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Expanding Risk-adapted Early Detection of Prostate Cancer: A Call to Action for Men at High Risk

Maike K. Klett [a,b,c,*], *Peter Albers* [b,d,e], *Adam Kibel* [c,f], *Jale Lakes* [b,d], *Huma Q. Rana* [c], *Michael Serzan* [c], *André Karger* [a,b], *Alicia K. Morgans* [c]

[a] *Clinical Institute of Psychosomatic Medicine and Psychotherapy, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany;* [b] *Center for Integrated Oncology Aachen/Bonn/Cologne/Düsseldorf, Düsseldorf, Germany;* [c] *Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [d] *Department of Urology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany;* [e] *Division of Personalized Early Detection of Prostate Cancer, German Cancer Research Center, Heidelberg, Germany;* [f] *Department of Urology, Mass General Brigham, Harvard Medical School, Boston MA, USA*

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1. Introduction

Early detection of clinically significant prostate cancer (PCa) poses a major challenge worldwide. Widespread opportunistic screening has led to overdiagnosis and overtreatment, especially among men aged >70 yr, which results in unnecessary costs and patient burden with only a limited cancer-specific survival benefit in the general population [1–4]. Current PCa screening strategies remain insufficient for individuals at elevated PCa risk, particularly those with heritable risk.

Identification of those at high risk via an individualized risk assessment strategy is essential for early detection of clinically significant PCa, especially as ~57% of PCa risk is attributable to inherited genetic factors [5]. Both a family history of PCa and pathogenic germline variants (PGVs) have been associated with higher PCa incidence and mortality, earlier disease onset, and more aggressive tumor phenotypes [6–8]. Recent advances in genetic research, particularly the identification of single-nucleotide polymorphisms (SNPs), have led to the development of polygenic risk scores (PRS) to refine risk prediction [9,10]. Ancestry is another important but often under-represented modifier of PCa risk [11,12].

While risk-adapted strategies for early detection have been successfully implemented in other cancer types, most notably in breast and ovarian cancer, genetic testing and tailored screening for PCa have yet to be implemented despite guideline recommendations [13].

A shift towards structured, risk-adapted early detection of PCa is essential to: (1) minimize overdiagnosis and

* Corresponding author at: Clinical Institute of Psychosomatic Medicine and Psychotherapy, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany.
E-mail address: maike.klett@med.uni-duesseldorf.de (M.K. Klett).

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overtreatment in individuals with low PCa risk; and (2) improve early detection and survival among individuals with high PCa risk.

Broader access to genetic testing has implications beyond early detection. Genetic characteristics play a critical role in guiding treatment decisions, such as eligibility for targeted therapies (eg, PARP inhibitors in metastatic disease) and suitability for active surveillance [14–16]. With this call-to-action paper, our aim is to underscore the urgent need for structured, risk-adapted screening pathways for individuals at elevated risk of PCa, highlight current practice gaps, and set out clear recommendations for implementation.

2. Defining high-risk populations

PCa risk is multifactorial, with age, family history, hereditary syndromes, and ancestry well established as primary risk factors [17]. Among these, family history has been associated with higher risk of high-grade PCa and earlier onset of PCa [6,18]. The highest risk has been observed in men with first-degree relatives affected by PCa, and this risk is inversely associated with the age of onset in the family member [19,20]. Of note, family history of breast, ovarian, or colorectal cancer is also associated with higher PCa risk because of overlapping PGVs in DNA repair and mismatch repair pathways [18].

Familial PCa risk is driven in part by inherited PGVs, particularly in DNA repair genes such as the homologous recombination genes *BRCA1*, *BRCA2*, *HOXB13*, *ATM*, *CHEK2*, *PALB2*, *TP53*, *RAD51*, and *NBN*, and the mismatch repair genes associated with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) [21,22]. PGVs in *BRCA2* and *HOXB13* have been associated with the highest increase in PCa risk, with *BRCA2* PGVs also related to more aggressive PCa [23–26]. PGV prevalence is related to PCa aggressiveness, with prevalence ranging from 4.6% in localized disease to 11.8% in metastatic and 16.2% in metastatic castration-resistant PCa [27–29]. Nicolosi et al [30] reported a PGV rate of 17.2% among individuals with a history of PCa irrespective of disease stage (rates per gene: *BRCA2* 4.74%, *CHEK2* 2.88%, *ATM* 2.03%, and *BRCA1* 1.25%). Importantly, 37% of PGVs occurred in individuals without a family history of PCa, which indicates the limitations of testing solely on the basis of family history [30].

Beyond high-penetrance PGVs, it has been shown that SNPs account for a substantial proportion of inherited PCa risk. Genome-wide association studies have revealed more than 451 SNPs associated with PCa [10,31], and their cumulative effect can be quantified using PRS. PRS use has been shown to improve the detection of clinically significant PCa in prospective studies, complementing magnetic resonance imaging (MRI) and prostate-specific antigen (PSA) testing [9]. However, current genetic testing is unlikely to capture all relevant genetic risk variants, with earlier PRS models based on 269 SNPs that capture only ~30–40% of familial relative risk [31]. Therefore, family history remains a separate risk factor in addition to genetic risk. A combination of familial risk, high PRS, and lifestyle factors is associated with threefold higher risk of death from PCa before the age of 75 yr [32].

Ancestry further modifies risk. Black men in the USA face markedly elevated PCa incidence and mortality rates [33]. Genetic risk in men of African ancestry is on average 2.18-fold higher (95% CI 2.14–2.22) than in men of European ancestry, whereas men of East Asian ancestry have a 0.73-fold lower risk (95% CI 0.71–0.76) [31]. Germline variant prevalence also varies by ancestry, and is highest in Ashkenazi Jewish (22.7%) and White (17.8%) men, and lowest in African American (10.1%) and Hispanic (6.4%) men [30]. However, PCa incidence and mortality exhibit pronounced global disparities that are probably driven not only by biological but also by social determinants of health, such as health care availability and other social factors [34–36]. Non-White populations remain under-represented in research and germline testing guidelines, which results in a lower diagnostic yield and higher rates of variants of uncertain significance [37,38]. This highlights the urgent need for inclusive genomic data and ancestry-informed strategies for early detection [11,12].

3. Current care gaps

Despite growing evidence on the genetic and familial risk of PCa, clinical integration of risk-adapted early detection, and thus intensified screening for high-risk individuals, remains limited. In contrast to breast and ovarian cancer, for which risk assessment and screening programs are well established, significant gaps persist in PCa screening. Several studies have highlighted substantial gender disparities in the uptake of genetic testing between women with breast or ovarian cancer and men with PCa, as well as among their unaffected relatives, which results in missed opportunities for cascade testing and potential treatment adaptations [39–42]. Reasons discussed for the underutilization of genetic testing in men include limited awareness among patients and clinicians, and gender-related social roles, consistent with men's lower engagement in general preventive care [43–46]. Genetic test results are communicated to male relatives less often within families, probably because of underestimation of the relevance of female family history and germline variants for men [47–49]. In addition, men report difficulty in finding tailored information, which underscores the need for resources focused on male PCa risk [50,51].

Early detection of PCa remains largely opportunistic in many countries and is not yet targeted at the individuals who are at the highest risk [13]. This leads to skewed uptake of PSA testing, with higher use among wealthier, more educated men and lower uptake among minority groups [52,53]. Overdiagnosis and overtreatment, especially in men aged >70 yr, remain key harms, while the reduction in cancer-specific mortality is small [1,2,4]. By contrast, although guidelines recommend earlier screening in men at high risk of PCa, implementation is mostly confined to research studies [54,55]. Structured clinical screening pathways and guidance written for use by patients themselves still need to be developed. Furthermore, there is no consensus on the precise group of PGVs that are universally deemed to be associated with high risk and included in intensified screening programs. Finally, insurance coverage for genetic testing varies greatly by region, which limits access even for those with explicit family histories.

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One additional area in need of consideration is an evaluation of the potential psychosocial burden of genetic testing, particularly among men at high PCa risk, who remain under-represented in such studies. Prospective data from the IMPACT study showed low and largely stable psychosocial distress levels among *BRCA1/2* PGV carriers over time [56]. However, a subgroup of PGV carriers reported heightened distress. These individuals may benefit from tailored psychological screening and support structures, which are currently not implemented in regular care [57,58]. Therefore, genetic counseling approaches must address the individual situation of each patient and take into account the potential psychosocial burden of genetic testing. This also concerns psycho-oncological health care professionals, who are often the first contact point for patients experiencing psychosocial distress, but who may lack specific training in clinical issues related to genetic testing.

Addressing these care gaps in early detection of PCa will require multidisciplinary and political action. Governments are beginning to pilot risk-adapted strategies for early detection. For example, Sweden has launched a pilot screening program, and Germany has issued funding calls for the development and evaluation of risk-based screening algorithms [59]. The following section outlines evidence-based recommendations and current research efforts to expand early detection of PCa, with a particular focus on men at elevated risk.

4. Expanding early detection of prostate cancer for men at elevated risk: recommendations

4.1. *Risk assessment, communication, and awareness*

Low referral rates, information gaps, and lack of centralized access points limit genetic testing and risk-adapted screening for high-risk men. The establishment of defined screening pathways for use in primary care, proactive patient outreach programs, and patient navigation strategies is essential for successful implementation of high-risk PCa screening [60].

The first step is to define standardized criteria for genetic testing eligibility based on family history and hereditary risk, that include men with PCa. Current guidelines partly overlap, but also differ in definitions [22,54,55]. Standardization of these guidelines would improve the comparability of studies linking family history to PGVs. Routine risk assessment that includes ancestry and family history of PGVs and breast, ovarian, and colorectal cancers should be implemented in primary care to ensure application of these guidelines to all eligible patients. To facilitate standardized referral to genetic counseling from primary care, validated, easy-to-use tools are needed to assess familial cancer history and ancestry and to identify known genetic variants in a family (analogous to breast cancer tools [61] such as Helix Tool [62]). For men with PCa who meet genetic testing criteria (family history, metastatic disease), the treating urologist or oncologist should initiate referral at diagnosis and before treatment, as the results may affect the choice of therapy and trigger cascade testing [22,55]. Genetic counseling should involve shared decision-making and address ethical, legal, and social aspects.

For expansion of cascade testing, targeted provider and patient education should correct misconceptions and highlight the importance of PGVs, especially in *BRCA1/2,* for male relatives. Family letter templates should be offered to PGV carriers to support communication of test results and to provide information on access to genetic testing [63]. For patients, centralized information materials should be developed in lay language.

Any expansion of germline genetic testing must consider the potential financial burden and the limited availability of trained genetic professionals. Nevertheless, as testing costs continue to decline and resource-sparing models emerge, the value of germline testing is becoming increasingly evident when weighed against the potentially substantial costs associated with treating advanced PCa [30,64,65].

Table 1 – Example of risk-adapted screening as used in Germany for men at familial and hereditary risk of prostate cancer[a]

Population and risk group	Recommended screening
High-risk individuals aged ≥45 yr with no PGVs[b]	
Low risk[c]	PSA annually mpMRI if PSA rises at a rate >0.7 ng/ml/yr
Intermediate risk[c]	PSA annually mpMRI after 1 yr and then every 5 yr , or earlier if PSA rises at >0.7 ng/ml/yr
High risk[c]	MRI/ultrasound fusion biopsy. If the result is negative: – PSA annually – mpMRI after 1 yr and then every 5 yr , or earlier if PSA rises at >0.7 ng/ml/yr
Individuals aged ≥40 yr with PGVs	
Low risk[c]	PSA annually mpMRI after 1 yr and then every 5 yr , or earlier if PSA rises at >0.7 ng/ml/yr
Intermediate or high risk[c]	MRI/ultrasound fusion biopsy. If the result is negative: – PSA annually – mpMRI after 1 yr and then every 5 yr, or earlier if PSA rises at >0.7 ng/ml/yr

PGV = pathogenic germline variant (in *ATM, BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PMS2, TP53*); PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; ERSPC-RC 4 = European Randomized Study of Screening for Prostate Cancer risk calculator 4.

[a] Suggested algorithm for men at higher risk of prostate cancer on the basis of family history and/or PGV status. Risk stratification is based on baseline PSA and mpMRI results; the detailed algorithm has been described by Lakes et al [72] the starting age is based. on the model described by Van Poppel et al [74].

[b] High PCa risk = family history or hereditary risk, Black/African ancestry.

[c] Low risk: PSA <3 ng/ml and PI-RADS 1–2. Intermediate risk: PI-RADS 3 with ERSPC Risk Calculator 4 score of <12% irrespective of PSA; or PSA ≥3 ng/ml and PI-RADS 1–2. High risk: PI-RADS 3 with ERSPC Risk Calculator 4 score of >12%; or PI-RADS 4–5, both irrespective of PSA. Restratification of risk only after performing MRI. If PI-RADS 4–5 is detected on MRI, MRI/ultrasound fusion biopsy or MRI in-bore biopsy is performed.

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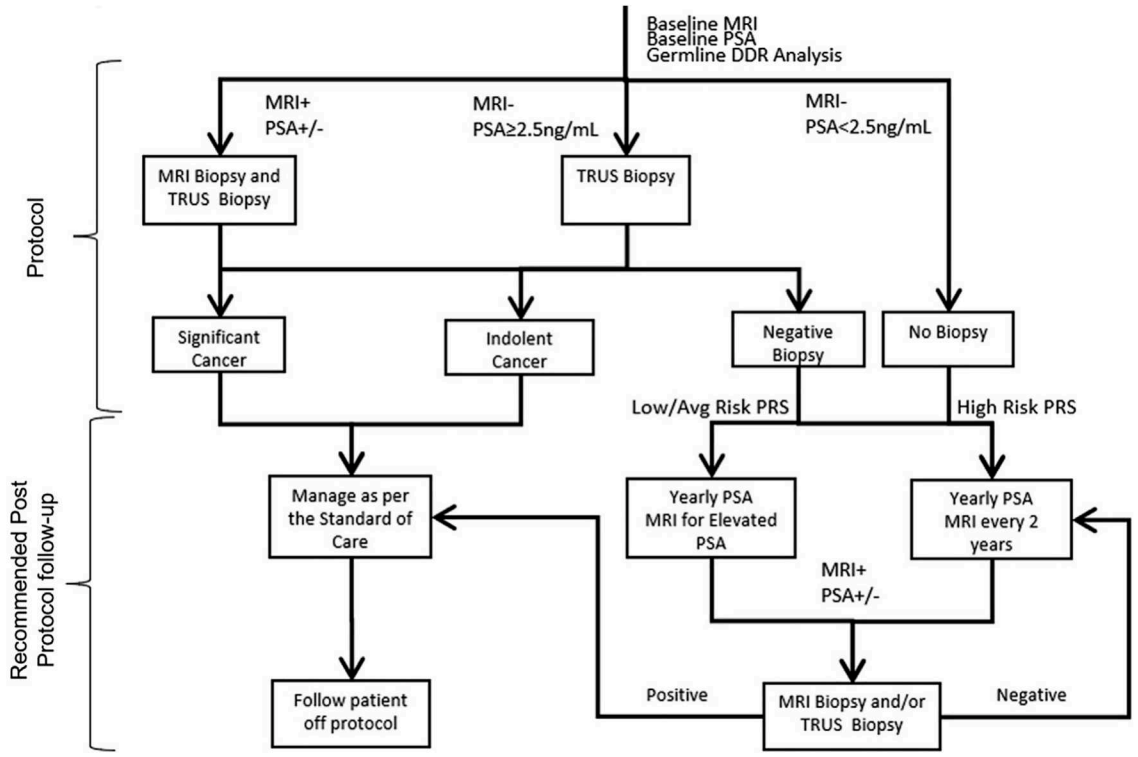

Fig. 1 – Example of a possible genetic risk-adapted screening protocol. PSA = prostate-specific antigen; MRI = magnetic resonance imaging; DDR = DNA damage response; TRUS = transrectal ultrasound; Avg = average; PRS = polygenic risk score.

4.2. *Structured risk-adapted screening pathways*

Implementation of risk-adapted screening pathways for high-risk men is crucial to balance sensitivity and overdiagnosis. Importantly, a negative germline test does not negate the need for intensified screening for men with a positive family history. Exact definitions of risk groups and which PGVs to include need to be established. Prospective trials have demonstrated the clinical utility of risk stratification based on baseline PSA with adjunct MRI in the general population [66–68]. However, in the context of emerging imaging modalities and biomarker-based approaches, the optimal risk-stratified screening strategy remains under investigation. Growing evidence on PRS and risk calculators may further refine risk stratification [69]. Even with the need for further validation of screening algorithms, men with high PCa risk need to be provided with recommendations regarding intensified screening [55,70,71].

Table 1 outlines a proposed screening pathway adapted from the first dedicated clinic for early detection of PCa in Germany, with trial validation pending (NCT05681416), that relies on baseline PSA testing and mpMRI for risk stratification in men with a family history of cancer or a PGV [72]. Figure 1 provides one example of a PCa screening pathway that includes a PRS currently under investigation in a clinical trial in the USA (NCT06398639). On the basis of recent evidence demonstrating the poor performance of digital rectal examination as a standalone screening tool for PCa, as well as the lack of added benefit when combined with PSA screening, both recommendations rely on MRI and PSA to identify clinically relevant PCa that requires biopsy [73].

Importantly, adequate counseling and shared decision-making regarding the pros and cons of PSA testing and PCa screening are essential to ensure guideline compliance. To reduce disparities in PCa screening, policies to set up intensified, risk-adapted screening for high-risk men without additional out-of-pocket costs will be necessary. To facilitate optimized implementation of risk stratification, risk-adapted screening, and counseling as an integrated workflow, reliance on specialized, interdisciplinary centers (analogous to centers for breast/ovarian cancer) is recommended. However, the financial sustainability of such comprehensive prevention centers is a central concern, and this strategy might not be feasible in many parts of the world. Investigation of the cost effectiveness of risk-adapted screening and prevention centers therefore remains crucial in order to inform broader adoption in public health care systems.

Importantly, the expansion of screening strategies for high-risk men should align with structured, risk-adapted screening in the general population to reduce overdiagnosis and overtreatment and to ensure that high-risk individuals are proactively reached. Beyond routine assessment of family history, eligible men should receive invitations to PSA testing, and testing should be performed only when indicated [13]. Ongoing trials are still investigating the appropriate age range and screening intervals, and the European Association of Urology has proposed a screening algorithm for the general population of men aged 50–70 yr [74,75].

5. Conclusions

We argue that even amidst research still investigating best-practice pathways for risk-adapted early detection of PCa, implementation of intensified screening for high-risk men is needed. We propose that genetic testing of index patients and appropriate cascade testing should become more broadly available. This testing should use established criteria with validated tools and proceed with standardized referrals to genetic counseling as necessary. Provider and patient education, together with dissemination of information about men's risk of cancer and the importance of communicating genetic test results to male relatives, are crucial. Importantly, men for whom high risk is identified should be offered risk-adapted PCa screening, possibly via specialized interdisciplinary PCa centers if available. A coordinated agenda covering research, financing, and implementation is essential to fill the evidence gaps for early detection of high-risk PCa. These efforts will require interdisciplinary collaboration among stakeholders, including clinicians, researchers, health insurance companies, regulatory authorities, patient advocates, and industry, to align evidence generation, secure sustainable funding, and facilitate successful long-term implementation of early detection programs.

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