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Prostate cancer screening in Switzerland: a literature review and consensus statement from the Swiss Society of Urology

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Summary

Over a decade ago, the United States Preventive Services Taskforce (USPSTF) recommended against prostate-specific antigen (PSA)-based screening for prostate cancer in all men, which considerably influenced prostate cancer screening policies worldwide after that. Consequently, the world has seen increasing numbers of advanced stages and prostate cancer deaths, which later led the USPSTF to withdraw its initial statement. Meanwhile, the European Union has elaborated a directive to address the problem of implementing prostate cancer screening in "Europe's Beating Cancer Plan". In Switzerland, concerned urologists formed an open Swiss Prostate Cancer Screening Group to improve the early detection of prostate cancer. On the 20th of September 2023, during the annual general assembly of the Swiss Society of Urology (SGU/SSU) in Lausanne, members positively voted for a stepwise approach to evaluate the feasibility of implementing organised prostate cancer screening programs in Switzerland. The following article will summarise the events and scientific advances in the last decade during which evidence and promising additional modalities to complement PSA-based prostate cancer screening have emerged. It also aims to provide an overview of contemporary strategies and their potential harms and benefits.

Introduction

Over a decade ago, the United States Preventive Services Taskforce (USPSTF) recommended against prostate-specific antigen (PSA)-based screening for prostate cancer in all men due to concerns about a high rate of over diagnosis and overtreatment. This considerably influenced prostate cancer screening policies worldwide [1]. Emerging evidence suggests that the incidence of advanced-stage and metastatic prostate cancers increased in the United States after that [2–5]. As the evidence from sizeable international screening trials matured, the USPSTF amended its statement against PSA-based prostate cancer screening in 2018, recommending PSA-based screening in men aged 55–69 years based on an individual evaluation and shared decision-making [6, 7]. Furthermore, various studies have demonstrated the potential value of diagnostic tests, such as magnetic resonance imaging (MRI), and biomarkers and PSA testing for prostate cancer screening. As a result, the European Union recently issued a directive supporting its member states in evaluating the feasibility of organised prostate cancer screening through their "Europe's Beating Cancer Plan" [8].

In Switzerland, concerned urologists formed an open Swiss Prostate Cancer Screening Group to improve prostate cancer screening. On the 20th of September 2023, during the annual general assembly of the Swiss Society of Urology (SGU/SSU) in Lausanne, members positively voted for a stepwise approach to evaluate the feasibility of implementing organised prostate cancer screening programs in Switzerland. The following article summarises the discussions and results of this voting, which should play a pivotal role in the future of prostate cancer screening in Switzerland (figure 1). The board of the Swiss Society of Urology (SGU/SSU) has approved the wording of this manuscript. Finally, the article summarises the events and scientific advances in the last decade during which evidence and promising additional modalities to complement PSA-based prostate cancer screening have emerged. It also aims to provide an overview of contemporary strategies and their potential harms and benefits.

How it all began

The story of prostate cancer screening mirrors the story of PSA testing. This serum tumour marker was first identified in the 1960s and was used until the late 1980s exclusively to monitor disease progression in men who had been diag-

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nosed with prostate cancer [9]. In the early 1990s, the PSA test gained popularity as a tool for prostate cancer screening because it was believed that it may lead to better patient outcomes [10]. To support this hypothesis, two large-scale clinical trials named European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) were initiated to assess the effectiveness of prostate cancer screening using PSA testing in Europe and in the USA, respectively [11, 12]. These studies aimed to determine whether PSA-based screening could reduce prostate cancer mortality rates.

Prostate cancer screening trials

European Randomized Study of Screening for Prostate Cancer (ERSPC)

The multinational ERSPC trial was initiated in 1993. The protocols differed slightly between the eight participating countries. Men aged 50 to 74 were randomly assigned to the screening or control group. The screening group received regular PSA tests (every two to four years) and follow-up if PSA levels exceeded an established threshold. Men with a PSA ≥3.0 ng/mL were referred for a systematic prostate biopsy. The screening interval was four years in most centres. The control group was not offered PSA testing. The first results were reported in 2009 after a median of nine years of follow-up of over 160,000 men [11]. The rate ratio for prostate cancer death in the screening versus the control group was 0.80 (95% CI 0.65 to 0.98). The absolute prostate cancer mortality risk difference was 0.71 prostate cancer deaths per 1000 men. This, together with an excess incidence of 34 prostate cancer patients per 1000 men, translated into 1410 invited men (number needed to invite) and 48 additional prostate cancer patients (number needed to diagnose) to avoid one death from prostate cancer. Of note, of the men who underwent biopsy for an elevated PSA value, 13,308 (75.9%) had a negative biopsy result. Of those diagnosed with prostate cancer, 72.2% had a Gleason score of 6 or less, which means that the majority of patients harboured low-grade disease.

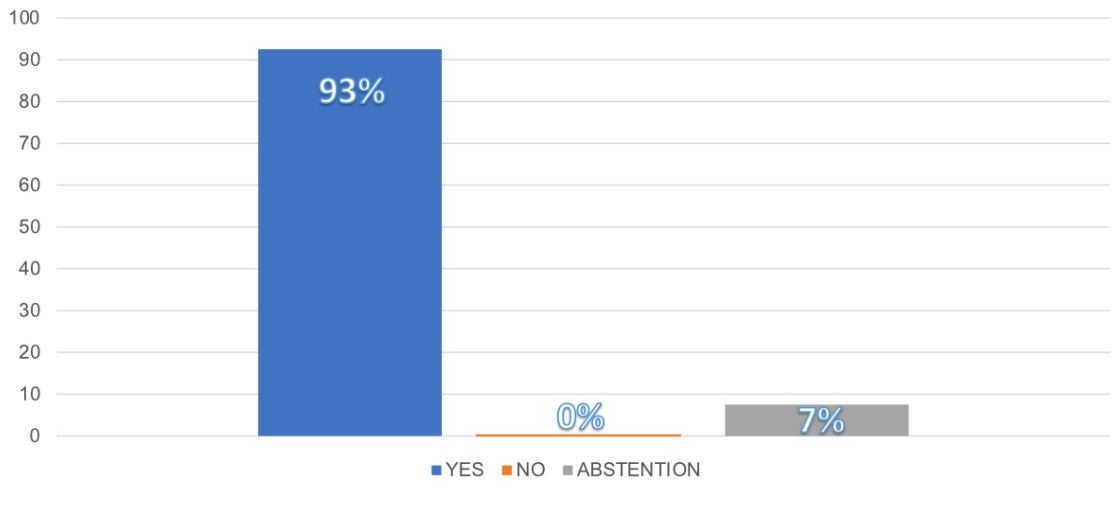
Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO)

In the same year (2009), the first results of the prostate arm of the PCLO trial were reported [12]. This trial enrolled 76,693 men in the United States between the ages of 55 and 74 from 1993 to 2001. Those in the screening group received annual PSA testing for six years and digital rectal examinations annually for four years. After follow-ups of seven years [12] and 13 years [13], the trial failed to demonstrate an effect of PSA screening on prostate cancer mortality. The relative incidence of prostate cancer in the screening group was 1.12 (95% CI 1.07 to 1.17), and the relative risk of prostate cancer-related death was 1.09 (95% CI 0.87 to 1.36] compared to the control group. In this trial, 67.7% of the biopsied men had no prostate cancer, and from those with malignant histology, 65.7% had a Gleason score of 6 or less [14].

The "United States Preventive Service Task Force (USPSTF)" statements and statements by medical societies

In subsequent years, the USPSTF weighed mortality benefits against the harms associated with PSA testing, detection, and treatment based on the reported data from the ERSPC and PLCO studies. In 2012, the USPSTF panel stated that there was convincing evidence that the number of prostate cancer deaths prevented by PSA testing was minimal and harms associated with the diagnosis and treatment of prostate cancer were common. The panel concluded that the benefits of PSA-based screening for prostate cancer do not outweigh the harms and recommended against testing for all men [1]. A health technology assessment by the Swiss Medical Board published in 2011 came to similar conclusions and recommended against routine PSA testing in Switzerland [15]. Readers may remember these announcements, which also affected how men and primary

Figure 1: Results of the Swiss Society of Urology voting on 20th September 2023 concerning the potential future of prostate cancer screening in Switzerland: "Considering the evidence and the significant amount of ongoing opportunistic screening, Switzerland should take a stepwise approach, including piloting and further supporting research to evaluate the feasibility of implementation of organised programs aimed at assuring appropriate management and quality of prostate cancer screening".



care physicians in Switzerland dealt with PSA testing. In 2012, the Swiss Society of Urology (SGU/SSU) articulated a statement from a Swiss perspective. Diverging from the USPSTF's stringent recommendation, the SGU/SSU still suggested that PSA testing could be extended to "well-informed men" from the age of 50 or 45 in the presence of risk factors and a life expectancy >10 years. However, it explicitly withheld support for PSA testing within a population-wide screening program [16]. The same recommendation is still endorsed by the current European Association of Urology Guidelines (EAU) and by the American Association of Urology Guidelines (AUA), which emphasise shared decision-making and patient education before PSA testing [17, 18].

It has taken several years to evaluate objectively the potential effects of the recommendations against PSA testing for prostate cancer screening. Following the initial USPSTF recommendation, recent study results from the United States indicated a significant reduction in the detection rate of localised prostate cancer and an increase in the incidence of advanced and metastatic prostate cancer (figure 2). Furthermore, the annual continuous mortality reduction since the introduction of widespread PSA testing in the early 1990s until 2012 was no longer observed but reached a plateau [3].

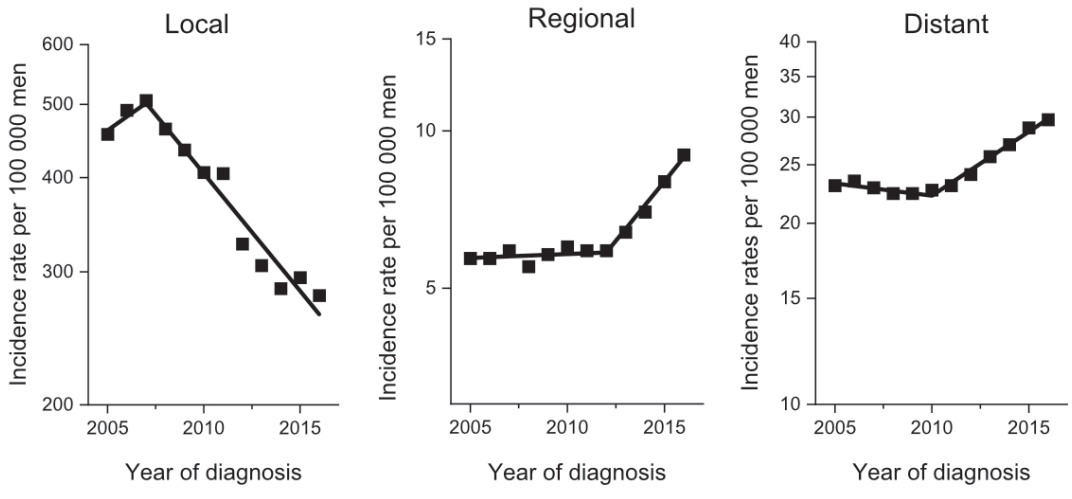
The contentious interpretation of the data is believed to result from either overlooking or misinterpreting the significant methodological flaws in the PLCO trial [19, 20] and the preliminary nature of the ERSPC data. In the PLCO trial, the contamination rate was too elevated to draw conclusions from PSA screening because nearly half of the men had undergone previous PSA testing before entering the trial, and 90% of the control group had received PSA testing [19]. Furthermore, less than half of the men with elevated PSA levels underwent prostate biopsies [20–22]. With longer follow-up of the ERSPC study, the absolute prostate cancer mortality risk difference increased and the numbers needed to invite and diagnose decreased [23, 24]. After 16 years, the number needed to invite decreased to 570 and the number needed to diagnose decreased to 18. The absolute risk reduction, although low, doubled from 0.07 to 0.18%. Twelve-year follow-up data from four centres showed a 50% reduction in metastatic disease at the time of diagnosis and a 30% reduction overall, including metastasis detected during follow-up [23, 25]. As a comparison, in the Nordic-European Initiative on Colorectal Cancer trial (NordICC), 455 were invited to avoid one case of colon cancer in a screening setting [26]. Furthermore, colorectal cancer mortality could not be significantly reduced by screening (relative risk: 0.90; 95% CI: 0.64 to 1.16), and 3,333 invitations would have been necessary to prevent one death from colon cancer (NNI). Furthermore, in breast cancer screening, the effectiveness depends heavily on the age group examined. Accordingly, the spread of the numbers given in the literature is vast (377 to 2000 invitations to prevent one breast cancer death). In the more “optimistic” scenarios, at best, it overlaps with those for ESPRC but certainly not in the less effective screening scenarios (table 1, [27]). In 2018, the USPSTF guidelines changed prior guidance against routine screening for prostate cancer, issuing new recommendations similar to the SGU/SSU endorsing individual decision-making for men aged 55 to 69 years based on a discussion of the potential benefits and harms [2, 6]. Since then, no further recommendations have been made, but we await future amendments [28].

Prostate cancer screening in Europe

In Switzerland, organised programs for screening breast and colorectal cancer are active. Additionally, efforts are underway to establish a similar program for detecting lung cancer [29]. However, regarding prostate cancer, no comparable initiative has been considered thus far.

Across other European countries, the topic of screening for prostate cancer has been the subject of intense discussion in recent years, driven in part by the efforts of

Figure 2: Incidence rates of prostate cancer between 2005 and 2015 in the United States, stratified by localised disease, regional lymph node metastasis, and distant metastasis, demonstrating the effects of the United States Preventive Service Task Force recommendations against PSA testing of men above 75 years of age in 2008 and in all men in 2012. From: Jemal A, Culp MB, Ma J, Islami F, Fedewa SA. Prostate Cancer Incidence 5 Years After US Preventive Services Task Force Recommendations Against Screening. J Natl Cancer Inst. 2021 Jan 4;113(1):64-71. doi: 10.1093/jnci/djaa068, by permission of Oxford University Press.



the European Association of Urology (EAU). In December 2022, the Council of the European Union updated its recommendations on cancer prevention, responding to a proposal from the European Commission. This update included a decision to expand targeted cancer screening to include prostate cancer based on emerging scientific evidence [8, 30]. The recommendation urges member states to explore the feasibility and effectiveness of organised screening programs for prostate cancer. Sweden has already taken a proactive stance in this regard. In 2018, the Confederation of Regional Cancer Centres in Sweden was tasked with assisting all regions in establishing organised prostate cancer testing programs [31]. This initiative was spurred by various factors, including prostate cancer being the leading cause of cancer death in Sweden, unlike the rest of Europe, where lung cancer holds that position, owing to Sweden's low smoking rate. As a result, such programs have been implemented or are in the process of initiation across almost all regions in Sweden [32].

Reducing harms of prostate cancer screening

The policy change on prostate cancer screening in Switzerland, the European Union and North America is only partially motivated by (1) the reported methodological flaws of the PLCO trial, (2) the maturing results of the ERSPC and (3) the increase in advanced and metastatic prostate cancer patients through reduced PSA testing. Even so, the policy change is strongly supported by emerging evidence indicating that innovative novel diagnostic strategies have the potential to decrease the risk of over diagnosis and overtreatment resulting from organised screening programs for prostate cancer. Simultaneously, these strategies aim to improve the detection of aggressive forms of the disease.

Studies have indicated that in the context of traditional diagnostic algorithms [33], unorganised, opportunistic PSA testing is routinely practised in Switzerland with a rate of up to 50% [34–36] and is associated with a negative cost-benefit ratio [37]. In the current standard practice of opportunistic PSA testing, men who receive an abnormal PSA result would most likely undergo a diagnostic process, including imaging and prostate biopsy, even though only a small proportion of them are likely to have aggressive prostate cancer [3, 38]. Moreover, relying on shared decision-making to guide opportunistic PSA testing has led to an uneven distribution of prostate cancer screening rates, with higher rates of PSA testing among those who are wealthier and more educated [34, 35]. Finally, many men diagnosed with cancer through biopsies opt for either surgery or radiotherapy, sometimes along with androgen deprivation therapy, even when they have low-risk tumours that are unlikely to result in cancer-related health problems or death [39].

Recognising the limitations of traditional prostate cancer diagnosis, intensive research efforts have been made in recent decades to develop new diagnostic methods and screening algorithms. These are specifically designed to optimise the identification of men with clinically relevant prostate cancer, defined as a Gleason Score ≥7 (or ISUP Grade Group ≥2), while minimising the detection of clinically irrelevant cancers. While the PSA value exhibits good sensitivity for detecting early-stage prostate cancer, it is characterised by low specificity. In the moderately elevated range (3–10 ng/ml), the cause is often non-specific inflammation or hyperplasia rather than carcinoma. While MRI of the prostate is minimally invasive and radiation-free, a prostate biopsy, even when performed transperineally according to current standards, is associated with potential risks [40]. Both MRI and biopsy expose healthy and asymptomatic men to physical and psychological stress. With improved diagnostics, rates of false-negative biopsies and the detection of clinically irrelevant cancers have been significantly reduced. For example, the use of multiparametric prostate MRI to detect prostate lesions in combination with targeted prostate biopsies has resulted in a significant reduction in the detection rate of clinically non-relevant tumours [41]. Moreover, the detection rate of clinically significant diseases, which were previously often missed by systematic biopsies (e.g. in the ERSPC study), has been increased through image-guided fusion biopsies. Indeed, two new prospective randomised studies from Sweden have demonstrated the benefits of MRI in a screening setting and suggest that men with a normal MRI may no longer need to undergo a biopsy [42, 43]. Even though both studies exclusively used a biparametric MRI without contrast agents (as opposed to multiparametric MRI), the necessary resources and associated costs on a population level for such a program, where imaging would only be performed based on PSA values, cannot be underestimated. Therefore, future screening programs should evaluate additional triage tests that relieve valuable and time-consuming MRI resources while still being effective and cost-efficient in screening [44].

Biomarkers as a triage test

PSA is a well-established triage test for screening. Below a value of 1.5 µg/l, the risk of clinically relevant prostate cancer is extremely low. Fortunately, 65% of men (across all age groups) exhibit a value lower than this threshold [45].

Table 1:
The number needed to invite (NNI), number needed to diagnose (NND), and number needed to treat (NNT) to avoid one prostate cancer-specific death.

	NNI	NND/NNT
Prostate cancer [24]	570	18
Colon cancer [26]	3333 (PPA: 667)	–
Breast cancer [27]	337–2000	–
Beta blocker after myocardial infarction [66]	–	42
Antiplatelet medication after myocardial infarction [66]	–	153
Statins after myocardial infarction [66]	–	94
ICD implantation [67]	–	6–22

ICD: implantable cardioverter-defibrillator; PPA: per-protocol analysis

However, over one-third of men above 40 exhibit a PSA level above this threshold. A higher cut-off in the range of 3.0 to 4.0 µg/l has been used in most screening trials to reduce the number of false positive tests [46], but a relevant number of prostate cancers in the range of 1.5 to 3.0 µg/l have been missed with this approach [47]. A suggested concept to increase the screening program's efficiency to reduce costs has been the development of biomarkers as reflex tests in men with elevated PSA as a triage before imaging. Several tests have become commercially available in recent years, such as the Prostate Health Index (PHI), isoPSA, Proclarix, PCA3, ExoDx, MyProstateScore (MPS), Select MDx, 4Kscore and Stockholm3. All tests except the latter two have been developed and validated exclusively in high-risk populations planned for prostate biopsy, which questions the calibration in a screening setting. Furthermore, urine tests require a prior digital rectal examination, making them less suitable for organised screening. While consistent data on the performance of the Stockholm3 test in population-based screening programs in Sweden have been reported, the 4Kscore is currently being investigated in Finland in a comparable setting. To our knowledge, only Proclarix, SelectMDX and Stockholm3 are commercially available in Switzerland.

The Stockholm-3 test

The Stockholm-3 blood test combines five protein biomarkers (total PSA, free PSA, human kallikrein 2, beta-microseminoprotein and macrophage-inhibitor cytokine) and 232 genetic single nucleotide polymorphisms (SNPs). SNPs are variations in DNA sequences that occur at specific positions within a genome and are the most common type of genetic variation in humans, which are associated with certain diseases. The Stockholm-3 test can provide an estimate of the risk of having clinically relevant prostate cancer with clinical parameters that can be assessed without the involvement of a specialist (age, family history of prostate cancer, previous negative prostate biopsy, use of a 5-alpha-reductase inhibitor) and may thus be used within a population-based prostate cancer screening program. The test was compared to PSA in two extensive population-based studies in Sweden [47, 48]. Remarkably, clinically significant cancers were found in the PSA range of 1.5 to 3.0 µg/l. Depending on the selected Stockholm-3 threshold ("11%" or "15%" risk of prostate cancer), the use of the Stockholm3 test in men with a PSA level of >1.5 µg/l may increase the detection of significant carcinomas by 20% or reduce the number of needed MRIs by almost half, all without any urological assessment or investigation before imaging. The validity of the test for Swiss men has been recently shown in a prospective multicentre trial [49].

The 4Kscore

The 4Kscore test measures free, intact, and total PSA levels and human kallikrein 2 in the blood and is combined with age, digital rectal examination findings, and prior biopsy history [50]. This application of the 4Kscore test results in a notable reduction in unnecessary biopsies, ranging from 30 to 50%, while maintaining >90% detection of Gleason scores ≥7 and >97% of Gleason scores ≥4+3 = 7 cancers [51, 52]. Although performed prospectively with a robust methodology, all three trials were performed in men with elevated PSA, and its performance in a screening setting is eagerly awaited. The ongoing Finnish ProScreen trial will evaluate a screening algorithm, including PSA, the 4Kscore test, and MRI, with targeted biopsies for a population-based screening program [53]. Although prostate cancer-specific mortality after 15 years will be the primary endpoint, data on the performance and cost-effectiveness of the 4Kscore will soon be available.

Developing a roadmap for prostate cancer screening in Switzerland

Given the described developments, the USPSTF recommendation against general PSA testing has been withdrawn [11]. In response to the ongoing developments in the European Union, the Swiss Prostate Cancer Screening Group took proactive measures. On the 20th of September 2023, they facilitated an official vote to determine the overall stance of the members of the SGU/SSU regarding screening for prostate cancer in Switzerland. Closely following the official statement from the European Union, the following wording was voted on and agreed upon (Figure 1; 80 yes, 6 abstentions, 0 no):

"Considering the evidence and the significant amount of ongoing opportunistic screening, Switzerland should take a stepwise approach, including piloting and further supporting research to evaluate the feasibility of implementation of organised programs aimed at assuring appropriate management and quality of prostate cancer screening."

Starting from this full endorsement, the Swiss Prostate Cancer Screening Group aims to prepare and execute pilot studies to develop a roadmap for the potential introduction of prostate cancer screening in Switzerland. After extensive literature research and including expert opinions, the group has identified several areas to be considered in future research.

Identification of ideal age groups for prostate cancer screening

Recent study results from a randomised Swedish screening cohort of the ERSPC Trials ("Göteborg-1") indicated that systematic early PSA testing provides a significant survival advantage [54]. If the first PSA screening is conducted at age 55, the risk of death from prostate cancer is halved compared to men who receive their first PSA test at age 60. Others have proposed to begin screening at an earlier age, as the PSA value in younger men is less influenced by confounding factors, such as benign prostatic hyperplasia [55]. These considerations should be weighed against the potential to detect insignificant prostate cancer at young ages.

Standardisation and optimisation of active surveillance

One of the fundaments of reducing the risk for overtreatment includes the concept of active surveillance for prostate cancer. Long-term studies have recently demonstrated that active surveillance is a safe approach for low-risk prostate cancer [56, 57] and should, therefore, be investigated and implemented further to establish standardised inclusion criteria and follow-up routines in Switzerland. In this context, it should be evaluated if the

inclusion criteria for active surveillance might include patients with favourable ISUP Grade 2 and otherwise low-risk features [58].

Cost-effectiveness analyses

First, the willingness of the Swiss male population to undergo different screening scenarios should be evaluated to receive a rough estimate of the potential costs associated with it. Furthermore, the cost-effectiveness and cost impact of an organised prostate cancer-screening program depends on several factors, including the strategies used for screening. In this context, the performance and the cost-effectiveness of MRI- and potential biomarker-based screening algorithms (based on local availability) need to be determined in the context of Switzerland. Hence, different promising screening algorithms should be evaluated and compared to the cost-effectiveness of the current situation with ongoing opportunistic PSA testing in approximately 50% of all Swiss men [34, 35] versus a situation without screening. This should consider the potential increased uptake of opportunistic PSA testing, MRI testing and/or biomarker testing in the Swiss male population in the following years, based on the increased visibility and discussion of prostate cancer screening in the Swiss and European health politics.

MRI studies

After triage, some men will proceed to receive an MRI of the prostate. The "Göteborg-2" trial suggested that prostate cancer diagnostics should include PSA testing and, to prevent over diagnosis, a biopsy may only be performed in the case of abnormal prostate MRI [42]. This novel approach should also be evaluated in a Swiss population and compared to screening algorithms that include “non-targeted” randomised biopsies [41]. The MRI capacity and associated healthcare resources in Switzerland should also be evaluated, and the role of biparametric MRI should be investigated further because the latter could be performed quicker, potentially saving healthcare resources and allowing a higher capacity with better cost-efficiency [59]. The role of bpMRI as a primary screening tool is being evaluated further, and we await the results (VISIONING, NCT03749993). Finally, our ability to implement artificial intelligence (AI) to interpret and deliver high-quality imaging beyond expert centres should be investigated [60], such as within the current ongoing research of AI in the Prostate Imaging-Cancer AI (PI-CAI) challenge (https://pi-cai.grand-challenge.org/). Finally, the quality of MRI protocols and readings is known to differ between institutions, and therefore, protocol differences and inter-reader variability should be assessed. Moreover, programs to increase standardisation and comparability throughout Switzerland should be enforced [61, 62].

Risk calculators and risk factors

Prostate cancer risk calculators can be sophisticated tools for prostate cancer risk evaluation [63] and have been suggested as a measure for risk stratification for prostate cancer screening. Such risk calculators have been derived from specific populations, such as large prospective trials like the ERSPC [64]. However, they may provide different discriminative properties when evaluating Swiss men, and their generalizability and calibration need to be carefully evaluated [65]. Data availability must be considered when discussing the use of risk calculators for population-based prostate cancer screening. While some risk calculators rely on anamnestic, clinical information (e.g., age, family cancer history, personal cancer history, and use of 5-alpha reductase inhibitors), others require additional data, such as results from digital rectal examinations, prostate volume, PSA dynamics, or MRI. In a population-based screening program, such additional information from testing or imaging may not be available. Therefore, risk calculators, including readily available anamnestic information, may be considered for population-based prostate cancer screening, while a more specific risk prediction could be provided for men for which additional data is available (e.g., after MRI examination in case of an elevated PSA). Several European-organised testing programs in the framework of PRAISE-U (https://uroweb.org/praise-u) will evaluate the feasibility of a risk-adapted approach using risk calculators in the future.

Conclusion

Recent studies have shown that a contemporary risk-based approach to prostate cancer screening, which combines PSA testing with MRI and/or modern biomarkers as well as targeted biopsies, reduces the over diagnosis of non-life-threatening prostate cancer and improves the identification of men with clinically relevant prostate cancer. Further research is needed to determine how these promising novel diagnostic tools and risk stratifications can be best utilised to optimise individual and population outcomes. Considering the significant scope of ongoing opportunistic PSA testing in Switzerland, the introduction of a Swiss population-based organised prostate cancer screening program should be evaluated following a stepwise approach, including pilot projects and targeted studies to assess the acceptance, feasibility, effectiveness and cost-effectiveness of its implementation. These programs should be supported by health policymakers and coordinated by the Federal Office of Public Health by leveraging the individual benefits of PSA, biomarkers and MRI in prostate cancer screening in Switzerland.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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