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EDITORIAL

Genetics in prostate cancer: from precision treatment to precision prevention

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Introduction

The management of prostate cancer is undergoing a profound transformation. For decades, our clinical decisions have been based primarily on age, prostate-specific antigen (PSA), tumor stage, histological grade and imaging. These parameters remain essential, but they no longer provide the complete biological picture of the disease.
Genetics is progressively adding a new dimension to prostate cancer care. What began as an instrument for understanding hereditary susceptibility has become relevant to screening, prognosis, therapeutic selection and family counseling. More importantly, genetic information may allow us to move beyond the traditional concept of treating an established tumor towards a more ambitious objective: identifying individuals at increased risk before clinically significant disease develops.
This transition—from precision treatment to precision prevention—may represent one of the most important changes in contemporary uro-oncology.

Genetics begins before prostate cancer

Family history has always been part of prostate cancer risk assessment. However, family history is an imperfect surrogate for inherited susceptibility. Germline testing allows us to identify pathogenic variants associated with increased prostate cancer risk and, in some cases, with more aggressive biological behavior [1].
Among the genes implicated in hereditary prostate cancer, *BRCA2* currently has particularly important clinical relevance, while *BRCA1*, *ATM, CHEK2*, *HOXB13* and mismatch repair genes including *MSH2* and *MSH6* contribute to a broader spectrum of inherited susceptibility [1]. The clinical consequences are already becoming evident. Men carrying pathogenic *BRCA2* variants should not necessarily follow the same early-detection pathway as the general population. Prospective data from the IMPACT program have demonstrated that PSA-based screening in *BRCA2* carriers identifies prostate cancer at a younger age and, importantly, detects a higher proportion of clinically significant tumors [2, 3]. Current European recommendations reflect this evidence by supporting earlier PSA testing in *BRCA2* carriers, beginning at 40 years of age [4].
This represents an important conceptual change. Screening is progressively moving away from a model based almost exclusively on chronological age towards one incorporating biological and genetic risk. In the future, the fundamental question may therefore no longer be simply "When should PSA screening begin?" but rather "What is this man's individual probability of developing clinically significant prostate cancer?"

Germline and somatic genetics: two different questions

The growing use of molecular testing requires a clear distinction between germline and somatic alterations.
Germline variants are inherited and present in virtually every cell of the body. Their identification has implications not only for the patient but potentially for his relatives. Somatic alterations, in contrast, are acquired by the tumor and provide information about its biological characteristics and potential therapeutic vulnerabilities.
These two dimensions should not be considered alternatives. They are complementary components of precision oncology. This is particularly evident in metastatic prostate cancer, where contemporary recommendations increasingly incorporate both germline and tumor genomic testing. Molecular characterization can identify alterations in DNA damage repair pathways, mismatch repair deficiency and other genomic abnormalities that may influence therapeutic strategies [5-7].
Consequently, genetic testing is no longer an investigation performed exclusively after all conventional therapeutic options have been exhausted. It is increasingly becoming part of the initial molecular characterization of advanced prostate cancer.

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BRCA2: from susceptibility gene to therapeutic biomarker

Perhaps no gene illustrates this evolution better than *BRCA2*.

BRCA2 is simultaneously a susceptibility gene, a prognostic marker and a predictive biomarker. Germline pathogenic variants increase prostate cancer risk and are associated with clinically important disease, while *BRCA2* alterations within the tumor may identify a biological vulnerability that can be therapeutically exploited [1-3].

The development of poly (ADP-ribose) polymerase (PARP) inhibitors has translated the concept of synthetic lethality from molecular biology into clinical practice.

Tumors deficient in homologous recombination repair (HRR) may become particularly dependent on alternative mechanisms of DNA repair. Inhibition of PARP can exploit this vulnerability, producing selective tumor cell death. Trials evaluating olaparib, rucaparib, niraparib and talazoparib, either alone or in combination with androgen-receptor pathway inhibitors, have established DNA repair alterations as clinically relevant therapeutic biomarkers in advanced prostate cancer [8-11].

However, one of the most important lessons from these studies is that not all HRR alterations are equivalent. The strongest and most reproducible therapeutic signal has generally been observed in patients harboring *BRCA* alterations, particularly *BRCA2*. Responses associated with alterations in other DNA repair genes are more heterogeneous [7, 11].

This distinction is critical. Precision medicine cannot simply classify patients as "HRR-positive" or "HRR-negative". The specific gene, the pathogenicity of the variant, monoallelic versus biallelic involvement, the genomic context and the stage of disease may all influence the clinical significance of a molecular finding. Precision oncology therefore requires not only genomic testing, but also precision in genomic interpretation.

Genetics as a prognostic instrument

Genetic information may also refine our understanding of tumor aggressiveness.

Pathogenic germline *BRCA2* variants have repeatedly been associated with adverse clinicopathological characteristics and aggressive prostate cancer phenotypes. This observation raises an important question regarding patients with apparently localized disease [4].

Should inherited genomic risk modify our approach to active surveillance?

At present, established clinical and pathological parameters remain fundamental, and genomic information should not automatically determine treatment. Nevertheless, it is reasonable to expect that future prospective studies will increasingly integrate germline and tumor genomic information into risk stratification models. A patient with Grade Group 1 disease, negative magnetic resonance imaging (MRI) findings and favorable PSA density may not necessarily have the same long-term biological risk if he also carries a pathogenic *BRCA2* variant.

The challenge will be to determine when genetic risk should influence surveillance intensity and when it should alter therapeutic thresholds, while avoiding unnecessary overtreatment.

When one diagnosis becomes a family diagnosis

The implications of germline testing extend far beyond prostate cancer treatment. When a pathogenic inherited variant is identified, the information belongs biologically not only to the patient but potentially to an entire family.

A *BRCA2* pathogenic variant identified in a man with prostate cancer may indicate increased susceptibility to prostate and other malignancies among male relatives and may also have implications for breast, ovarian and pancreatic cancer risk within the family [1]. This transforms the clinical meaning of a prostate cancer diagnosis. The patient becomes the potential starting point for cascade genetic testing, allowing healthy relatives carrying the same pathogenic variant to enter personalized surveillance programs before cancer develops [1].

Few developments illustrate the convergence between oncology and preventive medicine more clearly. The urologist treating prostate cancer may therefore indirectly contribute to preventing or detecting cancer earlier in brothers, sons, daughters and other relatives.

Beyond *BRCA*: the polygenic future

High-penetrance pathogenic variants explain only a proportion of inherited prostate cancer susceptibility. Most prostate cancer risk is considerably more complex and results from interactions between age, ancestry, environmental exposures, lifestyle, family history and a large number of common genetic variants, each contributing a relatively small individual effect.

This has stimulated increasing interest in polygenic risk scores (PRS). By combining information from multiple prostate cancer-associated genetic variants, PRS may eventually allow more refined estimation of individual susceptibility. Their greatest potential may emerge when genetic information is integrated with traditional clinical variables [4].

The prostate cancer screening pathway of the future may combine family history, germline pathogenic variants, polygenic risk, PSA and PSA kinetics, prostate volume, biomarkers and multiparametric MRI within integrated prediction models [4]. Artificial intelligence may further facilitate interpretation of these multidimensional datasets. Such an approach could identify men requiring earlier or more intensive surveillance while simultaneously reducing unnecessary investigations among those at genuinely low risk.

The ultimate objective would therefore not be more screening, but better-targeted screening.

The changing role of the urologist

These developments have important implications for our specialty. Historically, genetic testing was often considered the responsibility of geneticists or medical oncologists. This distinction is becoming increasingly artificial.

The urologist frequently diagnoses prostate cancer, discusses its prognosis, performs definitive treatment and follows patients for many years. We are therefore ideally positioned to recognize hereditary cancer patterns and identify patients who may benefit from genetic evaluation. This does not imply that urologists should replace genetic counselors. Rather, genetic literacy should become a fundamental component of contemporary urological oncology.

We need to understand which patients should be tested, which genes are clinically relevant, how germline and somatic testing differ, what a pathogenic variant means, and—equally importantly—what a variant of uncertain significance does not mean. Multidisciplinary collaboration between urologists, oncologists, radiation oncologists, pathologists, molecular biologists and genetic counselors will therefore become increasingly important.

From precision treatment to precision prevention

The genomic revolution in prostate cancer initially focused on the treatment of advanced disease [1]. Molecular alterations were identified primarily because they could provide new therapeutic targets. The next phase may be even more important. Genetics offers the possibility of moving upstream in the natural history of prostate cancer: from selecting treatment after metastatic progression to identifying susceptibility before cancer develops. This is the transition from precision treatment to precision prevention.

In the coming years, we may increasingly be able to identify the man at increased risk before his PSA rises, personalize the age at which screening begins, determine the appropriate intensity of surveillance and integrate genetic information with imaging and biomarkers to identify clinically significant disease earlier.

Genetics will not replace PSA. It will not replace MRI, pathology or clinical judgement. Instead, it will provide the biological framework connecting these different elements.

The challenge will be to ensure that technological capability translates into meaningful clinical benefit. More genomic information does not automatically mean better medicine. Appropriate patient selection, high-quality genetic counseling, correct interpretation of variants, equitable access to testing and prospective validation of risk-adapted strategies will remain essential.

Nevertheless, the direction of travel is increasingly clear. The future of prostate cancer management will not be defined solely by how effectively we treat an established tumor. It will also depend on how accurately we can identify who is at risk, who requires early detection, which tumors are biologically aggressive, and which molecular vulnerability can be therapeutically exploited. In this evolving landscape, the genome is becoming part of the patient's clinical history.

And perhaps the most important contribution of genetics to prostate cancer will ultimately not be helping us treat cancer differently, but helping us identify the right patient before aggressive cancer has the opportunity to develop.

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