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Original Article

Shifting risk-stratified early prostate cancer detection to a primary healthcare setting

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Objective

To evaluate the feasibility of multivariable risk stratification for early prostate cancer (PCa) detection in a primary healthcare diagnostic facility with regard to its effects on the referral rate and subsequent PCa diagnoses compared to a PSA threshold of 3.0 ng/mL as the current referral indicator.

Patients and Methods

In 2014, the Erasmus MC Cancer Institute and the primary healthcare diagnostic facility STAR-SHL (located in Rotterdam city centre) initiated this observational study, in which general practitioners (GPs) could refer men who wished to undergo PCa screening to STAR-SHL for consultation by specially trained personnel. Referral recommendations to secondary healthcare were based on the outcome of application of the Rotterdam Prostate Cancer Risk Calculator (RPCRC) and were compared to the current Dutch GPs' PSA referral threshold of 3.0 ng/mL. For data collection on PCa diagnoses, the study cohort was linked to the Dutch nationwide pathology databank (PALGA).

Results

Between January 2014 and February 2021, 507 men were referred for consultation and in 495 men prostate-specific antigen (PSA) was tested. The median (interquartile range) follow-up from consultation to PALGA linkage was 43 (25–65) months. In total, 279 men (56%) had a PSA level ≥3.0 ng/mL, of whom 68% (95% confidence interval [95% CI] 63–74) were considered at low risk according to the RPCRC. Within 1 year after consultation, one of these men (0.52%; 95% CI 0.092–2.9) was diagnosed with clinically significant (cs)PCa (i.e., International Society of Urological Pathology Grade Group ≥2). Thereafter, another four (2.1%; 95% CI 0.82–5.3) low-risk men were diagnosed with csPCa. Of the high-risk men who were biopsied within 1 year after consultation (n = 61), 77% (95% CI 65–86) were diagnosed with PCa and 49% (95% CI 37–61) with csPCa.

Conclusion

In a primary healthcare diagnostic facility, the RPCRC could reduce up to 68% of referrals to secondary healthcare, as compared to a PSA referral threshold of 3.0 ng/mL. Deploying the RPCRC in this setting resulted in a high csPCa detection rate in those men biopsied. This strategy can be considered safe since the observational data showed low proportions of csPCa among men at low risk.

Keywords

early detection, general practitioners, primary healthcare, prostatic neoplasms, prostate-specific antigen, risk assessment, secondary healthcare, #PCSM, #ProstateCancer, #uroonc

Introduction

Prostate cancer-specific antigen (PSA)-based screening reduces prostate cancer (PCa)-specific mortality [1,2], but at the cost of overdiagnosis. Although PSA testing on invitation for early PCa detection is, therefore, not recommended by the Dutch College of General Practitioners (NHG) guidelines [3], this test is regularly requested by the male population, or at the insistence of family or friends who are aware of PCa as a potentially lethal disease. Furthermore, although Lower Urinary Tract Symptoms (LUTS) are more suggestive of benign prostatic hyperpasia in the aging male population [4], one often associates LUTS with PCa. These common urinary complaints, along with the public awareness of PCa, can lead to opportunistic screening [5]. This unstructured way of screening is shown to have no clear effect on PCa-specific

mortality and is, in fact, associated with even more overdiagnosis compared to organized screening [6].

To reduce this overdiagnosis, new risk stratification tools have been developed. The Rotterdam Prostate Cancer Risk Calculator (RPCRC) is one such tool. The RPCRC predicts the risk of finding PCa based on multiple clinical variables [7] and can reduce more than half of unnecessary biopsy procedures in an outpatient clinic compared to the generally accepted and applied PSA threshold of ≥3.0 ng/mL. This implies that, since this PSA threshold is currently used by the NHG guidelines as a referral indicator to secondary healthcare [3], many unnecessary referrals could result which subsequently puts pressure on healthcare costs and workload in hospitals.

We, therefore, hypothesized that implementing the RPCRC in a primary healthcare setting could prevent unnecessary referrals for further PCa diagnostics to secondary care. We previously investigated this principle, with promising results [8]; however, the cohort at that time was still relatively small and had a short follow-up. Hence, we aimed to evaluate the feasibility of the RPCRC implemented in a primary healthcare setting, relative to the current referral indicator of PSA ≥3.0 ng/mL, in a larger cohort and, most importantly, with extended follow-up, including those men considered to be at low risk and not referred.

Patients and Methods

Study Design and Population

In 2014, the Erasmus MC Cancer Institute and the primary healthcare diagnostic facility STAR-SHL initiated this prospective observational study. GPs from the catchment area of STAR-SHL in central Rotterdam could refer men to STAR-SHL for a so-called 'prostate consultation' if they were aged ≥18 years without previous PCa diagnosis, wished to undergo screening for PCa, or had LUTS. We included all men in whom a PSA test was performed. To validate the NHG guidelines' statement that no further diagnostics are needed among men with PSA <3.0 ng/mL, prostate consultation was offered also to these men [3]. All participants provided written informed consent. More details on the study protocol and ethical approval have been described previously [8].

Procedures and Data Collection

Consultations were performed by clinical researchers with a medical degree and clinical experience in urology, trained and supervised by the Department of Urology at the Erasmus MC Cancer Institute. In general, consultation could be planned within 1 week of referral by the GP. Consultation consisted of digital rectal examination (DRE) and transrectal ultrasound of the prostate (TRUS). The risk of finding PCa was calculated by the RPCRC (https://www.prostatecancer-riskcalculator.com/) using the outcomes of these examinations and the PSA test [7]. Men who had a negative biopsy more than 4 years ago were considered biopsy-naïve [9].

General practitioners were advised to refer men to the urologist who were considered high-risk according to the RPCRC and in whom further evaluation was expected to be beneficial according to estimated life expectancy and comorbidity. One was considered high-risk when the probability of having a positive biopsy (i.e., finding any PCa) was ≥20%, or ≥12.5% in combination with a probability of finding clinically significant (cs)PCa of >4%. These cut-off values were previously determined by the development study of the RPCRC [7]. csPCa was defined as International Society of Urological Pathology (IUSP) Grade Group ≥2.

Since one-time screening is ineffective in reducing PCa-specific mortality [10] and csPCa can be missed in men considered to be low-risk [11], a PSA retesting strategy was recommended for these men. GPs were advised to cease future PSA testing in men who were expected not to benefit based on old age or extensive comorbidity.

General practitioners made the final decision whether or not to refer to one of the region's hospitals according to the patient's or GP's preference. To evaluate the effect of the prostate consultation with use of the RPCRC in terms of diagnosed cancers, all available pathology records related to prostate tissue (i.e., obtained from both biopsy or transurethral resection of the prostate) were retrieved by matching the study cohort with the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA) [12]. Patients were excluded if follow-up after consultation was <6 months at the time of linkage with PALGA to avoid missing pathology of patients with a delayed referral.

Outcomes

The primary outcomes were the proportion of men with PSA level ≥3.0 ng/mL who were considered low-risk and could be withheld from referral according to the RPCRC; the proportions of PCa diagnosis among high-risk men; and the proportion of csPCa diagnosis among low-risk men to assess the safety of this strategy. Since, the RPCRC calculates the risk of finding PCa at that moment in time and this risk can change over time, a distinction was made between diagnoses <1 year after consultation and ≥1 year after consultation. Secondary outcomes were median time to diagnosis ≥1 year after consultation to assess delayed diagnoses.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0.: IBM Corp. (Armonk, NY, USA).

Descriptive statistics were used. Categorical data were reported as count (percentage) and continuous data as median (interquartile range [IQR]).

Results

Patient Characteristics

From January 2014 to February 2021, 507 men were referred by their GP for a prostate consultation at the primary healthcare diagnostic facility STAR-SHL. In 495 men, PSA levels were tested and these men were eligible for analysis. The men's baseline characteristics are presented in Table 1. The median (IQR) follow-up from consultation to PALGA linkage was 43 (25–65) months. For the entire cohort, the median (IQR) probability of finding any PCa according to the RPCRC was 6.7% (2.7%–13.4%) and for csPCa 1.2% (0.41%–3.0%). In total, 68 men were diagnosed with PCa. The median (IQR) follow-up of these men was 52 (35–69) months. The median (IQR) follow-up of men without PCa diagnosis was 40 (23–65) months.

Table 1 Baseline characteristics (n = 495).

Age at time of 1st consultation, years	
Median (IQR)	64 (57–70)
Follow-up, months	
Median (IQR)	43 (25–65)
Indication, *n* (%)	
PCa screening	217 (44)
LUTS	79 (16)
PCa screening and LUTS	199 (40)
Consultations, *n* (%)	
One	479 (97)
Two	16 (3.2)
Previous biopsy*, *n* (%)	
No	486 (98)
Yes	9 (1.8)
PSA, ng/mL	
Median (IQR)	3.2 (1.2–5.4)
Prostate volume, mL	
Median (IQR)	42 (30–61)
DRE, *n* (%)	
Non suspicious	436 (88)
Suspicious	59 (12)
TRUS, *n* (%)	
Non suspicious	453 (92)
Suspicious	41 (8.3)
Unknown	1 (0.20)
RPCRC outcome, %	
Median (IQR)	
Probability any PCa	6.7 (2.7–13.4)
Probability csPCa†	1.2 (0.41–3.0)
Risk group according to RPCRC, *n* (%)	
Low-risk	393 (79)
High-risk	102 (21)

*DRE, digital rectal examination; IQR, interquartile range; LUTS, Lower Urinary Tract Infections; PCa, prostate cancer; PSA, prostate-specific antigen; RPCRC, Rotterdam Prostate Cancer Risk Calculator; TRUS, transrectal ultrasound of the prostate. *In the past 4 years. †Defined as International Society of Urological Pathology (ISUP) Grade Group ≥2.*

Low-Risk Men

The outcomes of the PALGA linkage per PSA and risk group are presented in Fig. 1. Of all men with PSA ≥3.0 ng/mL, 191 (68%; 95% CI 63–74) were considered low-risk according to the RPCRC and reflect the referrals that could be prevented. Within 1 year after consultation, only one low-risk man (0.52%; 95% CI 0.092–2.9) was diagnosed with csPCa. More than 1 year after consultation, another four low-risk men (2.1%; 95% CI 0.82–5.3) were diagnosed with csPCa, with a median (IQR) time to diagnosis of 22 (14–29) months. At their first consultation, these men were advised to repeat PSA testing. One of them visited STAR-SHL 2 years later for a second consultation and was reclassified as high-risk because of increased PSA level and thus PSA density, and suspicious DRE. For the other men, data on referral were unknown.

Two low-risk men (0.85%; 95% CI 0.26–3.4) with low PSA levels were diagnosed with csPCa <1 year after prostate consultation. One of those men had a very low PSA level (<1 ng/mL) and presented with severe LUTS and questionable DRE. Referral to the urologist because of LUTS ultimately revealed high-grade PCa (5 + 4).

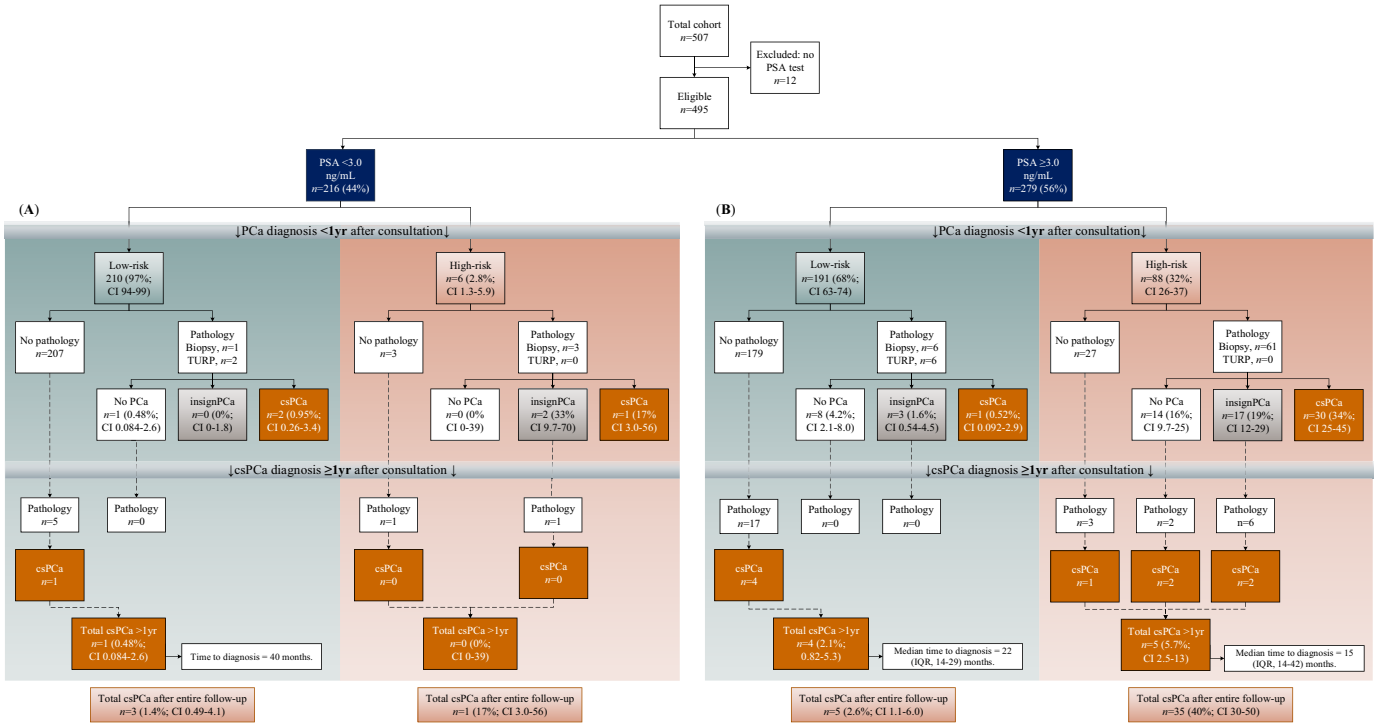
High-Risk Men

Of all men with PSA ≥3.0 ng/mL, 88 (32%; 95% CI 26–37) were considered high-risk according to the RPCRC, of whom 61 men were biopsied <1 year after consultation. Of these 61 men, 77% (95% CI 65–86) were diagnosed with any PCa and 49% (95% CI 37–61) with csPCa. In two of 14 men with negative biopsy, prostatitis was found. More than 1 year after consultation, another five men (6%) were diagnosed with csPCa with a median (IQR) time to diagnosis of 15 (14–42) months. Four men were reclassified from no PCa or insignificant PCa to csPCa.

Discrepant Referral Advice According to RPCRC Outcome

Of all high-risk men (n = 94), five (5%) were advised not to be (immediately) referred to the urologist. These included men with old age or comorbidity, for whom watchful waiting was recommended, or men with suspicion of recent urinary tract infection, for whom repeating the PSA test was recommended. Eventually, one man from the latter group was biopsied, with a negative outcome. Of all low-risk men (n = 401), 10 (2%) were advised to be referred because of patient or doctor anxiety, often based on highly suspicious DRE or TRUS findings, or a calculated risk near the threshold (e.g., 4% probability of finding csPCa), and in combination with other factors such as African descent, PSA rise, young age, or PCa among family members. Of those men, four were biopsied, of whom two were diagnosed with insignificant PCa.

Fig. 1 Flowchart of the Rotterdam Prostate Cancer Risk Calculator results for PSA level subgroup (**A**) <3.0 ng/mL and (**B**) ≥3.0 ng/mL, and all available pathology records. CI, 95% confidence interval; csPCa, clinically significant prostate cancer; insignPCa, clinically insignificant prostate cancer; PCa, prostate cancer; PSA, prostate cancer-specific antigen; TRUS, transrectal ultrasound of the prostate.



Discussion

To streamline referrals to secondary healthcare for early PCa detection, we started a collaboration with a primary healthcare diagnostic facility where Dutch GPs could refer their patients for an individualized risk assessment. Our study showed that implementing multivariable risk stratification by the RPCRC in a primary healthcare setting could reduce more than two-thirds of the referrals to secondary healthcare compared to the current PSA referral threshold of ≥3.0 ng/mL of the NHG guidelines. This was at the cost of missing csPCa in only 1% of low-risk men <1 year after consultation and delayed diagnosis of csPCa in 2% of low-risk men. Furthermore, our observational data support the NHG guidelines which recommend not to perform further diagnostics in men with PSA <3.0 ng/mL as we found a low rate of csPCa diagnoses among such men (2%). These findings show great potential for safely reducing healthcare costs, waiting time, and workload in secondary healthcare by multivariable risk prediction in a primary healthcare setting. To illustrate this, the same consultation in a Dutch outpatient clinic is approximately seven times more expensive than at STAR-SHL [8] and the median (IQR) waiting time for consultation at a urologist is currently 6 (3–9) weeks [13] compared to approximately 1 week at STAR-SHL.

There are several explanations why so many referrals to secondary care could be avoided. One of those is the low specificity of the PSA threshold on which referrals are currently based. The detection of csPCa in only 1%–2% of low-risk men with PSA ≥3.0 ng/mL confirms that PSA in itself is a poor referral indicator. Another explanation is the low median probability of finding PCa in the entire cohort, which represents a primary healthcare population. Previous research reported a somewhat lower percentage of biopsies saved according to the RPCRC (54%) [7]. However, that previous analysis was performed on the initial screening cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC), which was a population-based cohort in the 1990s with no pre-screening and pre-selection at all and therefore contained more high-risk men with higher PSA levels compared to a contemporary primary healthcare cohort [14].

The 68% of the referrals that could be prevented according to the RPCRC, however, might not reflect daily clinical practice. A small proportion of referral advice (5%) was not in line with the RPCRC recommendations because, although the strongest predictor in the RPCRC, PSA density still has its limitations. For example, PSA density can be elevated because of underlying prostatitis and such an infection can even mimic a palpable tumour. Therefore, when prostatitis is suspected, PSA retesting can be considered as was done in our study instead of immediate referral. Conversely, some men were advised to be referred because of persistent anxiety for having PCa despite being at low risk. Within this study,

none of these men were diagnosed with csPCa. This persistent anxiety can also be a burden and referral can therefore be considered in close consultation with the patient. Both these scenarios illustrate the importance of a clinical assessment and shared decision-making, which can never fully be replaced by an objective probability calculation.

A remarkable finding was that initially approximately one-third of the high-risk men were not biopsied, although Osses et al. [8] showed a high compliance rate (94%) of GPs with the referral advice. In addition to the 5% of men who were advised not to be referred and the expected small proportion of non-compliance, this discrepancy can be attributed to men who received an MRI with a negative outcome and therefore in whom no subsequent biopsies were performed. That being said, expanding the prostate consultation by offering MRI to high-risk men could be an interesting consideration. By referring only those with positive MRI, the number of potentially unnecessary referrals can be further reduced. Subsequently, urologists only have to focus on the "true" high-risk men for whom their expertise is required.

Despite the one-third of high-risk men who were not biopsied, the proportions of insignificant cancers (19%) or negative biopsy outcomes (16%) among men considered high-risk are not negligible. To elaborate, this study was initiated in 2014 and the European Association of Urology guideline recommendations did not include MRI in the standard diagnostic evaluation of PCa up to 2019. Thus, a proportion of the biopsy results in the current study derive from systematic biopsy schedules with an increased risk of insignificant PCa outcomes [15]. Combining risk prediction models, such as the RPCRC or the Stockholm3 test, with MRI-targeted biopsy is associated with reduced detection of these insignificant diagnoses and improved sampling for csPCa [11,16]. In the current study, this might be reflected in the few men who were initially diagnosed with insignificant PCa or who had a negative biopsy and were later diagnosed with csPCa. The relatively short median time to diagnosis among these men supports the theory that there was initial undersampling instead of overestimation of risk. Because of further risk stratification possibilities and improved sampling in the current MRI era, future results from ongoing data collection within this longitudinal ongoing study may show fewer insignificant biopsy outcomes.

As an update to our previous work [8], we were able to perform a unique, prospective assessment of the performance of multivariable risk stratification in a primary healthcare diagnostic facility with a long follow-up time in a large cohort. Nevertheless, this study has some limitations. Because the study had an observational design, most low-risk men with elevated PSA were not offered prostate biopsy. In addition, although interval testing was recommended as a safety net, we only know how many csPCa cases were missed within the limits of our follow-up period (3%). The same applies to men with PSA <3.0 ng/mL. Nevertheless, previous research on the use of the RPCRC, in which all men with PSA ≥3.0 ng/mL were biopsied, showed, albeit in a clinical cohort, a comparable percentage of missed csPCa of 4% [7]. Furthermore, other than these follow-up data on PCa diagnosis obtained from PALGA, we had no data on, for example, repeated PSA measurements, which makes assessment of RPCRC performance over time difficult, neither did we have data on other biomarkers such as on MRI that may have been performed after referral. Although this would provide additional insight into further risk stratification, this was outside the scope of the current study, which focused on risk stratification in a primary healthcare diagnostic facility. Lastly, although we offered a structured approach, PSA was not tested on invitation in an organized setting but instead, for example, in men who requested a PSA test on their own initiative. Not all of these men benefit from PSA testing, for instance, men who are more likely to die from causes other than PCa. By offering the presented strategy on invitation to those men who are most likely to benefit, its full potential in balancing harms and benefits of early PCa detection can be reached. Europe's Beating Cancer Plan Committee now encourages the European Council to consider including PCa screening in the update of the European Council recommendations on cancer screening in 2022. This will result in detailed research on screening practices and needs in all European Union member states and will possibly lead to a tailored organized programme. This may not fit within the daily clinical practice of urologists in secondary healthcare. Our study showed a potentially suitable solution in this matter: by organized risk-stratified early detection of PCa outside the daily clinical practice of secondary healthcare, opportunistic screening is tackled, primary healthcare settings are spared unwanted PSA requests, and secondary healthcare settings are spared unnecessary referrals. In the near future, the prostate consultation will be offered at more STAR-SHL locations and collection of data will continue. So far, these consultations have been performed by researchers from the Department of Urology. On a larger scale, the prostate consultation could be and will be performed by, for example, trained physicians assistants or radiodiagnostic laboratory technicians [17].

In conclusion, multivariable risk stratification with the RPCRC in a primary healthcare diagnostic setting can reduce more than two-thirds of referrals to secondary healthcare compared to the PSA threshold of ≥3.0 ng/mL as the current referral indicator of Dutch GPs. Observational data showed low proportions of csPCa among men considered low-risk. Hence, the presented strategy for early PCa detection showed the potential for safely reducing healthcare costs, waiting times and workload in secondary healthcare, and might play

an important role in a possible future organized early PCa detection programme.

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Disclosure of Interests

The authors have no conflicts of interest to declare.

References

1 **Schröder FH, Hugosson J, Roobol MJ et al.** Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009; 360: 1320–8
2 **Tsodikov A, Gulati R, Heijnsdijk EAM et al.** Reconciling the effects of screening on prostate cancer mortality in the ERSPC and PLCO trials. *Ann Intern Med* 2017; 167: 449–55
3 **Blanker MH, Breed S, van der Heide WK et al.** NHG Standaard: Michtieklachten bij mannen. 2014
4 **Egan KB.** The epidemiology of benign prostatic hyperplasia associated with lower urinary tract symptoms: prevalence and incident rates. *Urol Clin North Am* 2016; 43: 289–97
5 **Weight CJ, Kim SP, Jacobson DJ et al.** The effect of benign lower urinary tract symptoms on subsequent prostate cancer testing and diagnosis. *Eur Urol* 2013; 63: 1021–7
6 **Arnsrud Godtman R, Holmberg E, Lilja H, Stranne J, Hugosson J.** Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Göteborg randomized population-based prostate cancer screening trial. *Eur Urol* 2015; 68: 354–60
7 **Roobol MJ, Steyerberg EW, Kranse R et al.** A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010; 57: 79–85
8 **Osses DF, Alberts AR, Bausch GCF, Roobol MJ.** Multivariable risk-based patient selection for prostate biopsy in a primary health care setting: referral rate and biopsy results from a urology outpatient clinic. *Transl Androl Urol* 2018; 7: 27–33
9 **Roobol MJ, Zhu X, Schröder FH et al.** A calculator for prostate cancer risk 4 years after an initially negative screen: findings from ERSPC Rotterdam. *Eur Urol* 2013; 63: 627–33
10 **Martin RM, Donovan JL, Turner EL et al.** Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. *JAMA* 2018; 319: 883–95
11 **Alberts AR, Roobol MJ, Verbeek JFM et al.** Prediction of high-grade prostate cancer following multiparametric magnetic resonance imaging: improving the Rotterdam European randomized study of screening for prostate cancer risk calculators. *Eur Urol* 2019; 75: 310–8
12 **Casparie M, Tiebosch AT, Burger G et al.** Pathology databanking and biobanking in the Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol* 2007; 29: 19–24
13 Available at: https://www.zorgkaartnederland.nl/wachttijden/urologie-2. Accessed February 2022
14 **Hugosson J, Roobol MJ, Månsson M et al.** A 16-yr follow-up of the European randomized study of screening for prostate cancer. *Eur Urol* 2019; 76: 43–51
15 **Drost FH, Osses DF, Nieboer D et al.** Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev* 2019; 4: CD012663
16 **Nordström T, Discacciati A, Bergman M et al.** Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. *Lancet Oncol* 2021; 22: 1240–9
17 **Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ.** A European model for an organised risk-stratified early detection programme for prostate cancer. *Eur Urol Oncol* 2021; 4: 731–9

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Abbreviations: csPCa, clinically significant prostate cancer; IQR, interquartile range; NHG, Dutch College of General Practitioners; PCa, prostate cancer; RPCRC, Rotterdam Prostate Cancer Risk Calculator.