Received: 31 January 2020 | Revised: 6 April 2020 | Accepted: 7 April 2020

DOI: 10.1002/ijc.33045

INVITED REVIEW SERIES ON PERSONALIZED PREVENTION

Personalized strategies in population screening for prostate cancer

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Funding information
Publication fees were covered by Stichting Wetenschappelijk Onderzoek Prostaatkanker (SWOP)

Abstract

This review discusses evidence for population-based screening with contemporary screening tools. In Europe, prostate-specific antigen (PSA)-based screening led to a relative reduction of prostate cancer (PCa) mortality, but also to a substantial amount of overdiagnosis and unnecessarily biopsies. Risk stratification based on a single variable (a clinical variable or based on the presence of a lesion on prostate imaging) or based on multivariable approaches can aid in reducing unnecessary prostate biopsies and overdiagnosis by selecting men who can benefit from further clinical assessment. Multivariable approaches include clinical variables, and biomarkers, often combined in risk calculators or nomograms. These risk calculators can also incorporate the result of MRI imaging. In general, as compared to a purely PSA based approach, the combination of relevant prebiopsy information results in superior selection of men at higher risk of harboring clinically significant prostate cancer. Currently, it is not possible to draw any conclusions on the superiority of these multivariable risk-based approaches since head-to-head comparisons are virtually lacking. Recently initiated large population-based screening studies in Finland, Germany and Sweden, incorporating various multivariable risk stratification approaches will hopefully give more insight in whether the harm-benefit ratio can be improved, that is, maintain (or improving) the ability to reduce metastatic disease and prostate cancer mortality while reducing harm caused by unnecessary testing and overdiagnosis including related overtreatment.

KEYWORDS

clinical decision making, medical overuse, prostatic neoplasms, prostate-specific antigen, risk assessment

Abbreviations: 4K, 4-kallikrein; CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer; csPCa, clinical significant prostate cancer; DRE, digital rectal examination; EAU, European Association of Urology; ERSPC, European Randomized Study of Screening for Prostate Cancer; G2, Göteborg prostate cancer screening 2; hK2, Kallikrein-related peptidase 2; ISUP, International Society of Urological Pathology; miRNA, microRNAs; mpMRI, multiparametric MRI; PCA, prostate cancer; PCA3, prostate cancer gene 3; PCPTRC, Prostate Cancer Prevention Trial Risk Calculator; PHI, Prostate Health Index; PLCO, Prostate Lung, Colorectal and Ovarian Cancer Screening Trial; PRECISION, Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?; PROBASE, Prostate Early Detection Study Based on a "Baseline" PSA Value in Young Men; PROMIS, Prostate MR Imaging Study; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RPCRC, Rotterdam Prostate Cancer Risk Calculator; SNP, single nucleotide polymorphisms; STHLM3, Stockholm 3; TRUS, transrectal ultrasonography.

This article was published online on 3 June 2020. A typographical error was subsequently identified in page 3. This notice is included in the online and print versions to indicate that both have been corrected on 12 June 2020.

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1 | PROSTATE-SPECIFIC ANTIGEN-BASED SCREENING, ONE SIZE FITS ALL

In the mid-1990s a decrease in prostate cancer (PCa) mortality was observed.[1-3] This reduction can be attributed to both advances in treatment modalities and early detection, that is, prostate-specific antigen (PSA) testing. A modeling study showed that the rate of PCa mortality would increase without PSA testing while it would decrease with PSA testing.[4] PSA testing accounted for 45% to 70% of the reduction in PCa mortality, implying an improvement in PCa-specific survival and more favorable tumor characteristics in PCa cases detected with PSA testing. The effect of PSA-based screening and PCa specific mortality was evaluated in several randomized trials. One of such randomized trials, the European Randomized Study of Screening for Prostate Cancer (ERSPC), demonstrated with a follow-up of 16 years a 20% relative PCa mortality reduction in favor of men screened, translating in an absolute difference in PCa mortality of approximately 18 less PCa deaths per 10 000 men screened.[5] To prevent one man dying of PCa, 570 men needed to be invited for screening, and as compared to a no-screening situation 18 additional PCa cases needed to be diagnosed. The above numbers relate to the intention-to-treat analysis, adjusting for noncompliance and PSA contamination (screening in the control arm) showed an even larger PCa mortality reduction in favor of screening ranging from 22% to 32% within different ERSPC centers.[6-8]

The counterpart of the ERSPC in the United States (the Prostate Lung, Colorectal and Ovarian Cancer Screening Trial [PLCO]) did not show a reduction in PCa mortality.[9] However, this trial was criticized due to the high PSA contamination in the control arm.[10-13] Modeling studies suggest that with higher biopsy compliance and less contamination in the PLCO trial, it would most likely showed comparable results to the ERSPC trial.[10,14]

The ERSPC study also confirmed the hypothesis that with active screening more cancer would be detected.[5,12,15,16] It must however be noted that a lot of these screen-detected cancers were low-grade tumors defined as Gleason 3 + 3 or International Society of Urological Pathology (ISUP) grade group 1 PCa cases that, due to their very low potential of causing harm to the patient can be considered as being overdiagnosed. The rate of overdiagnosis has been estimated based on lead time (ie, the time that screening advances diagnosis compared to the time of the diagnosis without screening), the excess incidence between screened men and nonscreened men, and the presence of low-grade tumor on either biopsy, radical prostatectomy or autopsy.[17] These different approaches resulted in estimates of rates of overdiagnosis between 1.7% and 67% for men with screen-detected PCa. To elaborate, based on radical prostatectomy studies the rate of overdiagnosis ranged from 2% up to 47% and from autopsy studies the rate of overdiagnosis ranged from 19% to 43%. In a small pilot study of ERSPC Rotterdam with currently a median follow-up of 19 years a total of 55% of the diagnoses in the screening arm were graded as Gleason 3 + 3 (ISUP grade group 1), of which a considerable part can safely be considered as overdiagnosis.[18]

From the long-running and high-quality ERSPC study,[19] several lessons could be learned. The relative PCa mortality reduction of 20% was only observed when applying multiple screening interventions,[20] potentially explaining why no reduction in PCa mortality was observed in the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial.[21] PSA-based screening is associated with a considerable rate of overdiagnosis, unnecessary PSA testing (only 23% of all PSA measurements were considered as a positive test) and unnecessary biopsies (only 24% of all prostate biopsies triggered by an elevated PSA level were positive).[5] So, while the data support the fact that there are life-threatening prostate cancers that with early detection and subsequent treatment can be cured or inhibited in their progression the way to selectively identify those cancers remains subject of many ongoing research projects worldwide. Taken into account all data above showing that some—but not all—men can benefit of screening and the fact that this screening coincides with high rates of overdiagnosis strongly suggests that the "one size fits all" approach does not hold for PSA-based screening.

The European Association of Urology (EAU) recently published a statement in which they favor PSA-based screening, but with a critical note that overdiagnosis, unnecessary testing and overtreatment should be reduced.[22] The goal of nowadays PSA-based screening (eg, PSA tests at the general practitioner) should be in detecting the cancers that have the potential to metastasize or to grow outside the prostatic gland. In other words, PSA-based screening should not be aimed at detecting as much as PCa as possible but selectively focus on detecting those cancers that can harm if left undetected and untreated. This reduction in unnecessary testing, overdiagnosis and coinciding subsequent overtreatment could be achieved with personalized risk stratification with the aim to identify those men that will very likely benefit from screening.

2 | HOW SHOULD WE SCREEN TO KEEP THE BENEFIT AND REDUCE THE HARM

2.1 | Risk stratification

Risk stratification is a method to quantify the risk that a patient has for the event of interest, for example, the probability of detecting PCa or clinically significant (cs)PCa on prostate biopsy. In this review, we defined csPCa as Gleason 3 + 4 or ISUP grade group 2 and indicated if otherwise defined in the study discussed in this review. The goal of risk stratification is to select only those men that are considered to have an increased risk for further assessment with often (more) invasive procedures. However, it is essential to differentiate between population-based screening studies and studies in the clinical, daily practice setting (often referred to as opportunistic screening). The latter type of screening starts with risk stratification at, for example, the general practitioner and often include PSA but certainly also other characteristics like urinary complains and comorbidities. Subsequently, after referral to the urologist a second risk stratification is often done leading to a higher risk population as compared

to the population-based setting as described in the currently available literature. In these population-based trials, all men within a certain age range are invited and then risk stratified on the basis of only PSA. Those with elevated PSA are immediately eligible for biopsy resulting in a population with a lower a priori (before biopsy) risk on having PCa (and csPCa) as compared to the population referred for biopsy in the opportunistic/clinical setting. More contemporary population-based screening studies now include additional risk stratification tools to increase this a priori risk and will be discussed in a separate section of this manuscript.

The result of the risk stratification process can be used in the decision making process in the form of a so-called decision aid where individually calculated probabilities are presented with recommendations on how to continue. Available research has shown that the implementation of decision aids in clinical practice lead to improved decision quality.[23-26] A simple risk stratification in the pathway potentially leading to the detection of csPCa can be achieved by assessing a single PSA measurement at age 40 to 55[27] or at age 60.[28] For example, applying a cut-off for further assessment (detection and treatment) for men aged 60 with a first PSA > 1.06 ng/mL could potentially have avoided 91% of all metastatic disease that surfaced during the 25 year observation period (missing 0.37% of the total of 3.7% of men that were diagnosed with metastatic disease over 25 year). A total of 95% of all deathly cases could have been detected earlier (missing 0.15% of the total of 3.0% of men dying of PCa over 25 year). At the same time this data suggest that men aged 60 with a PSA level ≤ 1 ng/mL could refrain from any further screening since the probability of being confronted with a life-threatening PCa is low. Another study showed that the 13-year cumulative incidence for csPCa of men aged 55 to 60 with a first PSA between 0.50 and 0.99 ng/mL was as low as 1.5%, which increased to 5.4% for men with a first PSA between 1.00 and 1.99 ng/mL. These data also suggest that men within this age category and a PSA < 1.00 ng/mL are at very low risk of harboring csPCa and could consider to refrain from further screening.[29] In addition, other studies investigating PSA kinetics, for example, PSA velocity, in the field of early detection could not confirm that PSA kinetics were more predictive than the absolute level for the diagnosis of PCa.[30-32]

Next to risk stratification based on a single clinical variable, multivariable model-based approaches estimate the relation between relevant clinical variables and the outcome (eg, PCa on biopsy) for men with clinical suspicion of PCa. There are numerous of these so-called prediction models to detect csPCa.[33-35] The difference between all predictions models is the selection of (clinical) variables. However, for the generalizability of a prediction model, it is essential to test the performance of the model outside the development setting. This so-called external validation is often lacking.[34,36,37] Two well-validated risk calculators which are also being recommended by the EAU[38,39] are the Rotterdam Prostate Cancer Risk Calculator (RPCRC)[40,41] and the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) 2.0.[32,42,43] For the RPCRC, data of the Dutch part of the ERSPC study were used to develop a model to predict the presence of PCa at prostate biopsy using data of relevant clinical prebiopsy variables.[44] In this model, PSA and prostate volume were the strongest predictors for the detection of PCa, followed by digital rectal examination (DRE) and transrectal ultrasonography (TRUS). However, models should differentiate between men with prior biopsy or without previous biopsy as it was demonstrated that the relation between PSA level and the presence of PCa is different in men with a prior biopsy.[45] These findings are combined in the RPCRC to allow individualized predictions for the probability of detecting PCa and csPCa at biopsy.[40,41] This individual risk-based strategy as compared to a strategy of biopsying all with a PSA ≥ 3.0 ng/mL showed a reduction of 33% of all biopsies for men biopsied for the first time while 14% of all PCa and 7% of all csPCa would not be detected.[41] For men with previous biopsy, 37% of biopsies would be avoided while 16% of all PCa and 9% all csPCa would not have been detected. Next to the RPCRC, another widely used prediction model is the risk calculator from the PCPTRC 2.0.[32] This risk calculator calculates the probability of finding no PCa, any PCa, and csPCa based on PSA, age, race, family history of PCa, DRE and the presence of a previous biopsy. An external validation of these two risk calculators did not show much difference for the prediction of csPCa: the RPCRC showed a slightly better discrimination and a slightly higher net benefit, while the PCPTRC 2.0 showed a slightly better calibration.[46] The difference between these and the Finne, Chin, Karakiewicz, Sunnybrook, Prostataclass and PCPT 1.0 risk calculators were further studied in a head-to-head comparison.[47] In this study, the authors did not find any difference in discrimination in the prediction of any PCa. However, in the prediction of csPCa the RPCRC showed the most superior discrimination and the highest net benefit followed by the PCPTRC 2.0. The authors also showed that offering biopsies if the model-based probability of csPCa was ≥4%, applying the RPCRC would lead to reduction of 32% of all biopsies while 5% of all csPCa would not have been detected. For the PCPTRC 2.0, 16% of biopsies would have been reduced while 3% of all csPCa would not have been detected.

Next to risk stratification using model-based approaches, other risk stratification tools involve the use of an MRI in case of clinical suspicion of PCa. However, the role of the MRI as a triage test for the detection of PCa remains debated. Some authors proposed that a negative MRI (ie, PI-RADS < 3) of the prostate can be used to refrain from prostate biopsies.[48,49] Men in the Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not? (PRECISION) trial did not receive a biopsy in case of a negative MRI, which led to a reduction of 28% of all biopsies.[50] In this trial, 29% of all positive PI-RADS lesions were defined as PI-RADS score 3, 40% as PI-RADS score 4 and 31% as PI-RADS score 5. However, follow-up data of these men is yet not available so it remains unclear if these men are actually free from csPCa or whether detection remains in time. Another study found that 20% of indolent PCa and 3% of csPCa would not have been detected if biopsies were only offered to men with a positive MRI.[51] In this trial, 13% of all positive PI-RADS lesions were defined as PI-RADS score 3, 43% as PI-RADS score 4 and 44% as PI-RADS score 5. The so-called Prostate MR imaging study (PROMIS) showed that if the MRI would be used as a triage test, 27% of biopsies could be avoided on basis of a negative MRI at the cost of not detecting 7% of all Gleason ≥4 + 3 PCa (ISUP grade group ≥ 3) or

PCa with a maximum cancer core length of ≥6 mm.[52] In this trial, 39% of all positive PI-RADS lesions were defined as PI-RADS score 3, 29% as PI-RADS score 4 and 32% as PI-RADS score 5. While these trials showed a considerable amount of reduction in biopsies, MRI cannot be currently used as the sole triage test, currently available data come from very different study settings which lead to highly variable performance characteristics.[53] In addition, interobserver variability and the fact that MRI is likely to miss tumors of smaller size, with a lower PSA density, a lower Gleason score, a multifocal appearance, and nonindex tumors warrants further research.[54] While previous studies focused on finding (cs)PCa, another study suggested that MRI can also be used to identify indolent PCa.[55]

Another promising imaging modality which might have a role in de detection of PCa is the prostate-specific membrane antigen (PSMA) PET/CT. A retrospective cohort of men with a negative or contraindications on MRI showed that the PSMA PET/CT was positive in 56% of all men, of which 44% was diagnosed with any PCa of which 36% was csPCa.[56] However, it should be noted that this study did not differentiate between men with a negative MRI or men with contraindications for undergoing MRI, so it cannot be concluded that the PSMA PET/CT detects tumors missed by MRI. Further evaluation of the potential of PSMA PET/CT will be done in the prospective PRIMARY trial in which men will receive both the PSMA PET/CT and an MRI.[57] However, it should be mentioned that the relative short half-life of the tracer and the relative higher cost of the image modality as compared to the MRI can limit the availability of the scan.

Next to risk stratification using an MRI in case of clinical suspicion of PSA, it has been suggested to incorporate the result of the MRI into a multivariable prediction model[58] or to perform an upfront risk classification to reduce the number of MRIs. One study referred men with a risk above the RPCRC threshold of 20% for any PCa and/or 4% for csPCa and showed that 51% of the MRIs could have been avoided at the cost of not detecting 25% of all indolent PCa and 10% of all csPCa.[59] In another study including only biopsy naïve men, upfront risk stratification using the RPCRC would have avoided 37% of all multiparametric (mp)MRI while missing only 4% csPCa.[60] Next to upfront risk stratification to refer men for MRI, other groups included the PI-RADS score in their prediction model to estimate the probability of PCa. One of those models used age, African American ethnicity, prior negative biopsy, results of the DRE, PSA and the PI-RADS score to predict the presence of csPCa at biopsy.[61] They found that the discrimination of the model increased from 0.72 to 0.84 when including PI-RADS score and MRI-derived prostate volume. The authors also found that compared to biopsying all men with a positive MRI their model could have avoided 18% of biopsies without missing any csPCa. This was confirmed by other studies where discrimination increased with the inclusion of the MRI results in the prediction model.[62-65] One of those studied combined the RPCPC with the PI-RADSv1.0 score for predicting csPCa, and found for biopsy naïve men that discrimination increased from 0.81 to 0.83.[63] In contrast, the increase in discrimination was larger for men with previous biopsy, showing an increase in discrimination from 0.66 to 0.81. Recently, the RPCRC has been updated to incorporate the results of MRI.[65] This model showed that for men with previous negative biopsy with a risk threshold of 5% csPCa, 27% of biopsies could have been reduced while 3% of all csPCa would not have been detected. A risk threshold of 10% csPCa would lead to a reduction of 36% biopsies while 4% of all csPCa would not have been detected. However, for biopsy naïve men this updated risk calculator might be questionable, since, with a threshold of 5%, only 2% of biopsies would be reduced while missing 15% of csPCa compared offering all men a biopsy with a PSA ≥ 3.0 ng/mL.

All taken together, individualized predictions as an aid at decision making can assist the physician to select those patients most likely to benefit from further clinical assessment[66] as opposed to the one size fits all approach. This individualized risk-adapted strategy for the detection of PCa is recommended by EAU.[38,39] To ease interpretation of a model, it can be visualized in a so-called nomogram[67-70] or in eHealth and mHealth applications, such as RPCRC[71] and the PCPTRC 2.0[72] to ease clinical decision making. In addition, models have been suggested which incorporate both the probability of aggressive cancer and the life expectancy to make a recommendation about referral to the urologist.[73,74]

2.2 | Biomarkers to aid in risk stratification

Proteomics like, for example, the PSA protein and its subforms can be detected in both blood and urine. One of those blood-based biomarkers is the Prostate Health Index (PHI) which combines total, free and [−2]proPSA into one score. Several studies demonstrated that the PHI showed better discrimination for (cs)PCa than PSA[75-82] and even better discrimination was observed for PHI density.[83] For example, in one study, the discrimination for detecting csPCa was 0.71 for PHI, compared to 0.55 for total PSA.[81] Also, the same study showed that offering biopsy for men with a PHI cut-off above 28.6 would have avoided 30% of biopsies while 5% of Gleason ≥ 7 (ISUP grade group ≥ 2) would not have been detected. In addition, a multicenter European and Asian study showed that the effect of PHI differed between cohorts: for European centers, the discrimination for predicting Gleason ≥3 + 4 (ISUP grade group ≥ 2) was 0.63 for PSA and 0.71 for PHI, while this was for Asian centers 0.54 for PSA and 0.84 for PHI.[75] That same study also showed that a similar sensitivity of 90% was reached in European centers with a PHI cut-off of 40 in which 40% of biopsies could have been reduced while 10% csPCa would not have been detected. In Asian centers, this 90% sensitivity was reached with a PHI cut-off of 30 in which 56% of biopsies could have been reduced while 11% csPCa would not have been detected, suggesting that regional differences should be taken into account. Other studies have shown that PHI can improve the discrimination of the RPCRC,[84,85] and the PCPTRC 2.0.[85] In the latter study, the discrimination of the PCPTRC 2.0 for csPCa increased from 0.58 to 0.70 with PHI; the discrimination of the RPCRC increased from 0.65 to 0.71.[85] Finally, studies have shown that PHI next to MRI have led to better discrimination for csPCa as shown in an Asian population[86] and in the United Kingdom.[87] The advantage of the PHI test is that it is

based on a blood test without the need of clinical variables, and is relatively cheap with prices between 30 and 90 euro.[35,88]

Next to PHI, another available biomarker panel for the detection of PCa is the 4-kallikrein (4K) score which is next to the clinical variables age, and DRE based on total, free, and intact PSA, kallikrein-related peptidase 2 (hK2), and was updated to include the history of previous biopsy. The discrimination of a model predicting any PCa including age, total PSA, and DRE increased from 0.72 to 0.84 with the addition of free PSA, intact PSA and hK2.[89] However, effects for csPCa were minimal as the discrimination increased from 0.87 to 0.90. In contrast, another study showed that discrimination of csPCa increased for screening naïve men from 0.68 to 0.80 with the addition of the 4K score in the model and from 0.72 to 0.83 for men with previous screening.[90] This model showed that for screening naïve men 74% of all biopsies could be reduced if biopsies were offered from a model-based probability of 20% but this would lead to 26% csPCa not being detected; for previous screened men, 41% of biopsies could be reduced in which only 2% of csPCa would not be detected. While the former studies showed that the 4K score should be preferred over a model without the 4K score, other studies did not find that the 4K score showed a better discrimination than PHI[91] or the RPCRC including cribriform growth in the definition of csPCa.[92]

Another type of blood-based biomarkers for the detection of (cs) PCa is based on microRNAs (miRNA). There are over 50 miRNAs identified, but an essay is not yet implemented in clinical practice.[93,94] It was previously demonstrated that a model with both miRNAs and PSA improved prediction compared to PSA alone.[95] However, validation of miRNA studies are yet lacking and larger studies are needed before miRNA can be considered in the clinical setting.[96] In addition, head-to-head comparisons with other prediction models and biomarkers are needed to assess the superiority of miRNA essays.

Next to blood-based biomarkers, urine-based biomarkers are also available. One of those urine-based biomarkers is prostate cancer gene 3 (PCA3) which is calculated as the ratio of the PCA3 mRNA and PSA mRNA in urine voided after DRE. The discrimination for any PCa pooled over 46 studies was 0.75,[97] which is better than total PSA,[98-100] but lower compared to PHI.[101-103] However, another study showed that there was no difference in discrimination for any PCa using only the PCA3 or only the PHI.[104] Discrimination of the model increased significantly from 0.71 to 0.77 with both PCA3 and PHI in the model.

Another urine-based biomarker is SelectMDx which was initially based on the proteins HOXC6, TDRD1 and DLX1 and showed a discrimination for csPCa of 0.77, which was higher than PCA3 alone (0.68) or PSA alone (0.72).[105] Combing the HOXC6 and TDRD1 and DLX1 with PSA showed an increase discrimination of 0.81. A validation study of these markers showed that the protein TDRD1 actually did not improve discrimination, but that discrimination was improved when including information like PSA density and having had a previous biopsy. The discrimination increased significantly from 0.81 to 0.86.[106] In the same study, it was also shown that the SelectMDx score outperformed the PCPTRC 2.0 and the PCPTC 2.0 with PCA3. More recently, it was shown that the SelectMDx score was positively related to the PI-RADS score, but unfortunately, the authors did not report the discriminative ability of a model containing both the information from SelectMDx and the PI-RADS score.[107]

One of the latest developed multivariable risk models is the so-called Stockholm 3 (STHLM3) risk-based model. This model predicts the probability of csPCa based on a combination of plasma protein biomarkers, genetic single nucleotide polymorphisms (SNPs), and clinical variables.[108] In that development study, they showed that the discrimination of csPCa with total PSA was 0.56, which increased with additional information from risk factors (age, family history, the presence of previous biopsies) to 0.58, and with the addition of biomarkers (one genetic score for all SNPs, beta-microseminoprotein, macrophage inhibitory cytokine 1, free PSA, intact PSA and hK2), to 0.70, which further increased to 0.74 with the addition of DRE and prostate volume. This model showed that offering biopsies if the model probability was ≥10%, 32% for all biopsies would have been reduced, 44% of benign biopsies would have been detected, and 17% of indolent PCa would not have been detected without missing any csPCa compared to offering a biopsy in all men with PSA ≥3 ng/mL. However, all biomarkers were added to the model in one step which makes it impossible to disentangle the unique effects of every single biomarker.[109] The application of the STHLM3 in current clinical practice in Sweden showed that with this model based threshold of 10%, 53% of biopsies and 76% of benign biopsies would have been reduced.[110] Other research studied the effect of the STHLM3 and MRI.[111] In this study, they showed that men with a positive STHLM3 and a positive MRI with systematic biopsies, 38% of all biopsies could have been reduced in which 8% of all csPCa could have been missed compared to only MRI (including systematic biopsies) approach.

All taken together, there are several biomarkers available. At the moment, it is impossible to draw conclusions on superiority for the detection of csPCa since head-to-head comparisons comprising both multivariable models and biomarkers are lacking. The conclusion we can, however, make from these studies is the fact that all multivariable approaches outperform a PSA-based strategy in reducing unnecessary biopsies and overdiagnosis, see Figure 1 and Table 1. According to Figure 1, a men with clinical suspicion can either undergo univariable risk stratification including a PSA measurement or risk stratification solely on MRI, or multivariable risk stratification including risk calculators with or without MRI or proteomics and genomics. This clinical suspicion can originate from urinary complains, family history of PCa or the wish of the patient. We favor the use of multivariable risk stratification over an univariable approach with the currently available tools. Men with low risk according to the risk stratification should be referred to clinical follow-up or should be refrained from further clinical follow-up when they are at very low risk of harboring csPCa. Men with elevated risk according to the risk stratification should receive targeted and/or systematic biopsies. If no cancer is found, men should be referred to clinical follow-up, while men diagnosed with PCa should be referred to treatment including active surveillance.

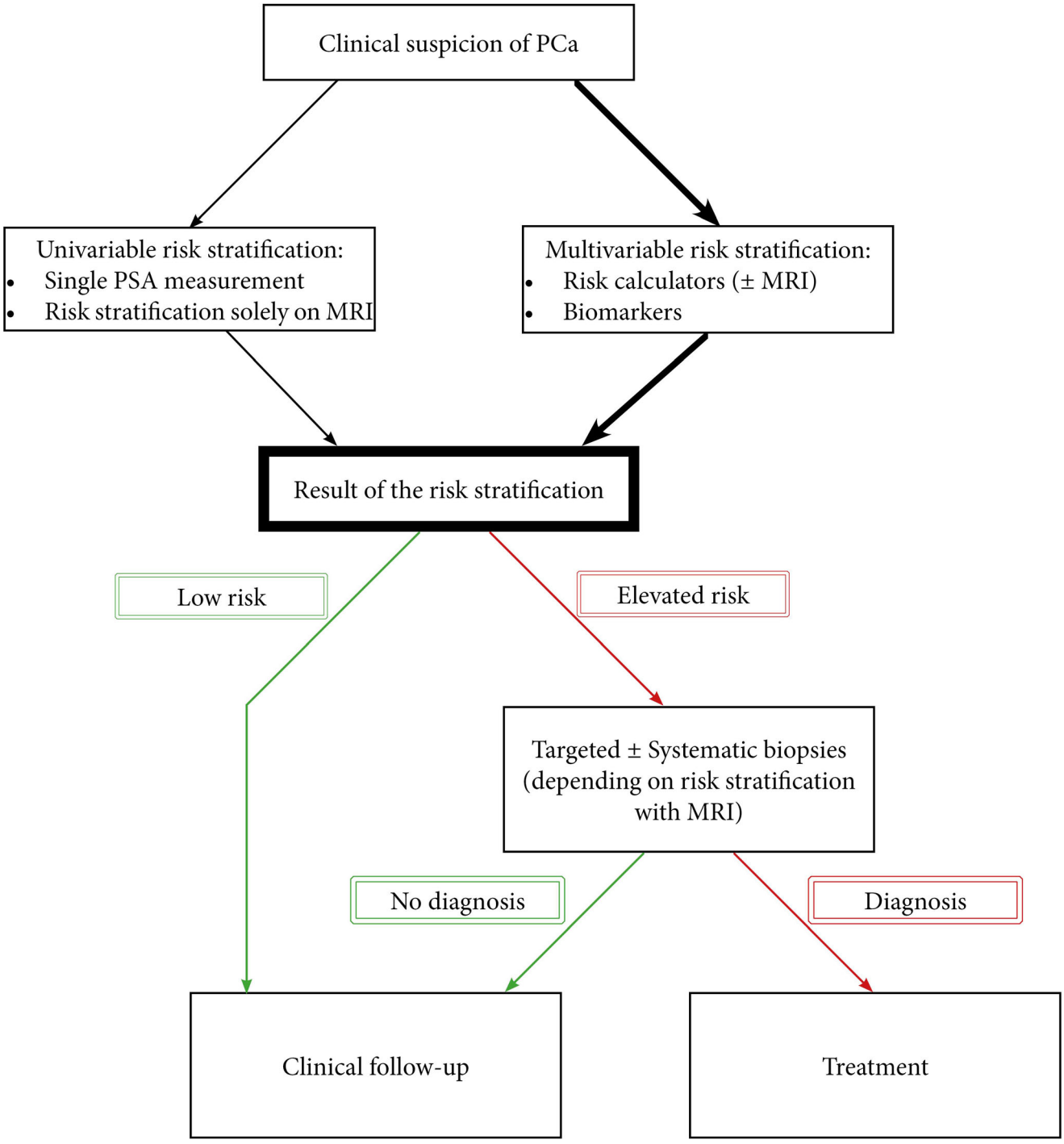

FIGURE 1 Flowchart of men with suspicion of PCa combined with risk stratification [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Which men are most likely to benefit from screening

Considering the natural history of PCa, it is clear that screening a man in his 80s or 90s when comorbidity is an issue is not the way to go. In a modeling study, it was simulated that a single screening at age 55 would result in 27% overdiagnosis which doubled to 56% for a single screening at age 75.[112] However, elderly men should not automatically be excluded from screening simply based on age. It has been shown that men screened for the first, and last time at age 70 to 74 can still be confronted with the diagnosis of csPCa. The risk is small (approximately 3% with a maximum follow-up of 24 years) but still despite the high age, 26% of all these men die of PCa.[113] This suggests that age is not the only and perhaps not the correct factor to decide to continue or start screening. To selectively identify elderly men that are at high risk of being diagnosed and die of PCa, again multivariable risk stratification including taking into account life expectancy and comorbidities is advised.[74]

TABLE 1 Summary of key results of various decision-making approaches

Risk stratification tools (cut-off)	Setting	References	Reduced biopsies (%)	Reduced indolent PCa diagnosis (%)	Missed csPCa (%)
Univariable					
PSA test (≥3.0 ng/mL)[a]	Population based screening	5, 9, 12, 15, 16	N/A	N/A	N/A
MRI in triage setting (≥PI-RADS 3)	Clinical suspicion	50-52	27-29	20	3-7
Multivariable					
RPCRC (compared to PSA ≥3.0 ng/mL)	Clinical suspicion + biopsy naive	41	33	14	7
RPCRC (compared to PSA ≥3.0 ng/mL)	Clinical suspicion + prior negative biopsy	41	37	16	9
RPCRC (≥4%)	Clinical suspicion	47	32	25	5
PCPTRC 2.0 (≥4%)	Clinical suspicion	47	16	15	3
RPCRC + MRI (≥5%)	Clinical suspicion + biopsy naive	65	2	10	15
RPCRC + MRI (≥5%)	Clinical suspicion + prior negative biopsy	65	27	14	3
PHI (90% sensitivity)	Clinical suspicion	75, 81	30-56	31-33	5–11
4K score (≥20%)	Clinical suspicion + biopsy naive	90	74	38	26
4K score (≥20%)	Clinical suspicion + prior negative biopsy	90	41	73	2
STHLM3 risk-based model (≥10%)	Clinical suspicion	108, 110	32-53	17-76	0

Note: Head to head comparisons cannot be made based on the data in this table and performance of risk stratification tools should be confirmed in an external validation.

[a]In the population-based screening studies there were no biopsies performed if the PSA was lower than 3.0 ng/mL. Therefore, it is not possible to assess the missed cancers following this strategy.

Next to the issue of screening or not screening elderly men, there is also the question on when to start screening. The Prostate Early Detection Study Based on a "Baseline" PSA Value in Young Men (PROBASE) trial randomized 50 000 men aged 45 at an immediate screening arm or a delayed screening arm at age 50 with screening intervals based on their "baseline" PSA level.[114] The first results of this trial show that only 14% complied with the invitation and of the men randomized to immediate screening, only 1.8% showed a PSA ≥3.0 ng/mL, of which 43% based on a confirmatory second PSA test had a PSA ≥3.0 ng/mL.[115] Updated results of this trial show similar results; 1.5% of men randomized to immediate screening showed PSA ≥3.0 ng/mL, of which 53% is confirmed at repeat PSA testing.[116] Of the men with confirmed PSA ≥3.0 ng/mL, 33% of men were diagnosed with PCa, of which 68% was csPCa. These findings suggest that early detection at age 45 in men with relatively high PSA values considering their age and thus the absence of benign prostatic hyperplasia is indicated, especially since almost 70% of PCa is considered csPCa. Longer follow-up data will show whether the delay of 5 years is acceptable or not and whether early detection and subsequent treatment will indeed reduce suffering and dying from PCa. With the latter preferably resulting in a higher mortality reduction as is currently seen in the randomized trials that all started at a higher age.

3 | FUTURE OF SCREENING

We should also mention there are challenges for pathologists to improve the grading of the PCa.[117] In addition, aggressive cancer is usually defined as ISUP grade group 2, but the aggressiveness of these tumors is under debate.[118,119] Other challenges at the moment are involved with the use of biparametric MRI as opposed to mpMRI, although the sensitivity and specificity of the modalities are similar.[120] At the moment, there are ongoing several population-based screening studies next to the previous discussed PROBASE trial in Germany. In Sweden, two trials are recruiting. The Göteborg prostate cancer screening 2 (G2) trial recruits men from September 2015 till the end of 2019.[121,122] In this trial, over 40 000 men aged 50 to 60 are randomized between a screening and a control group. In the screening group, men are randomly assigned into three arms. Men assigned to the first arm and with a PSA ≥ 3.0 ng/mL will receive standard biopsies, DRE, and mpMRI; for men with positive MRI targeted biopsies will be offered. Men with a PSA is below this threshold will not receive further testing and will be re-invited. Men assigned to the second arm and a PSA ≥ 3.0 ng/mL will only receive targeted biopsies in case of a positive MRI and no systematic biopsies; men with a negative MRI will be re-invited. Men assigned to the third arm and a PSA cut-off ≥1.8 ng/mL will only receive targeted biopsies and no

systematic biopsies. All men assigned to the second and third arm with a PI-RADS 5 will undergo both systematic biopsies and targeted biopsies. Re-invitation interval is based on the PSA level: men with a PSA < 0.6 ng/mL will be re-invited 8 years later, men with a PSA between 0.6 and 1.19 ng/mL will be re-invited 4 years later and men with a PSA between 1.2 and 2.99 ng/mL will be invited after 2 years (see recent changes in amendment 2, https://www.g2screening.se/wp-content/uploads/2019/12/Amendment-2.pdf). Men will be invited twice, after which men with a PSA ≤ 0.59 ng/mL will be screened until they reach the age of 62, men with a PSA between 0.60 and 1.19 ng/mL will be screened until they reach the age of 65, men with a PSA between 1.2 and 1.79 ng/mL will be screened until they reach the age of 70, and men with a PSA above 1.8 ng/mL will be screened until they reach the age 75 (see recent changes in amendment 10, https://www.g2screening.se/wp-content/uploads/2020/02/Amendment-10.pdf). Nonattenders will be re-invited after 3 months and after 9 months. The primary outcome of this trial is the rate of overdiagnosis, defined as small insignificant tumors that would never be detected within one's life without screening.

Another population-based screening study in Sweden is the STHLM3-MR Phase 2 trial.[123] In this trial, 25 000 men aged 50-74 will be invited and men with an elevated risk will be randomized. The PSA and STHLM-3 test define elevated risk: a PSA ≥3 ng/mL or a PSA ≥1.5 ng/mL with STHLM3 > 11%. Men will be randomized in a 2 (control arm): 3 (experimental) ratio. Men in the control arm will receive only systematic biopsies and men in the experimental arm will receive an MRI. Men with a positive MRI will receive both targeted and systematic biopsies; men with a negative MRI will receive systematic biopsies if the STHLM3 test is ≥25%, or no biopsies if the STHLM3 < 25%. Primary outcome in this trial is the number of detected csPCa and indolent PCa between the diagnostic pathways.

In Finland, the ProScreen trial which started in 2018 randomized 67 000 men aged 55-67.[124] Randomization is in a 1 (screening arm): 3 (control arm) ratio. Men in the screening arm will be offered PSA test; men with a PSA ≥ 3.0 ng/mL will receive an additional 4K test. Men with increased risk (ie, 4K score ≥ 7.5) will undergo mpMRI. Biopsies will only be taken in men with a positive MRI. Men with a positive screening (ie, PSA ≥3.0 ng/mL) will be re-invited every 2 years until they complete five screening rounds. Men with a negative screening and a PSA between 1.5 and 3.0 ng/mL will be re-invited after 5 to 6 years and after 9 to 10 years. Men with PSA below 1.5 ng/mL will be re-invited after 7 to 8 years. The primary outcome of this trial is PCa mortality.

4 | CONCLUSION

In Europe, PSA-based screening showed a relative reduction of PCa mortality of 20%. However, this was accompanied by a substantial amount of overdiagnosis and unnecessary biopsies. In the past years, a large variety of tools has been developed to allow an individualized approach to select patients who would benefit from further clinical assessment. These risk stratification tools have shown to be able to reduce the number of biopsies and overdiagnosis, but head-to-head comparisons are lacking making it impossible to draw conclusions on the superiority of these tools. Current population-based screening studies are using a multivariable individualized approach with the aim to maintain reduction of PCa mortality and to reduce the number of biopsies and overdiagnosis. These trials will lead to new insights in the field of population-based screening for PCa. It is however not advisable to await these results and continue opportunistic screening activities based on PSA alone. Current guidelines based on contemporary knowledge should be implemented in clinical practice and decision making without delay.[125]

CONFLICT OF INTEREST

The authors do not report any conflicts of interest.

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How to cite this article: Remmers S, Roobol MJ. Personalized strategies in population screening for prostate cancer. *Int. J. Cancer*. 2020;147:2977–2987. https://doi.org/10.1002/ijc.33045