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A European Model for an Organised Risk-stratified Early Detection Programme for Prostate Cancer

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Abstract

Context: Overdiagnosis as the argument to stop pr.ostate cancer (PCa) screening is less valid since the introduction of new technologies such as risk calculators (RCs) and magnetic resonance imaging (MRI). These new technologies result in fewer unnecessary biopsy procedures and fewer cases of both overdiagnosis and underdetection. Therefore, we can now adequately respond to the growing and urgent need for a structured risk assessment to detect PCa early.

Objective: To provide expert discussion on the existing evidence for a previously published risk-stratified strategy regarding an organised population-based early detection programme for PCa.

Evidence acquisition: The proposed algorithm for early detection of PCa emerged from expert consensus by the authors based on available evidence derived from a nonsystematic review of the current literature using Medline/PubMed, Cochrane Library database, ClinicalTrials.gov, ISRCTN Registry, and the European Association of Urology guidelines on PCa.

Evidence synthesis: Although not confirmed by the highest level of evidence, current literature and guidelines point towards an algorithm for early detection of PCa that starts with risk-based prostate-specific antigen (PSA) testing, followed by multivariable risk stratification with RCs. All men who are classified to be at intermediate and high risk are then offered prostate MRI. The combined data from RCs and MRI results can be used to select men for prostate biopsy. Low-risk men return to a risk-based safety net that includes individualised PSA-interval tests and, if necessary, repeated MRI. Depending on local availability, the use of the different risk stratification tools may be adapted.

Conclusions: We present a risk-stratified algorithm for an organised population-based early detection programme for clinically significant PCa. Although the proposed strategy has not yet been analysed prospectively, it exploits and may

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even improve the most important available benefits of "PSA-only" screening studies, while at the same time reduces unnecessary biopsies and overdiagnosis by using new risk stratification tools.

Patient summary: This paper presents a personalised strategy that enables selective early detection of prostate cancer by combining prostate-specific antigen (interval) testing prediction models (risk calculators), and magnetic resonance imaging scans. This will likely lead to reduced prostate cancer–related morbidity and mortality, while reducing the need for prostate biopsy and limiting overdiagnosis.

1. Introduction

Locally advanced prostate cancer (PCa) is less susceptible to cure, and its treatment is more aggressive and more costly. The treatment of locally advanced and metastatic PCa is likely to have a significant negative impact on the quality of life [1]. Therefore, the main goal of early detection is to identify PCa in a phase where it needs less aggressive treatment with fewer side effects and a higher chance of cure.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) provided level 1 evidence that prostate-specific antigen (PSA) screening leads to a relative risk reduction of 20% of PCa-specific mortality after 16 yr of follow-up [2] and 30% of metastatic disease after 12 yr of follow-up [3]. This was at the expense of many unnecessary biopsy procedures and many cases of overdiagnosis and related overtreatment. The subsequent recommendations against PSA-based screening by the US Preventive Services Task Force for men aged $\geq$75 yr in 2008 and for all men in 2012 have led to an increase in late diagnoses of advanced and metastatic stages [4]. This shift is also seen in Europe. For example, in Germany, the incidence of stage T3 prostate tumours rose from 29% between 2008 and 2010 to 49.4% in 2017, and that of lymph node metastasis increased from 4.5% to 16.9% [5]. Currently, PCa has become the most diagnosed cancer among men and the second leading cause of male cancer death [6]. In addition, men become aware of their risk of developing PCa, which stimulates opportunistic screening that includes screening of the wrong target population with inadequate intensity and follow-up [7]. This unstructured approach to screening has been shown to coincide with the known harms, but not with the benefits of early detection: it is associated with even more cases of overdiagnosis and does not reduce the PCa-specific mortality rate [7].

In view of new technologies, "PSA-only"–based screening is considered an outdated strategy. The advent of magnetic resonance imaging (MRI), multivariable prediction models such as risk calculators (RCs), and increased knowledge on the natural course of different risk groups improve the individual balance between the harms and benefits of early detection. These developments enable early detection in well-informed men who are at risk of having PCa that would cause harm in the future.

The latest recommendations of the European Council on cancer screening date from 2003 and did not support a programme for PCa [8]. Besides, the European Association of Urology (EAU) guidelines on PCa give only a weak recommendation for a risk-stratified strategy for early detection of PCa [9]. However, the increasing harm of the rising incidence of locally advanced and metastatic PCa together with the on-going large-scale opportunistic screening reflects the urgent need for such a strategy on a population-based level [6]. With this in mind, we have recently published an opinion article with recommendations made for the European Union and European Commission policymakers, elaborated in a comprehensible algorithm that is presented in Figure 1 [10]. This algorithm anticipates the EAU guidelines on PCa and aims to provide an early detection strategy that can be applied in a population-based setting. The chosen strategy strives for both limited overdiagnosis and harmful overtreatment by implementing multivariable prediction models and MRI. This paper aims to provide expert consensus discussion of existing literature on the various steps within the algorithm and tries to identify future research topics to substantiate personalised approaches.

2. Evidence acquisition

A nonsystematic review of the current literature was performed using Medline/PubMed, Cochrane Library database, ClinicalTrials.gov, ISRCTN Registry, and the EAU guidelines on PCa. Using the existing literature, expert consensus by the authors was reached on the various possible steps within the proposed algorithm for early detection of PCa through online discussions. The expert panel consisted of three urologists, one (MRI) radiologist, and a decision scientist/epidemiologist, all experts in their respective fields of PCa.

3. Evidence synthesis of the diagnostic pathway: balancing capacity, underdetection, and overdiagnosis

The proposed risk-based algorithm has recently been published (see Fig. 1) [10]. In this paper, we will discuss the underlying literature and rationale of the various risk stratification steps in more detail.

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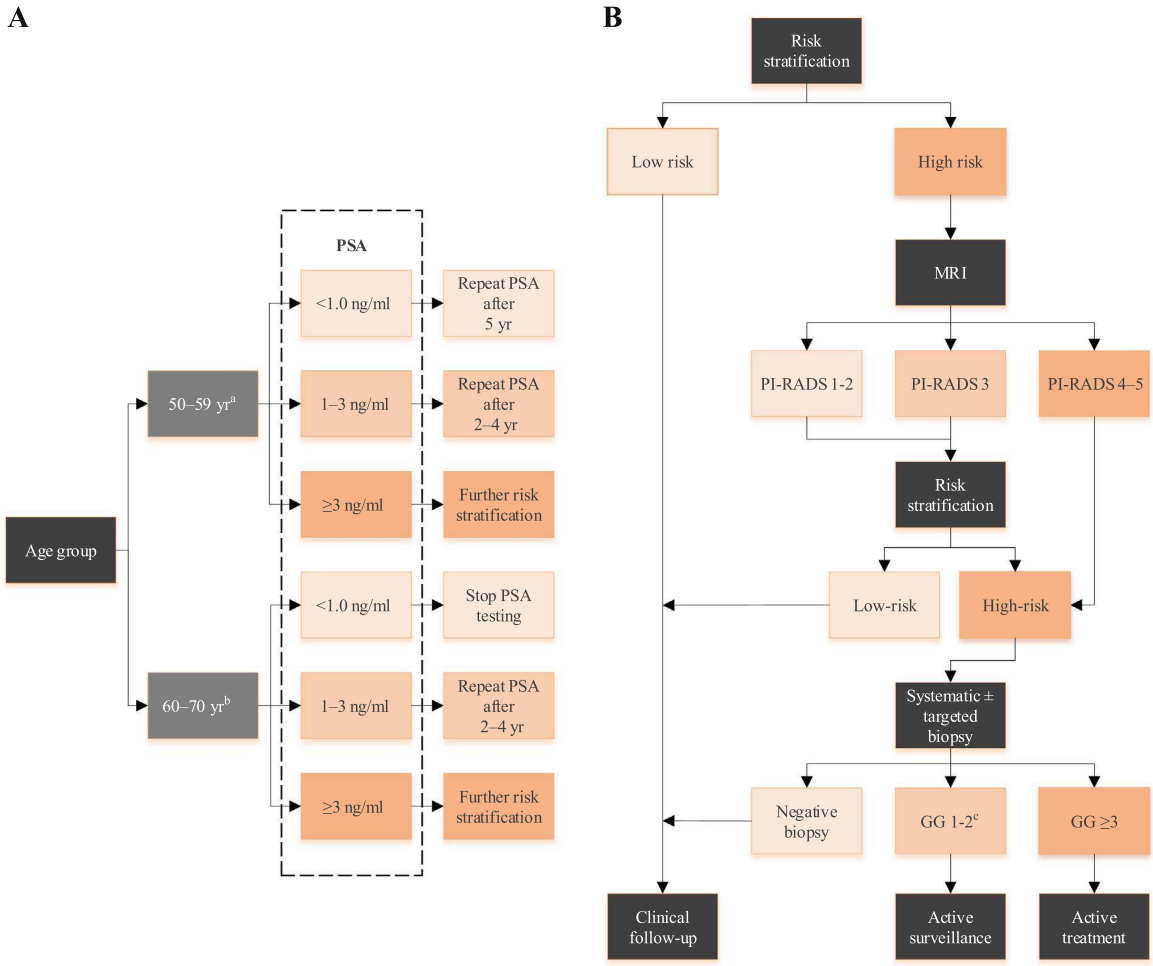

Fig. 1 – (A) Flow chart for PSA interval testing in different age groups. PSA = prostate-specific antigen. (B) Algorithm for a risk-stratified early detection strategy for prostate cancer in men with elevated PSA. GG = Gleason grade group; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System. [a] Follow the same schedule for men aged >45 yr with a family history of prostate cancer or African descent and for men aged >40 yr who carry BRCA2 mutations. [b] Follow the same schedule for men aged >70 yr with good performance status and life expectancy of at least 10–15 yr. [c] Only favourable intermediate-risk prostate cancer. Note: Reprinted from Eur Urol, 2021;Vol 79/issue 3, Van Poppel H., Hogenhout R., Albers P., van den Bergh R.C.N., Barentsz J.O., Roobol M.J., Early Detection of Prostate Cancer in 2020 and Beyond: Facts and Recommendations for the European Union and the European Commission, pp. 327-329, Copyright 2021, with permission from Elsevier.

3.1. *PSA testing*

3.1.1. *Shared decision-making*

During the diagnostic journey, adequate counselling and the provision of understandable information about the pros and cons of PSA testing are crucial. This will lead to a decreased desire of an individual man to request an ill-considered PSA test and will improve his compliance with the proposed tests and treatments [11]. To achieve the process of shared decision-making, the following points should be explained in every men's counselling: (1) the consequences of the PSA test result and the possibility of using an RC and, if indicated, followed by MRI to determine the need for prostate biopsy, (2) the pros to detect disease at an early stage when the chance of cure is higher with fewer side effects, and (3) the risks of diagnostic procedures such as biopsy complications, overdiagnosis with overtreatment, and the potential anxiety during the diagnostic process and eventually during active surveillance. The EAU's patient information leaflet on PSA testing can serve as a source of information [12].

3.1.2. *Risk groups according to age, family history, genetic predisposition, and ethnicity*

The recommendations of the EAU guidelines on PCa for early detection according to age are incorporated in the algorithm [9]. In general, men aged >50 yr are at an increased risk of clinically significant PCa (csPCa; ISUP grade group ≥2). Furthermore, male BRCA2 mutation carriers have an increased risk of early aggressive PCa and should therefore be offered a PSA test at the age of 40 yr [9,13]. Although the increased risk of early-onset PCa seems less marked in BRCA1 mutation carriers, further follow-up of the on-going trials (eg, the IMPACT study) is needed to

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determine the optimal early detection strategy for these men [13]. Men with a family history of PCa and/or African descent are more likely to be diagnosed with PCa and die of PCa at an earlier age [6,14]. This risk depends on how many relatives are affected and at what ages, and family degree. Therefore, although not supported by level 1 evidence, these men should be offered PSA testing at the age of 45 yr.

PSA testing in men beyond the age of 70 yr is an issue of debate, as death due to other causes is a competing risk to the progression of clinically insignificant PCa in this older population [15]. However, given the increasing life expectancy and age at which men remain fit, offering PSA testing in older men with little comorbidity and life expectancy of at least 10–15 yr can be considered [9]. The performance status of older men should be assessed and taken into account in this decision. All men, especially these older men, should be informed about the potential risks and benefits of early detection of PCa.

3.1.3. PSA threshold and testing interval

Once a man is well informed, a PSA test can be performed. To determine the indication for further risk stratification, the commonly used PSA threshold of 3 ng/ml can be maintained [2]. However, as one-time screening has shown to be ineffective in reducing PCa-specific mortality, an individualised retesting interval approach is implemented in our recently developed algorithm [10,16,17]. The initial baseline PSA level is related to the future risk of PCa development [17–21]. Therefore, the first testing interval can be adjusted to the baseline PSA level and thereafter to the last known PSA level. The intervals mentioned in the algorithm [10] are largely in line with the Memorial Sloan Kettering Cancer Center recommendations for PCa screening mainly based on high-quality screening trials (ERSPC, PLCO, and Malmö cohort) [22]. The evidence for longer testing intervals for those with low PSA levels is strong. Men with PSA $\leq$1.0 ng/ml do not have an increased risk of having csPCa with testing intervals up to 3–5 yr [23,24]. Annual or biennial screening in this group is therefore redundant. According to an analysis of ERSPC data, even an 8-yr testing interval could be used with only a small risk of missing csPCa [25]. Therefore, a retest interval of about 5 yr in men aged 50–59 yr with PSA $<$1.0 ng/ml seems sufficient. Given that the risk of developing future csPCa is low, men over 60–70 yr of age (life expectancy and performance status taken into account) with PSA levels below 1 ng/ml are unlikely to benefit from repeated tests and could therefore be excluded safely from future testing [19–21]. When using a 2–4-yr interval for baseline PSA levels of 1–2.9 ng/ml, both overdiagnosis and incidence of advanced PCa are limited [22,26,27]. To minimise overdiagnosis in this group of men, one could consider a 4-yr interval for older men and/or for men with a PSA level close to 1 ng/ml [22,26].

3.2. Risk stratification after PSA testing for MRI and prostate biopsy

In a screening setting, the classic approach of applying a PSA cut-off for further testing has proved its effectiveness in terms of PCa mortality and metastasis reduction [3]. However, since the specificity of PSA is low, additional diagnostic tests should be used to further stratify risks and identify the indication for prostate biopsy. This additional risk stratification will provide extra information on the risk of csPCa. Other blood-based biomarkers besides PSA, urine-based biomarkers, RCs, and MRI have been developed as risk stratification tools and are discussed below.

3.2.1. Novel blood-based and urine-based biomarkers

Osses et al [28] provided an extensive overview of the available biomarkers. The new blood-based biomarkers that showed good discriminative ability concerning the detection of csPCa are the Prostate Health Index and the Four-Kallikrein Panel. They contain the long-standing PSA derivatives (eg, free PSA and total PSA) and its more recently discovered isoforms (eg, benign PSA, proPSA, and intact PSA). Urine-based biomarkers that have been developed are Prostate Cancer Antigen 3 (PCA3), TMPRSS2-ERG, and urinary three-gene panel (*HOXC6*, *TDRD*, and *DLX*). Head-to-head comparisons and validation studies are needed to determine which biomarkers are preferred. Some of these biomarkers have led to new prediction models or have been implemented into existing ones to improve their diagnostic accuracy (eg, Stockholm-3 model and SelectMDx), although their performance is mainly driven by PSA density [29]. Additions to PSA density as a strong and easily available predictor should result in a considerable increase in stratifying capability to keep patient burden and costs of a population-based programme balanced.

3.2.2. Risk calculators

RCs give an individualised assessment of the potential risk of biopsy-detectable csPCa. Variables commonly incorporated are PSA, digital rectal examination (DRE), age, %free PSA, transrectal ultrasound (TRUS), previous biopsy status, and MRI result [30,31]. PSA density, derived from PSA and prostate volume determined by DRE or TRUS, is one of the strongest predictors within RCs and for many of the abovementioned biomarker prediction models [28]. Many RCs were developed and compared. A meta-analysis showed that only six prediction models with comparable overall high discriminative abilities (area under the curve [AUC] 0.66–0.79) were validated externally: Prostataclass, Finne, Karakiewcz, Prostate Cancer Prevention Trial (PCPT), Chun, and the ERSPC Risk Calculator 3 [30]. However, none of these RCs included the MRI result as a predictor variable. Mortezavi et al [31] showed, in a head-to-head comparison, improved discriminative ability of csPCa by the new-generation RCs that include MRI data (AUC 0.81–0.87). These RCs seem to be preferred when MRI data are available.

Selection of the optimal threshold above which further diagnostics are recommended can be challenging as it differs per RC and setting in which it is applied, and also depends on patient and doctor's preferences. Therefore, RCs have to be calibrated to the target population, and the threshold should be discussed in shared decision-making between the doctor and the patient.

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3.2.3. Magnetic resonance imaging

MRI has recently transformed the PCa diagnostic pathway. Foundational studies include the verification PROMIS study [32], the randomised international PRECISION and multicentre Canadian trials [33,34], and head-to-head systematic versus MRI-directed biopsy studies [35,36]. Taken together, the evidence indicates that MRI before biopsy can allow one-third of men to avoid an immediate biopsy and reduce overdiagnosis, with 40% fewer clinically unimportant cancers and approximately 15% more clinically important cancers detected [37]. The MRI-directed biopsy strategy for PCa diagnosis has received guideline endorsement for both biopsy-naïve patients and patients with prior negative biopsy [9]. This success has increased the demand for MRI machines and manpower resources, prompting the need to develop techniques that make MRI data acquisition and evaluation times faster and more consistent. Promising strategies include noncontrast MRI using the axial plane only. Systematic reviews of nonrandomised comparative studies have suggested that noncontrast MRI might be as accurate as MRI with contrast [38]. However, the Prostate Imaging Reporting and Data System (PI-RADS) Steering Committee warns against a large-scale use of noncontrast MRI by suboptimally trained radiologists [39]. A recent study of fast MRI (MRI without contrast medium in the axial plane only) yielded promising results [40].

Artificial intelligence methods that are trained with fast biparametric MRI have recently shown good discriminatory power and improved reader variability. They thus may be additionally helpful in enabling a "smarter" and faster MRI approach [41]. Definitive investigations of fast MRI for directing the PCa diagnosis pathway in prospective, multicentre, multiobserver settings are needed before large-scale implementation can be considered.

3.2.4. Sequence of risk calculators and MRI

After PSA testing, using an RC as the first risk stratification tool seems the most appropriate approach in the risk assessment of PCa for several reasons. RCs are accessible to every clinician, easy to use, inexpensive, and noninvasive. Moreover, performing MRI in all men with an elevated PSA level is redundant and impossible due to the sometimes limited availability of high-quality MRI and expert readers. This is illustrated by the Göteborg PCa screening 2 trial, which showed an excessive rate of negative MRI results of 75–77% using this strategy [42]. It is important to note that, even without the availability of MRI risk stratification, using the PSA level as guidance for retesting intervals and an RC is a strategy that may be regarded as second best but will still substantially reduce harm as compared with a purely PSA-based strategy, as was done by the ERSPC [2,3]. An RC as a pre-MRI risk stratification tool in a clinical cohort can prevent more than a third of prostate MRI scans (or biopsy procedures if MRI is not feasible) [43]. This amount is expected to be even larger in a screening cohort with a lower overall risk of PCa. Hence, MRI should be offered to selected intermediate-risk and high-risk men following an RC [44]. However, this approach leads to the risk of missing csPCa in some men who are considered to be at a low risk by RCs [43]. Therefore, monitoring these men by repeated PSA tests is mandatory.

Next, performing multiparametric MRI before biopsy, as strongly recommended by the EAU guidelines, not only has preferable detection rates, but could also reduce the number of biopsy procedures when MRI-negative men are excluded from prostate biopsy [9]. Depending on the a priori risk of the cohort in question, potentially a third to half of all biopsy procedures can be avoided if the most commonly used cut-off value of PI-RADS $\geq$3 is applied [36,37]. To further reduce unnecessary biopsy procedures, the conduct of biopsy in men with equivocal (PI-RADS 3) lesions is questioned. Several studies found that the exclusion of men with PI-RADS 3 lesions and a PSA density of $<$0.13–0.15 ng/ml/cc is a safe strategy [45–47]. However, exclusion of all men from biopsy with PI-RADS 1–2 or PI-RADS 3 lesions based on a low PSA density only, poses a risk of missing csPCa due to nonvisual PCa or misinterpretation of the reader. To limit the number of missed cancers, a multivariable risk-based patient biopsy selection can be performed after MRI. The MRI results can be integrated into an RC that also includes PSA density as a continuous variable. This enables a better assessment of the individual risk, which is crucial for the interpretation of the MRI results [9]. As a result, both biopsy-naïve men and men with previous negative biopsy will be offered systematic biopsy after negative MRI only if, according to an RC, the risk of detecting csPCa is high. Alberts et al [48] presented such a strategy in a multicentre study of 961 men and found that unnecessary biopsy procedures can be avoided. However, also with this strategy, a small number of csPCa cases can be overlooked. Therefore, a safety net should be provided by repeating the PSA test. Long-term data on the optimal PSA retesting intervals for low-risk men with elevated PSA levels, who are risk stratified through an RC and MRI, are not yet available. So far, two large retrospective studies assessed the csPCa diagnosis-free survival in biopsy-naïve men and men with previous negative biopsy after negative MRI [49,50]. Both studies found a diagnosis-free survival rate of $\geq$95% after 2–3 yr of follow-up. Up to now, a testing interval of 2–3 yr seems to be a safe strategy. An RC can be reused to determine the indication for MRI. Although further validation is required, a promising tool to determine whether longer intervals can be used is the future RC that predicts the individual 4-yr risk of biopsy-detectable PCa [51].

3.3. Biopsy technique and outcome

3.3.1. Biopsy technique

Until 2021, due to limited and sometimes contradictory literature concerning infectious complications, no clear preference was given according to either the transrectal or the transperineal route for prostate biopsy. A very recent meta-analysis of seven randomised studies provided level 1a evidence that transperineal prostate biopsy was associated with significantly reduced infectious complications compared with transrectal prostate biopsy [52]. Comparable findings were reported by a large population-based study [53] and a systematic review of 162 577 patients [54],

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although both studies found an increased risk of urinary retention with transperineal prostate biopsy. Nevertheless, especially on a large scale, the transperineal technique should be striven for to minimise potentially life-threatening infectious complications. The remaining question that has to be answered in the future is, if necessary at all, the following: which antibiotic prophylaxis should be given for transperineal prostate biopsy? Concerning detection performance, two systematic reviews showed a better detection rate of csPCa for MRI-targeted transperineal biopsy due to improved sampling of the anterior region of the prostate [55,56].

Sampling errors can occur due to intratumour heterogeneity [36] or are caused by interobserver variability between radiologists [57], variability in experience of biopsy performers, and systemic errors in the biopsy technique itself. Targeted cores are therefore not always considered sufficient. The reports about the added value of additional systematic biopsy cores in overcoming these sampling errors are contradictory [37,58,59]. As long as the evidence on the detection rate of csPCa by different biopsy techniques contradicts, and early detection of PCa is not carried out exclusively by experienced centres, extra biopsy cores are needed in biopsy-naïve men in order not to miss csPCa [9,36,43]. Whether these extra cores are perilesional or systematic is still an open question. To date, the EAU guidelines recommend systematic biopsy as extra cores [9]. In men with previous negative biopsies and positive MRI, only targeted biopsy will be sufficient [60].

The three available techniques for MRI-targeted prostate biopsy are cognitive registration TRUS targeted biopsy, MRI-TRUS fusion targeted biopsy (FUS-TB), and in-bore MRI targeted biopsy (MRI-TB). The randomised controlled FUTURE trial provided level 1 evidence that among these techniques, the differences in the detection rate of csPCa did not vary significantly [61]. Although FUS-TB is more time consuming and requires extra equipment, it has a better detection rate for smaller lesions, its performance is more standardised, and it is less dependent on operators' expertise [62]. These are important features when developing a population-based screening programme. MRI-TB is also expected to have better detection rates for smaller as well as ventral lesions, but needs expertise, is costly and time consuming, and could be associated with an increased infectious complication rate due to the rectal approach.

3.3.2. *Biopsy outcome*

Even with the state-of-the-art technology and knowledge, we can limit, but not completely overcome, overdiagnosis. However, with active surveillance, subsequent overtreatment can be avoided in men with clinically insignificant PCa. Active surveillance has emerged as an agreed treatment policy. It allows men to be excluded from active treatment and its subsequent side effects as long as their clinically insignificant PCa does not show progression and therefore remains curable. Owing to the growing knowledge on the natural course of the disease, active surveillance can be offered to more men as a safe follow-up strategy with less overtreatment. One of the new findings is that men with favourable intermediate-risk PCa do not have an increased risk of PCa-specific mortality compared with men with low-risk PCa [63]. These men could be offered active surveillance if they are well informed and will be monitored carefully.

Such a safe follow-up strategy is also indicated for men with negative biopsy results but who have a persistent suspicion of csPCa. As mentioned earlier, PCa can be missed in some men despite careful risk stratification and even after prostate biopsy. Therefore, repeated (targeted) biopsy should be taken into account when certain clinical risk factors are present. Triggers for repeated biopsy are high PSA levels or short PSA doubling time, DRE progression, and MRI progression. These data, including biopsy status, can be implemented in an RC [64,65], especially if they are not decisive when individually considered.

3.4. *Discussion*

To date, many different diagnostic pathways and risk stratification tools have been developed to select men for MRI and, if needed, prostate biopsy. However, the consensus is lacking on which ones are best. Furthermore, although MRI plays an important role in the risk assessment of PCa, its implementation is not (yet) realised in the whole of Europe and should therefore be regarded as a desirable option. Whatever be the pathway, RC, or biomarker, most importantly, the direct link between elevated PSA and immediate biopsy, as was done in the ERSPC, must be disconnected. Decoupling of these two will result in fewer biopsy procedures and less detection of insignificant PCa. Eventually, there will always be a compromise in terms of cancer detection rates and test availability, capacity, and costs, since we do not have the perfect risk stratification tool. Perhaps more important is that we do not know exactly beforehand which cancers will ultimately be lethal. The latter is a dynamic process between PCa and host features. Therefore, awareness of the strengths and weaknesses of the chosen pathway and responding adequately to its limitations is crucial. Based on the existing, limited literature and expert consensus opinion, we presented a risk-stratified strategy for an organised early detection programme for PCa that adequately balances the trade-offs between overdiagnosis and underdetection and provides a safety net to overcome its pitfalls.

Nevertheless, such a strategy will never be final through continuous innovation in this field and will be subject to constant improvements. New, sometimes better, or less costly alternative risk stratification tools are upcoming and could further refine the PCa risk assessment. For example, molecular biomarkers other than PSA, faster MRI techniques without contrast, radiomics, artificial intelligence methods, future RCs, and genetic profiles are currently being investigated. Their potential contribution seems promising but warrants further research, as the data are too limited [9,28]. A few of these new tools are already included in some of the on-going studies investigating new risk-stratified strategies. An overview of these studies can be found in Supplementary Table 1.

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Unfortunately, most of those on-going studies that cover our proposed algorithm have not yet been completed. Therefore, the efficiency of our strategy cannot be confirmed yet, but need to be monitored carefully once implemented and can continuously be adapted to new insights gained by experience and long-term data, which will become available in the future. Monitoring and evaluation after implementation can be done according to the procedure as described, for example, breast cancer screening [66] in the European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis [67,68]. Up to now, the benefits of RCs and MRI within the detection of PCa have been proved only from clinical cohorts. However, their improvements change the classic PSA-only early detection algorithm radically. The ERSPC showed clear benefits of PSA-based screening, but nearly 2 decades of follow-up were needed [2]. Validation studies of the new risk-stratified screening strategy are therefore expected to take a long time to finish. If we wait for these results, the incidence of advanced PCa will continue to increase unacceptably in the next decade. The currently available results of the use of RCs and MRI are convincing enough and are already recommended by the guidelines [9].

4. Conclusions

We present a new algorithm for an organised population-based early detection programme for life-threatening PCa, mainly based on consensus-based expert opinion. This algorithm combines the existing established benefits of PSA tests with new risk stratification tools. Combining these effective tools will reduce the incidence of locally developed and metastatic PCa and its associated morbidity and mortality. At the same time, it is associated with less overdiagnosis and overtreatment compared to the classic PSA-only diagnostic strategy. The new early detection algorithm begins with PSA interval tests in well-informed men, followed by multivariable risk-based patient selection for MRI and biopsy using an RC. All subsequent low-risk or biopsy-negative men will be offered a safety net consisting of PSA interval tests and repeated MRI if suspicion of clinically significant PCa persists. Although the proposed algorithm is not yet confirmed by direct evidence, we firmly believe that the growing burden of PCa on our society and the on-going large-scale opportunistic screening require a rapid introduction of this new risk-stratified strategy for early detection of PCa in a population-based, organised setting.

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Study concept and design: Hogenhout, Van Poppel, Albers, Barentsz, van den Bergh, Roobol.
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Appendix A. Supplementary data

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