Personalised Prostate Cancer Prevention

A new genetics-integrating service model for prostate cancer screening and early detection

General Explanation About Cancer Prevention

Cancer prevention comprises several components:

- Primary prevention aims to prevent cancer from developing in the first place by reducing risk factors.
- Secondary prevention focuses on detecting cancer at an early stage — often through screening — to allow for more effective treatment and improved outcomes.
- Personalised cancer prevention takes individual risk factors into account to implement both primary and secondary prevention more accurately and effectively.

The approach outlined below for preventing deaths from prostate cancer through early detection of clinically significant prostate cancer is intended for asymptomatic men aged 40 and above.

The Current Approach to Prostate Cancer Screening and Individual Early Detection

In Europe, prostate cancer is the most frequently diagnosed cancer in men and the third cancer-related cause of death in men (1).
Prostate cancer treatment outcomes depend on the extent of tumour spread at diagnosis; therefore, timely early detection and treatment of clinically significant cancers can prevent prostate cancer-related deaths.

Men may enter the diagnostic pathway for prostate cancer control through different indications, including clinical symptoms, individual early detection or screening (population-based). Men with clinical symptoms should seek primary consultation by GPs, urologists or andrologists.

The traditional expert consensus on implementing prostate cancer screening and early detection in Europe is summarised in the **European Association of Urology (EAU) guidelines** for prostate cancer management (2) and published also as "**EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer—2024 Update"** (3).

According to EAU guidelines, early detection may be initiated on an individual level. Men with risk factors include age > 50 years; men from 45 years of age with a family history of prostate cancer; men of African descent from 45 years of age; men carrying BRCA2 mutations from 40 years of age.
EAU recommends an individualised risk-adapted strategy for early detection to a well-informed man with a life-expectancy of at least fifteen years. Accordingly, informed men with one of the risk factors above (including age), a life expectancy of > 15 years and requesting investigation should be given **a PSA test** and undergo a digital rectal examination (DRE), after which a further diagnostic algorithm may be initiated.
EAU recommends: offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk:

- men with a PSA level of > 1 ng/mL at 40 years of age;
- men with a PSA level of > 2 ng/mL at 60 years of age;

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Postpone follow-up up to eight years in those not at risk.
The current EAU guidelines do not yet take into account important scientific evidence regarding the impact of polygenic risk on prostate cancer screening (4).

The EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer (2024 update) similarly recommend that, for asymptomatic men with a life expectancy of at least 10 years, early detection should include shared decision-making, PSA testing, DRE, family history, and ethnicity information for the initial risk assessment and further diagnostic pathway (3). This is an appropriate approach in the context of urologists and andrologists, but in reality, the prostate cancer risk of many men is also assessed using PSA tests outside specialist care, and more detailed management often depends on the PSA level. Such an approach also does not sufficiently take into account the genetic risks of prostate cancer.

Prostate cancer is the most heritable common cancer – inherited genetic factors explain around 58% of the risk (5). This underscores the importance of considering family history and genetic factors in prostate cancer risk assessment and prevention strategies. The problem is that important genetic risk factors are usually unknown for men, which is why genetics-based personalised prevention should begin in men in their forties.

There are basically three inherited risk factors that are consistently associated with prostate cancer: family cancer history, rare germline pathogenic mutations in single genes (monogenic pathogenic variants – MPVs), and common genetic single nucleotide polymorphisms (SNPs) in many genes – analysable with polygenic risk score (PRS) test.

MPVs in the *BRCA2* and *HOXB13* genes, but also in the genes *CHEK2*, *BRCA1, ATM, NBS1* have been suggested to increase the risk of prostate cancer. But they are very rare - in up to 1.6% of all men. Therefore, MPV testing in healthy men is recommended based on specific indications.

Increased polygenic risk, analysable with a PRS test, is much more common – in up to 20% of men and is not directly connected with familial prostate cancer history (6). Which is why PRS testing is recommended for all men.

At present, there are no evidence-based dietary or pharmacological interventions proven to effectively reduce the risk of prostate cancer. Moreover, standardised population-wide screening programmes are lacking, as uniform screening and treatment strategies for all men have not demonstrated sufficient clinical effectiveness. However, the burden of prostate cancer can be mitigated through early detection and, where appropriate, targeted intervention—particularly when guided by individual risk factors.

The New Approach to Prostate Cancer Early Detection and Screening

The current approach and service addresses individual early detection of prostate cancer in asymptomatic men from age 40 with aim to prevent possible deaths from prostate cancer.
This service can be integrated into a variety of clinical pathways, including:

- Consultations with urologists and andrologists (addressing genetic risk in combination prostate specific antigen (PSA) testing and with other prostate cancer risk factors);
- Consultations with medical geneticists and genetic counsellors (regarding prostate cancer hereditary risk and early detection);
- Evaluation by GPs and family physicians;
- Delivery via telemedicine services.

Prostate cancer screening and early detection have been typically conducted using the PSA (prostate-specific antigen) test and digital rectal examination. However, new scientific evidence clearly shows that this approach can miss a significant number of clinically important prostate cancers and is no longer considered the most effective strategy.

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In men with a high polygenic risk, PSA testing alone is often insufficient, as PSA levels may remain within the normal range even in the presence of clinically significant cancer. For this reason, recent evidence supports offering prostate multiparametric magnet resonance imaging (mpMRI) as a prostate control investigation specifically for men identified as genetically high-risk.

A new approach, personalised prostate cancer prevention, adds to prostate cancer early detection in addition to PSA testing **a man's polygenic risk testing** — a risk estimate based on the combined effect of many common genetic variants, , and includes also **a questionnaire about familial cancer histrory to determine the need for MPV testing**.
This genetic risk assessment helps identify men who are at significantly higher risk of developing prostate cancer, particularly aggressive forms.

Prostate cancer polygenic risk score (PRS) testing has not been widely implemented due to the lack of tests meeting relevant regulatory requirements. However, such a test is now available for use in the European Union and United Kingdom: the prostate cancer PRS test, AntePC. **https://antegenes.com/antepc-for-healthcare/**

In addition, **assessment of the need for testing for monogenic pathogenic variants (MPVs)** should be carried out based on an individual's family history of cancer.
The EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines recommend MPV testing for men without prostate cancer based on following criteria (3):

- Men with multiple family members diagnosed with clinically significant prostate cancer at age <60 yr or a family member who died from prostate cancer.
- Men with a family history of high-risk germline pathogenic variant or a family history of multiple cancers on the same side of the family.

We propose more specific criteria and an accompanying questionnaire to guide this process accordingly.
Indications for testing monogenic pathogenic variants (MPVs) associated with increased prostate cancer risk, the questionnaire for a patient:

- Are you aware of a pathogenic variant in a breast and ovarian or prostate cancer susceptibility gene (particularly *BRCA1* or *BRCA2*) in a first- or second-degree biological relative?
- Have two or more biological relatives been diagnosed with prostate cancer? If you answered YES to the previous question, please specify who and at what age was diagnosed (degree of relationship and age at prostate cancer diagnosis): ...
- Has your first- or second-degree biological relative died from prostate cancer?
- Has a first- or second-degree biological relative been diagnosed with breast cancer before the age of 50?
- Has a male first- or second-degree biological relative been diagnosed with breast cancer?
- Has a female first-degree biological relative been diagnosed with ovarian cancer, or experienced multiple primary breast cancers?
- Have three or more of your first- and second-degree biological relatives on the same side of the family been diagnosed with cancers associated with Lynch syndrome? These include colorectal, endometrial, gastric, ovarian, small bowel, pancreatic, urinary tract, bile duct cancers, or glioblastoma? If three or more such cancers have occurred on the same side of the family, please specify which relatives (e.g. mother, uncle, grandmother) and the type of cancer they were diagnosed with: ...

Recommendation: If you answered YES to any of the above questions, we recommend testing for monogenic pathogenic variants (MPVs) associated with increased prostate cancer risk.

The evidence for application of prostate cancer PRS in individual early detection and screening

As prostate cancer PRS is a significant risk factor for prostate cancer, it should be incorporated in risk-based early detection and screening of prostate cancer.

Cohort analysis of the impact of genetic risk on prostate cancer mortality
The cohort study conducted in the United States and Sweden by Plym et al. used a combined analysis of genotyped men without prostate cancer at inclusion and with lifestyle data in two prospective cohort studies in Sweden and the US (7).

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The study explored differences in risk of early prostate cancer death among men with higher vs lower genetic risk, using a prostate cancer PRS and familial cancer history to inform prevention efforts. In this cohort study of 19 607 men, men at higher genetic risk had a 3-fold increased risk of an early prostate cancer death. Thirty-six percent of the deaths in this group were estimated to be preventable through factors that are associated with a healthy lifestyle. These findings suggest that targeting men at increased genetic risk with prevention strategies may substantially reduce the number of early deaths from prostate cancer (7).

Findings from the BARCODE 1 Study

The BARCODE 1 study explored the feasibility and clinical utility of using polygenic risk scores (PRS) to guide prostate cancer screening in the general population (4). Conducted in the United Kingdom, the study recruited men aged 55–69 of European ancestry through primary care, using saliva-based home DNA kits to calculate each participant's polygenic risk.

A PRS was derived for 6,142 men, based on 130 known prostate cancer susceptibility variants. Men whose PRS fell above the 90th percentile (n = 745, 12.1%) were invited for prostate MRI and transperineal biopsy, regardless of their PSA levels. Of these, 558 attended screening, and 468 underwent biopsy, resulting in 187 prostate cancer diagnoses, with a detection rate of 2.8% in the total screened cohort.

Crucially, 63.6% (119/187) of diagnosed men had PSA levels below 3.0 ng/mL, a threshold often considered normal in traditional screening. Despite this, 55.1% of cancers were of intermediate or high risk, based on NCCN 2023 criteria. Additionally, the rate of aggressive cancers (Gleason >7) was significantly higher than in traditional PSA-based screening cohorts (55.1% in BARCODE 1 vs. 35.5% in the ERSPC, $p < 0.001$).

The findings underscore that PSA testing alone is insufficient for early detection in men with high polygenic risk, as a significant proportion of aggressive cancers occur in individuals with normal PSA values. The study demonstrated that PRS-guided screening enriches detection of clinically significant prostate cancers and supports a targeted approach involving MRI and biopsy for men identified as genetically high-risk.

The authors concluded that population-based prostate cancer screening programmes incorporating PRS can improve early detection of aggressive disease while reducing overdiagnosis in men at low genetic risk.

The Göteborg prostate cancer screening study, a key part of the European Randomised Study of Screening for Prostate Cancer (ERSPC), provides important insights into the limitations of PSA-based screening (8). According to Möller et al., among men with PSA levels below 3 ng/mL, which is typically considered within the normal range, 4.6% were found to have clinically significant prostate cancer.

Conclusions from the study emphasise that a non-negligible proportion of men with "normal" PSA values still harbour aggressive disease (8). This challenges the reliance on PSA as the sole indicator for further diagnostic evaluation and highlights the risk of missed diagnoses under current protocols.

To address this, the study supports a more refined screening approach that integrates genetic risk stratification. By identifying men with a high polygenic risk, clinicians can offer additional diagnostic tools such as multiparametric MRI, even when PSA levels are not elevated. This targeted strategy enables earlier detection of aggressive cancers in high-risk individuals and avoids unnecessary investigations in those at low genetic risk.

Recommendations based on PRS test (AntePC) results in combination with PSA testing

We emphasise that early detection and screening for prostate cancer should not follow a uniform approach for all men, regardless of their personal awareness or desire for screening. Instead, as recommended by the EAU guidelines and the EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines, it should be an individualised, personalised prevention and early detection strategy.

Background. According to the EAU recommendations, offer a risk-adapted strategy based on initial PSA level, with follow-up intervals of two years for those initially at risk (2):

- men with a PSA level of > 1 ng/mL at 40 years of age;
- men with a PSA level of > 2 ng/mL at 60 years of age;

Postpone follow-up up to eight years in those not at risk.

Recommendations based on PRS test AntePC risk level for PSA testing:

Low and Average Risk (< 0.5-1.49 times the average risk for the given age):

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Recommendation: PSA testing from the age of 40 or later, followed by a risk-adapted strategy based on PSA test results.
According to the European Association of Urology (EAU) guidelines:
PSA value at age 40–60: < 1 ng/ml – subsequent PSA testing at 8-year intervals.
PSA value at age 40–60: ≥ 1 ng/ml – subsequent PSA testing at 2-year intervals.
PSA value over age 60: < 2 ng/ml – subsequent PSA testing at 8-year intervals.
PSA value over age 60: ≥ 2 ng/ml – subsequent PSA testing at 2-year intervals.

NB! If your PSA level is above 3.0 ng/ml, seek consultation with a urologist or andrologist for a more detailed assessment of your prostate health.

Moderately Elevated Risk: PRS percentiles 80.–89., relative risk 1.5 – 1.9 times of the average risk for the given age:
Recommendations:
Due to the elevated PRS-based risk, **we recommend an additional consultation with an andrologist or urologist** to assess, based on PSA levels and other prostate cancer risk factors, whether further investigation with a magnetic resonance imaging (MRI) scan is indicated.

Elevated Risk, PRS percentiles 90.–100., > 1.9 times of the average risk for the given age, and based on the BARCODE-1 study (4):
Recommendations:
Due to an elevated PRS level, we recommend screening with PSA testing annually starting from the current age and prostate magnetic resonance imaging (mpMRI) beginning at age 50, performed at two-year intervals.
(Prostate cancer screening from the age of 50 or XX (if the man's age at the time of testing is over 50) at two-year intervals with PSA testing and a magnetic resonance imaging (mpMRI) scan.)

Comment on MRI screening in men with high PRS risk:
The BARCODE-1 study showed that MRI is not also a perfect method for diagnosing prostate cancer. However, this can be addressed by repeating the MRI at two-year intervals and, preferably, performing annual PSA testing while monitoring changes in PSA levels over time.

Management recommendations for men with a monogenic pathogenic variant associated with increased prostate cancer risk

If a pathogenic mutation in a monogenic risk gene (e.g. in genes *BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PMS2, ATM, CHEK2, PALB2*, etc.) has been identified, the following clinical measures are recommended:

- Prostate cancer screening starting from age 40, with PSA testing and, if available, digital rectal examination (DRE):

From age 40: every 2 years
From age 50: annually

- Consider prostate magnetic resonance imaging (mpMRI) latest from age 50 with 2 year intervals
- Breast self-examination starting at age 35
- Annual clinical breast examination by a physician from age 35

In addition, the patient should be referred to a medical geneticist for genetic counselling. A family history assessment and cascade testing of at-risk relatives should be carried out.

Essentially, the new service integrates the assessment of genetic risk for prostate cancer—comprising both polygenic risk and, where indicated, the evaluation of monogenic pathogenic variants—into the existing EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer. This represents a more precise advancement of the current approach. The subsequent diagnostic pathway would take genetic risk into account, while the rest of the guideline's recommendations and overall concept would remain unchanged.

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Information about the polygenic risk score test AntePC

AntePC is a genetic test that assesses a man's risk of developing prostate cancer using polygenic risk score (PRS) technology. It is a clinical tool that estimates the prostate cancer risk level of an individual for precise and efficient prevention and screening. Its aim is to reduce prostate cancer morbidity and mortality.
AntePC test is recommended for men between the ages of 40 and 70.

AntePC is a clinical grade test registered as a CE-marked medical device (in vitro diagnostics, IVD) in the EUDAMED database (UDI-DI: 04745010362040), in the Estonian Medical Devices Database (EMDDB code: 14952), and the UK MHRA Registry (GMDN code: 63668).

The test results provide information about the individual's polygenic risk level for prostate cancer. This includes a prostate cancer-specific PRS value, the absolute risk for prostate cancer in the next 10 years, and the relative risk in comparison to other men in the same age group and population on average.

Depending on the application, the test report may include individual clinical recommendations to reduce the risk of developing prostate cancer such as:

- What age the individual should start prostate cancer screening and how
- Whether the individual should take additional measures to prevent prostate cancer
- What possible changes and symptoms regarding his prostate should the individual focus on.

AntePC Test Methodology

For the PRS calculation, AntePC uses the patient's DNA data from genotyping and summarizes the impact of 121 prostate cancer-related single nucleotide polymorphisms (SNPs).

To develop the AntePC test, different PRSs and their risk differentiation estimations were validated using anonymous data from the Estonian Biobank and UK Biobank. Based on large-scale genetic data, various risk prediction models published in the international scientific literature were compared. The prediction accuracy of the best-performing model was evaluated on independent data and developed further for the test (6). The PRS underlying AntePC is adapted and independently validated for practical use based on the report by Schumacher et al. (9).
The test is based on genome-wide association studies of patients and study participants of primarily European ancestry. However, the test is adapted to other ethnicities based on the analyses of risk performance in the ethnically diverse UK Biobank data.

AntePC has been developed by the health-tech company Antegenes and is performed by Antegenes' medical lab as a CE-marked IVD.

AntePC Test Limitations

- AntePC cannot be used to diagnose prostate cancer.
- High risk does not necessarily mean that the patient will develop prostate cancer during his lifetime.
- Moderate or lower risk does not necessarily mean that the patient will never develop prostate cancer during his lifetime.
- AntePC test results are individual and patient specific. The AntePC test does not assess the risk for the patient's family members or relatives. The inheritance pattern of PRS is complex and each person has to be tested separately.
- AntePC does not analyse rare monogenic pathogenic variants in genes that significantly increase the risk of prostate cancer, such as *BRCA1, BRCA2, ATM, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6,* and others. If

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a man's biological relative has a monogenic pathogenic variant in these genes, or if a man has several prostate, breast, or ovarian cancer cases in his family, Antegenes recommends additional counselling and testing for such monogenic variants.

- AntePC test is based on the most recent scientific data, which may be supplemented and/or changed in the future if additional information becomes available. The field of genetics is constantly evolving, which may lead to changes in risk assessments over time, changes in test selection, and clinical recommendations.
- Different polygenic risk scores predicting risks of the same trait may give different estimates of the individual's risks due to differences in the genetic variants included in these models and their weights.
- The results of this test should be applied in combination with other relevant clinical data. In addition to genetic predisposition, other risk factors influence the risk of developing prostate cancer.

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