeat setting)[41]. An appropriate cut-off level with acceptable performance characteristics has been difficult to define for PCA3 and NCCN recommends a PCA3 score >35 as informative after a negative biopsy[10].

ConfirmMDx—ConfirmMDx is a tissue-based epigenetic test that can help decrease unnecessary repeat biopsy. The negative predictive value was 88% in a study of 350 men with negative biopsy and repeat biopsy within two years.[42] The test builds on a "field effect" phenomenon, i.e. benign prostatic tissue adjacent to a cancer focus showing distinct epigenetic alterations[42–44]. Because of limited available data, there is no recommendation

regarding the routine clinical application. The test is not FDA approved but performed in a CLIA-accredited laboratory.

Multiplex test: Stockholm-3

STHLM3—Recently, Grönberg *et al.* reported results from the Stockholm-3 (STHLM3) study, a large-scale study comprising 58,818 men between ages 50–69.[45, 46] The study was innovative in testing a multiplex "next-generation" screening strategy, in which men received a battery of protein biomarkers combined with genetic markers and clinical information: total, free, intact PSA, hK2, MSMB, MIC-1, DRE, prostate volume, age, family history and previous biopsy information. Consistent with prior observations (PHI, 4K-panel), adding kallikrein markers to the STHLM3 model improved predictions of high-grade PC over PSA alone (from 0.56 to 0.74), with excellent calibration.[45, 46] As compared to PSA only with a cut-off of 3 ng/mL to determine biopsy, use of the STHLM3 test in all men with PSA > 1 ng/mL decreased overdiagnosis by 17% and reduced the number of unnecessary biopsies by 32%.[45] The number of high-grade cancers caught and missed by utilization of the STHLM3 test, as compared to PSA alone, could not be assessed, due to the paired-screen positive study design of the trial in which not all men were biopsied to verify presence or absence of the diagnosis[47]. Moreover, because some components of the STHLM3 test were added before the plasma protein biomarkers in the statistical evaluation of the test, e.g. the genetic information and family history, it is difficult to compare the performance characteristics of STHLM3 test to other multiplex tests such as 4Kscore and the ERSPC- or PCPT-RCs.[47]

Multiplex test: "liquid biopsy"

A recent 2016 study on 319 patients with indication for prostate biopsy measured a panel of gene expression levels ("liquid biopsy") in plasma and urine (UAP1, PDLIM5, IMPDH2, HSPD1, PCA3, PSA, TMPRSS2, ERG, GAPDH, B2M, AR, and PTEN), along with serum PSA and age, to screen for best biomarker combinations to predict high-grade PC in a multivariable logistic model[48]. The AUC for the 13 variables was 0.85, and 0.80 if only eight were included. Whether this model improves predictions over clinical base models and reduces the number of biopsies is yet unknown.

MRI in the pre-diagnostic setting

mpMRI—MRI has long played a role in staging and surgical planning. However, because PC is often multifocal, use of MRI alone in the pre-diagnostic setting before biopsy has been a less attractive strategy, as compared to e.g. mammography or MRI in breast cancer screening. With the technological advancements in recent years and increasing experience among technicians, radiologists, urologists and pathologists, mpMRI has evolved as an increasingly appealing tool in the diagnostic arsenal, mainly to guide biopsies toward suspicious lesions, in order to maximize the detection of high-risk disease (Gleason ≥ 4+3) and limit the detection of low-risk disease (Gleason 6 or lower-volume 3+4)[10]. Several diagnostic strategies incorporating mpMRI are now undergoing investigation in prospective trials, e.g. the PROMIS study comparing mpMRI against TRUS-biopsy[49] and a prospective screening trial utilizing PSA and mpMRI, the "Göteborg-2" trial, ongoing in

Sweden. In a pilot study of 384 men within the Göteborg-1 screening trial, mpMRI with targeted biopsies for men with suspicious lesions and a PSA-level in the “gray zone” improved the detection of significant disease while reducing overdiagnosis (defined as T1c, PSAD <0.15, GS <7, ≤ 2 positive cores, unilateral cancer) compared to systematic biopsy.[50]

The recent 2016 NCCN guideline recommends consideration of “refined prostate biopsy techniques” (in addition to, or in spite of, biomarkers) for men with negative prostate biopsy, including MRI/ultrasound fused-guided biopsies, transperineal biopsies or saturation biopsy.[10] mpMRI in the pre-diagnostic setting can help find lesions that would otherwise be missed but the negative predictive value is not 100%. While mpMRI followed by targeted biopsy only to lesions with PI-RADS scores 3–5 can decrease overdiagnosis and improve the relative sensitivity of any and aggressive PC compared to TRUS and systematic biopsy, doing so may miss up to 20% of high-grade tumors.[51–56] Next to MRI targeted biopsy for PC detection, the value of keeping the TRUS-guided systematic biopsies with 11% detection of high-grade PC (values for individual studies ranging from 7% to 18%) cannot be neglected, when considering the suggestion to omit systematic TRUS-biopsies from the MRI targeted approach.[57]

One recent 2016 study evaluated the value of MRI among men with previous negative biopsy at a tertiary referral center. Upfront risk-based selection using an ERSPC-RC (PSA, DRE, TRUS and TRUS- volume) accurately predicted men with significant mpMRI findings and clinically important disease; use of the RC before imaging would have avoided 51% of mpMRIs and 25% of low-grade PC diagnosis while missing 10% of high-grade PCs at that time[58]. In sum, while MRI holds great promise in the pre-diagnostic setting, more large-scale prospective studies are needed and screening with PSA in conjunction with MRI is not ready for “prime time” as of 2016.

Conclusion and reflections on costs

In summary, there are numerous tests available that can help increase the specificity of PSA, in the initial and repeat biopsy setting. All are at certain, but generally small, cost of decreased sensitivity of detecting high-grade cancer. There is thus a balance between saving biopsies, reducing overdiagnosis and missing, or delaying, detection of high-risk PC. Moreover, the cost-effectiveness needs also to be taken into consideration as the costs of these tests and strategies are highly variable. As recently argued in a 2016 editorial by Dr. Eggener, the “value of these tests should be determined by clinical value and economic impact rather than marketing campaigns or size of the sales force”.[59]

Thus, the added value of refined approaches to reducing unnecessary testing, biopsy and overdiagnosis is hampered by the fact that all solutions also carry a risk of missing significant cancer diagnoses. The way forward is a multivariable risk assessment on the basis of readily available clinical data and potentially with the addition of PSA subforms, preferably at low cost. PSA and clinical parameters used in RCs perform similarly well as novel, most often more expensive biomarkers, but may be more difficult to implement in clinical practice. MRI in the pre-diagnostic setting is promising, but not ready for “prime

time". In men considered to be at high risk of having significant PC, MRI could be considered.

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Key points

- Early detection of PC has its benefits, but certainly also harms
- There are numerous options to improve early detection as compared to a purely PSA based approach, including reflex biomarkers and risk calculators. All have their strengths and drawbacks
- Cost-effectiveness analyses are crucial and needed
- MRI in the pre-diagnostic setting holds promise but is not yet ready for “prime time”