Germline testing and genetic counselling in prostate cancer

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Abstract | Genetic testing for prostate cancer is rapidly growing and is increasingly being driven by precision medicine. Rates of germline pathogenic variants have been reported in up to 15% of men with prostate cancer, particularly in metastatic disease, and results of genetic testing could uncover options for precision therapy along with a spectrum of hereditary cancer-predisposition syndromes with unique clinical features that have complex management options. Thus, the pre-test discussion, whether delivered by genetic counsellors or by health-care professionals in hybrid models, involves information on hereditary cancer risk, extent of gene testing, purpose of testing, medical history and family history, potential types of results, additional cancer risks that might be uncovered, genetically based management and effect on families. Understanding precision medicine, personalized cancer risk management and syndrome-related cancer risk management is important in order to develop collaborative strategies with genetic counselling for optimal care of patients and their families.

Prostate cancer is a common cancer in men, and a subset of men can have a hereditary predisposition to developing this disease[1,2]. Germline testing (hereditary cancer genetic testing) encompasses testing for genes linked to hereditary syndromes, such as hereditary breast and ovarian cancer (HBOC) syndrome, Lynch syndrome and hereditary prostate cancer[1–4]. Furthermore, germline testing now involves multigene testing of a host of additional genes, such as DNA repair genes, which might also confer increased risk of additional cancers and be important for therapeutic determination[1–7]. Germline testing for inherited mutations is important to estimate cancer risks above the general population, with magnitude of risk being gene specific[1,8]. Population risk for developing prostate cancer is 11%, whereas men with specific genetic mutations (pathogenic or probable pathogenic variants) can have a 2-fold to 10-fold increase in lifetime risk of developing prostate cancer, such as for mutations in *BRCA2* or *HOXB13* (REF.[1]). Risk-based screening for prostate cancer is evolving, with current guidelines from the National Comprehensive Cancer Network (NCCN) recommending initiation of prostate cancer screening for *BRCA2* carriers at the age of 40 years with consideration of the same for *BRCA1* carriers[9]. Furthermore, prostate cancer germline testing came to the forefront in the precision medicine era[1,2,4–6]. Multiple targeted agents, such as poly(ADP-ribose) polymerase (PARP) inhibitors and immunotherapeutic drugs, are FDA approved or have FDA designations for use in men with metastatic castration-resistant prostate cancer (mCRPC) owing to demonstrated clinical responses, particularly among men who carry mutations in DNA repair genes such as in *BRCA1, BRCA2, ATM*, or the DNA mismatch repair genes[1–7]. Thus, pre-test discussions with patients need to address the potential effects of treatment or screening, hereditary cancer risk and implications for blood relatives[1–4,8–10].

Many thousands of men could now be eligible for germline testing and, therefore, strategies for clinical genetic evaluation need to be implemented. Genetics care delivery can occur through genetic counselling or by employing a hybrid model (a health-care provider–genetic counselling collaborative approach). Genetic counselling is a specialized field and genetic counsellors are professionals trained in the principles and practice of genetic testing, hereditary cancer assessment, informed decision-making for genetic testing and the implications of genetic testing for patients and their families[10–13] (BOX 1). They perform an assessment of a patient's medical history and family history, discuss cancer heredity and options for genetic testing, implications of test results, and the benefits and risks of testing so that patients can make an informed decision[10–13]. Upon return of the results, genetic counsellors help patients to understand their results and discuss recommendations based on the results and the patient's medical history and family history. They also coordinate cascade testing (testing of blood relatives in families with a known genetic mutation) or additional genetic testing in a family[9–12].

In the current precision medicine era, in which genetic mutations might guide options for targeted

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Key points

- Germline (hereditary) genetic testing is rising in importance for treatment, screening and risk assessment of prostate cancer.
- Multiple hereditary cancer syndromes might be associated with prostate cancer, might confer risk of other cancerous and non-cancerous conditions, and can have hereditary cancer implications for family members. The rates of these syndromes can vary based upon the attributed genetic mutations.
- Multiple aspects of germline testing should be discussed in the pre-test setting for men to make an informed decision, including the purpose of genetic testing, the benefits and risks of testing, hereditary cancer risk, identification of additional cancer risks, familial implications and the state of genetic discrimination protections.
- Genetic evaluation can be conducted by genetic counsellors or a hybrid model can be employed, in which health-care providers deliver pre-test informed consent for testing, order testing and then determine referral to genetic counselling for appropriate patients.
- Precision medicine is increasingly driving decisions for germline testing. Poly(ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors and various other agents now in clinical trials have clinical activity in patients with certain hereditary cancer gene mutations, such as in DNA repair genes.
- Patients' experiences with germline testing can be variable; taking the patient's current experience into account, considering referral to genetic counselling when needed and offering germline testing for eligible men at repeated intervals if initially declined are important.

therapies and with the expanded indications for germline testing, a need for alternative delivery of germline testing initiated by health-care providers has arisen given the relative shortage of genetic counsellors and the need to limit additional visits and reduce barriers[13–17]. Hybrid models have emerged in practice to expand access to germline testing, in which joint care strategies are implemented between health-care providers and genetic counsellors to address pre-test consent strategies, management of men with pathogenic variants, management of subsets of men with variants of uncertain significance (VUS), management of subsets of men with negative results with strong family cancer history, and cascade testing[2,14].

Given the growth of indications for germline testing in prostate cancer[7,9], this Review addresses major autosomal-dominant hereditary cancer syndromes linked with prostate cancer, germline testing criteria, genetic testing strategies, genetically informed prostate cancer screening and precision management, delivery of genetic counselling or alternative genetic services and special considerations for this population. All of these issues are now of crucial relevance for optimal cancer risk assessment, screening and treatment of patients with prostate cancer or at risk of developing prostate cancer guided by genetic information.

Inherited cancer syndromes contributing to prostate cancer

Multiple hereditary cancer syndromes can be associated with prostate cancer, such as HBOC syndrome and Lynch syndrome, which have specific clinical manifestations and management[1,2] (TABLE 1). These syndromes require unique attention when performing genetic counselling and/or pre-test informed consent and germline testing (TABLE 1). HBOC is associated with mutations in *BRCA1* and *BRCA2* (REF.[9]). *BRCA1* and *BRCA2*, which are located on chromosomes 17 and 13, respectively, are tumour suppressor genes involved in DNA homologous recombination repair[18–20]. HBOC is inherited in an autosomal-dominant manner (in which a single copy of a mutation on a non-sex chromosome is sufficient to predispose to disease)[19,20] and is associated with breast cancer (male and female), ovarian cancer, pancreatic cancer, prostate cancer and melanoma[9]. Up to 15% of men with metastatic prostate cancer have been reported to carry germline mutations in DNA repair genes such as *BRCA1* and *BRCA2*, whereas ~5–7% of men with early-stage prostate cancer are carriers[1,2,21–23]. *BRCA2* mutations are more strongly associated with prostate cancer than *BRCA1* mutations, with an approximately eightfold versus approximately threefold increase in risk, respectively[1,24]. Furthermore, *BRCA2* mutations have been associated with aggressive prostate cancer with decreased prostate cancer-specific survival[1,25–27]. Individuals with Ashkenazi Jewish ancestry are at an increased risk of carrying a mutation in *BRCA1* or *BRCA2* owing to three known founder mutations in this population: 185delAG (*BRCA1*), 5382insC (*BRCA1*) and 6174delT (*BRCA2*)[28,29]. The combined population risk of carrying one of these variants is 1 in 40 for Ashkenazi Jewish individuals compared with 1 in 400 for the general population[28,30].

Hereditary prostate cancer, with generational and/or young onset of disease, is another hereditary syndrome associated with prostate cancer development[1,31]. *HOXB13*, the first classic hereditary prostate cancer gene identified in 2012 is associated with an approximately eightfold increased risk of prostate cancer and approximately tenfold increased risk of early-onset disease[1,24,32]. *HOXB13* is currently not known to confer increased risk of developing other cancers. The G84E pathogenic variant of *HOXB13* has an established association with prostate cancer; its overall frequency was reported to be 1.34% among men with prostate cancer in a pooled analysis across multiple studies[33], whereas the highest carrier rate of 6.25% has been reported in men with prostate cancer in Finland[34]. *HOXB13* codes for a homeobox transcription factor and is located on chromosome 17 (REF.[34]); this gene is part of a large group of transcription factors called the homeobox protein family, which has a role in prostate development[35]. *HOXB13* mutations are inherited in an autosomal-dominant manner[1,32].

Prostate cancer is also within the spectrum of Lynch syndrome cancers[1,24,36]. Lynch syndrome, classically known as hereditary non-polyposis colorectal cancer syndrome, predisposes to development of cancers of the colon and/or rectum, pancreas, ovary, uterus, upper bowel and urinary tract, and sebaceous carcinoma[36,37]. Lynch syndrome is associated with mutations in the following genes involved in DNA mismatch repair (MMR): *MLH1* (chromosome 3), *MSH2* (chromosome 2), *MSH6* (chromosome 2) and *PMS2* (chromosome 7) and is inherited in an autosomal-dominant manner[36,37]. Certain deletions in the *EPCAM* gene have also been shown to cause Lynch syndrome by causing an *MSH2* epimutation[37]. However, associated cancer risks vary based on the study and DNA MMR genes studied[1,36–39]. Overall, mutations in the DNA MMR genes, particularly

MSH2 and *MSH6*, are associated with an approximately threefold increased risk of developing prostate cancer[1,38].

Other genes, such as *CHEK2* or *NBN*, have varying degrees of association with prostate cancer, but are included in prostate cancer testing panels owing to implications for therapy[1,2]. Multiple other genes involved in DNA repair, such as *ATM, PALB2*, *RAD51C* and *RAD51D*, could also be important for testing to inform response to precision therapies such as PARP inhibitors[1,2,4,5].

These data show that multiple genes linked with a spectrum of hereditary cancer syndromes are associated with varying degrees of prostate cancer risk, disease characteristics and manifestations, and additional cancers[1,7,9,24]; thus, multigene testing for prostate cancer has become a standard of genetic testing practice[1,2,7]. Several of these syndromes have established guidelines to inform hereditary cancer assessment in families and guide screening for at-risk individuals[7,9,39] (TABLE 1).

Box 1 | **Basic elements of genetics care delivery and germline testing**

Aspects of germline genetic testing

- Testing DNA from non-cancerous cells to detect variation associated with potential risk of disease or effect on treatment.
- Disease risk is predominantly determined by the effect that the variant has on the ability of the gene to translate into a functioning protein.
- The goal of germline genetic testing in oncology is to assess an individual's cancer predisposition and understand why a specific cancer developed based on pathogenic variants in genes implicated in important cellular processes.
- Germline testing can also be conducted in oncology to inform targeted therapy options, particularly in the metastatic setting.
- Variants detected in germline testing can be passed down or inherited by offspring. Germline testing differs from somatic genetic testing of a tumour assessing for somatic variants, which are usually acquired in tumour formation. Confirmatory germline testing of somatic variants might be indicated to determine hereditary nature.

Aspects of genetic counselling

- Evaluating a patient's medical and family history to assess the likelihood of a genetic predisposition and advise appropriate genetic testing.
- Providing education regarding genetic testing, inherited health risk, or effect on treatment.
- Supporting patients in making genetic testing decisions.
- Interpreting genetic testing results and helping patients to understand and adjust to potential medical, familial and psychosocial implications.

Clinical scope of a genetic counsellor

- A medical professional with specialized training in advanced genetics and counselling.
- Genetic counsellors often work in a clinic or hospital setting along with physicians and other health-care providers as part of a patient's care team.
- They can specialize in different areas of genetics including, but not limited to, oncological, paediatric, prenatal or preconception, cardiovascular and neurological.

Aspects of a hybrid genetics care delivery model

- A collaborative care model between health-care providers and genetic counsellors.
- Health-care providers deliver pre-test informed consent.
- Health-care providers order germline testing, particularly focusing on the effect on treatment or management.
- Upon return of the results, health-care providers discuss implications for prostate cancer treatment, management or screening. Appropriate patients are referred to genetic counsellors.
  - Results of pathogenic or probable pathogenic variants
  - Results of variants of uncertain significance with strong family cancer history
  - Men with negative results with strong family cancer history
  - Complex genetic results
- Some patients might need to be referred to genetic counselling upfront.
  - Men who prefer to see a genetic counsellor
  - Men with a high level of anxiety or psychosocial issues
  - Men with known mutations in the family
  - Men with rare or complex syndromes

Germline testing criteria and approach to testing for prostate cancer

Germline testing criteria for prostate cancer encompasses personal cancer history, cancer features and pathology, family history and precision therapy indications[7,9]. The NCCN publishes guidelines for consideration of germline testing across multiple cancer types, including prostate cancer[7,9]. Germline testing criteria for prostate cancer have been provided by multiple NCCN panels[7,9], an international expert consensus statement from the Philadelphia Prostate Cancer Consensus Conference 2019 (REF.[2]), American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology (AUA/ASTRO/SUO) 2020 guideline for advanced prostate cancer[40], and the European Association of Urology (EAU) 2020 guideline[2,7,9,41] (BOX 2). Prostate cancer germline testing criteria from the NCCN are uniform among guidelines regarding cancer features (stage, grade) and ancestry; however, they differ by family history criteria[7,9]. NCCN guidelines agree regarding recommending germline testing for men with any one of the following: metastatic prostate cancer, regional or node-positive disease, very high-risk or high-risk prostate cancer (defined by grade group, T stage, and serum PSA levels at diagnosis), intraductal or cribriform histology, Ashkenazi Jewish ancestry, or family history of a relative or relatives with a germline mutation[7,9]. Eliciting family history of prostate cancer (age at diagnosis, known metastatic disease, death from prostate cancer) is important to inform for suspicion of hereditary prostate cancer and to help to inform regarding the full scope of genes to test[2,7,9]. Furthermore, knowing the family history of cancers of the breast, ovary, pancreas, colon and/or rectum, uterus, small bowel, urinary tract and skin is important[7]. Clinical practice might not be straightforward, but clinicians can refer to all guidelines to determine which family history criteria might match their patient's family history to determine eligibility for germline testing[7,9]. Thus, health-care providers need to become familiar with the nuances of these guidelines and remain current, as the guidelines are regularly updated.

Multiple professional organizations address germline testing for prostate cancer in various ways (TABLE 1; BOX 2). The EAU 2020 guideline[41] recommends conducting germline testing for men with metastatic prostate cancer. This guideline also recommends performing genetic testing for men with mCRPC for DNA repair mutations to determine eligibility for PARP inhibitors. The AUA/ASTRO/SUO 2020 advanced prostate cancer guideline[40] states that patients with metastatic prostate cancer should be offered genetic counselling and genetic testing regardless of age and family history[30]. It also recommends offering PARP inhibitors to patients with deleterious or suspected deleterious germline or somatic homologous

Table 1 | **Major hereditary cancer syndromes linked with prostate cancer**

Gene	Syndrome	Clinical manifestations affecting cancer management (patient and familial implications)[a]	Prostate cancer management considerations by selected guidelines for patients with mutations[b]
BRCA1 *BRCA2*	HBOC	Female and male breast cancer Ovarian cancer Prostate cancer Pancreatic cancer Melanoma	**NCCN Guidelines Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 1.2022 (REF.[9])** Prostate cancer: PSA screening starting at the age of 40 years with annual intervals Recommend screening for *BRCA2* carriers and consider screening for *BRCA1* carriers **NCCN Prostate Cancer (Version 2.2021)[7]** For mCRPC, DNA genes such as *BRCA1*, *BRCA2*, *ATM*, etc. might inform early platinum therapy or PARP inhibitor therapy **NCCN Prostate Cancer Early Detection (Version 2.2020)[49]** Consider shared decision-making for men with *BRCA1* or *BRCA2* mutations regarding prostate cancer screening starting at the age of 40 years and to consider annual versus biannual screening **Philadelphia Prostate Cancer Consensus Conference 2019 (REF.[2])** Recommend precision medicine clinical trials mCRPC: *BRCA2* and *BRCA1* inform PARP inhibitor therapy; also inform use of platinum chemotherapy. Consider immunotherapy for DNA MMR gene mutation carriers Consider *BRCA2* in active surveillance discussions Prostate cancer screening at the age of 40 years or 10 years before the youngest person in the family was diagnosed with prostate cancer and continue screening with annual intervals (recommended for *BRCA2* carriers with consideration for *BRCA1* carriers) **AUA/ASTRO/SUO Advanced Prostate Cancer 2020 (REF.[40])** Offer PARP inhibitors to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following previous treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Consider platinum-based chemotherapy as an alternative for patients who cannot use or obtain a PARP inhibitor **EAU Prostate Cancer 2020 (REF.[41])** Genetic testing for DNA repair mutations for PARP inhibitor therapy in mCRPC
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Lynch syndrome	Colorectal Endometrial Ovarian Urothelial cancer (renal pelvis, ureteral cancers) Gastric and/or small bowel Pancreatic Prostate Brain	**NCCN Prostate Cancer (Version 2.2021)[7]** For mCRPC, consider dMMR or MSI-H status for pembrolizumab **Philadelphia Prostate Cancer Consensus Conference 2019 (REF.[2])** Consider DNA MMR gene mutations for pembrolizumab Consider prostate cancer screening at age 40 years or 10 years before the youngest person in the family was diagnosed with prostate cancer and continue screening with annual intervals **AUA/ASTRO/SUO Advanced Prostate Cancer 2020 (REF.[40])** In patients with dMMR or MSI-H mCRPC, offer pembrolizumab
HOXB13	Hereditary prostate cancer	Prostate cancer	**Philadelphia Prostate Cancer Consensus Conference 2019 (REF.[2])** Consider prostate cancer screening at age 40 years or 10 years before the youngest person in the family was diagnosed with prostate cancer and continue screening with annual intervals

ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; dMMR, mismatch repair deficiency; EAU, European Association of Urology; HBOC, hereditary breast and ovarian cancer syndrome; mCRPC, metastatic castration-resistant prostate cancer; MMR, mismatch repair; MSI-H, microsatellite instability high; NCCN, National Comprehensive Cancer Network; PARP, poly(ADP-ribose) polymerase; SUO, Society of Urologic Oncology. [a]Clinical trials are important for patients with mutations concerning treatment and management of prostate cancer. Many of the hereditary syndromes in this table have cancerous and non-cancerous disease features beyond prostate cancer that also require management. [b]Multiple NCCN guidelines address management of cancer risks, risk reduction and treatment affecting men and their families.

recombination repair gene-mutated mCRPC following treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. It also recommends considering platinum-based chemotherapy as an alternative for patients who cannot use or obtain a PARP inhibitor and offering pembrolizumab to patients with MMR-deficient or microsatellite instability-high mCRPC.

Clinical germline testing has now progressed from single gene testing to multigene testing options for patients[2,3,42]. Multiple genetic testing laboratories offer germline testing options for patients with prostate cancer or those concerned about risk of prostate cancer. In general, testing options include guideline-focused panels, tumour-specific panels and large comprehensive

cancer panels[2,3] (TABLE 2). Furthermore, some genetic testing laboratories have the option of initially conducting testing with a small set of genes, and then reflex testing a larger set of genes if initial testing does not reveal pathogenic and/or probable pathogenic variants in the genes tested[2]. These reflex options typically need to be conducted within the laboratory-specified time frame of test ordering for the test to be cost free to patients in the USA.

Multigene panel testing has become the standard of care for many genetic testing indications[7,9]; thus, dedicated discussion of the considerations of panel tests is needed before a patient pursues genetic testing[2,42]. The size and availability of multiple gene panels varies by laboratory and the process of helping the patient choose the best panel for them can be complex[2,42,43]. A thorough discussion of benefits and limitations of panel testing is necessary before pursuing multigene panel testing, with recognition that these discussions need to be tailored to the purpose of testing[2,7,9,42,43]. For example, multigene testing in a patient with metastatic prostate cancer might include large panel testing to optimize targeted therapy or clinical trial options[2,4]; however, in early-stage prostate cancer, genetic testing might be more tailored and encompass genes that account for the patient's cancer and family history[2]. Patients need to understand the benefits and limitations of various multigene panel testing options[2,42,43]. Benefits of large-panel testing include potentially increased chance of uncovering a mutation, cost efficiency, and reduced testing fatigue, which can occur with repeat testing[42,43]. Limitations of large-panel testing include an increased rate of detecting VUS, unexpected secondary findings, mutations in genes in which the cancer risk is unknown or not well established, and finding mutations in genes without current management guidelines[2,3,7,9,42].

Acceptable specimens for germline genetic testing at most laboratories include peripheral blood, saliva, and cheek and/or buccal swab. For some patients, such as those with certain haematological malignancies or a history of transplant, a skin punch biopsy sample might be needed to avoid testing tumour cells for genetic mutations. Germline genetic testing through most commercial laboratories generally has a 3–4-week turnaround time depending on testing techniques, sample used and billing practices. Each laboratory has individual practice that providers should become familiar with.

Importantly, the difference between 'medical genetic testing' or 'clinical genetic testing' and 'recreational genetic testing' or 'direct-to-consumer' testing needs to be distinguished[44–47]. Medical or clinical genetic testing is a comprehensive process that involves extensive interrogation of multiple genes or genetic regions to detect thousands of pathogenic variants in disease-related genes of interest. The technology can detect multiple types of mutations and deletions and/or duplications and/or rearrangements. Genetic evaluation is guided by a genetics professional or health-care professional and is tailored to the patient's medical history, family history and personal preferences[2,7,9,42]. Recreational genetic tests or direct-to-consumer tests are primarily designed for population-level testing, with some advantages and important disadvantages to consider[45–47]. The main advantage is increased access to genetic testing without practice barriers or delays that can be involved in scheduling appointments with genetic counselling[15,45,46]. However, multiple important considerations need to be noted: the testing might not be suited to a particular patient's medical condition or address family cancer

Box 2 | **Examples of germline testing criteria for prostate cancer**

NCCN Guidelines Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic (Version 1.2022)[9]

- Personal history of prostate cancer at any age with
  - Metastatic, intraductal or cribriform histology, or high-risk or very-high-risk group (see NCCN Prostate Cancer guideline[7] criteria below) regardless of age
- Any NCCN risk group (see NCCN Prostate Cancer guideline[7] below) with the following
  - ≥1 close blood relative diagnosed with breast cancer at ≤50 years old, pancreatic, ovarian, or metastatic, intraductal or cribriform prostate cancer at any age
  - ≥2 close blood relatives with either breast or prostate cancer at any age
  - Ashkenazi Jewish ancestry

NCCN Guidelines Prostate Cancer (Version 2.2021)[7]

Regardless of age

- Metastatic prostate cancer
- Very high risk: T3b–T4 or primary Gleason pattern 5 or >4 cores with grade group 4 or 5
- High risk: T3a or grade group 4 or 5 or PSA >20 ng/ml

Any other risk group with any of the following

- Ashkenazi Jewish ancestry
- Prostate cancer family history: brother, father, or multiple family members diagnosed with prostate cancer at <60 years old or died from prostate cancer (grade groups 2–5)
- ≥3 cancers on the same side of the family (especially if diagnosed at ≤50 years old): bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (grade groups 2–5), small bowel, or urothelial

Philadelphia Prostate Cancer Consensus Conference 2019 (REF.[2])

Recommend to

- Men with metastatic prostate cancer
- Men with a family history of prostate cancer: men with one first-degree relative or ≥2 male relatives with one of the following:
  - Diagnosed with prostate cancer at the age of <60 years
  - Any of whom died from prostate cancer or had metastatic prostate cancer

Consider for

- Men with non-metastatic prostate cancer with one of the following
  - Diagnosed with prostate cancer at <60 years old
  - Advanced disease (T3a or higher)
  - Intraductal or ductal pathology
  - Grade group 4 (Gleason sum 8) or above
- Men with Ashkenazi Jewish ancestry
- Men with two or more cancers within the hereditary breast and ovarian cancer or Lynch syndrome spectrum in any relatives on the same side of the family (especially if diagnosed at <50 years old)

AUA/ASTRO/SUO Clinically Localized Prostate Cancer 2017 (REF.[89])

Referral to genetic counselling should be considered for patients (and their families) with high-risk localized prostate cancer and a strong family history of specific cancers (such as breast, ovarian, pancreatic, other gastrointestinal tumours)

AUA/ASTRO/SUO Advanced Prostate Cancer 2020 (REF.[40])

Patients with metastatic hormone-sensitive prostate cancer should be offered genetic counselling and genetic testing regardless of age and family history

EAU guidelines: Prostate Cancer[41]

Conduct germline testing for men with metastatic prostate cancer

ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; SUO, Society of Urologic Oncology.

Table 2 | **Prostate cancer panels available through experienced USA-based clinical laboratories**

Testing laboratory	Multigene panels and genes	Considerations
Invitae	Prostate cancer panel: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *EPCAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PMS2*, *TP53* Prostate cancer HRR panel: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51C*, *RAD51D*	Ability to customize gene panels[a] Reflex testing is available within a specific time frame Offers paired RNA testing[b] Accepts skin punch biopsy specimens for testing
Ambry Genetics	ProstateNext panel: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *EPCAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51D*, *TP53*	Ability to customize gene panels[a] Reflex testing is available within a specific time frame Offers paired RNA testing (RNAinsight)[b] Accepts skin punch biopsy specimens for testing
GeneDx	Hereditary prostate cancer panel: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *EPCAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51C*, *RAD51D*, *TP53*	Ability to customize gene panels[a] Reflex testing is available Accepts skin punch biopsy specimens for testing
Myriad Genetics	myRisk panel: *APC*, *ATM*, *AXIN2*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *GREM1*, *HOXB13 GALNT12*, *MLH1*, *MSH2*, *MSH3*, *MSH6*, *MUTYH*, *NBN*, *NTHL1*, *PALB2*, *PMS2*, *POLE*, *POLD1*, *PTEN*, *RAD51C*, *RAD51D*, *RNF43*, *RPS20*, *SMAD4*, *STK11*, *TP53*	*HOXB13* sequencing only Reflex testing from small panels to largest panel (Myriad myRisk) is available, but might require an additional specimen Accepts skin punch biopsy specimens for testing
Color	Hereditary cancer panel: *APC*, *ATM*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM*, *GREM1*, *MITF*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, *POLE*, *POLD1*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, *TP53*	*PMS2*: only covers exons 1–11. Variant interpretation outside of this area of the gene is difficult owing to a pseudogene *PMS2CL* that shares a similar coding sequence *HOXB13* not included

As of August 2021; furthermore, multiple additional cancer panels are available at these laboratories. HRR, homologous recombination repair. [a]Customization involves being able to choose the genes to test rather than a premade gene panel. [b]RNA testing involves assessing the function of DNA variants usually reported as variants of uncertain significance (VUS). These VUS are usually in genes associated with hereditary cancer and disrupt RNA splicing[88].

history; the testing might be incomplete compared with clinical genetic testing (testing only a few mutations versus complete sequencing and alteration assessment; limited genes tested)[44–47]; if test results return with no pathogenic variants, individuals might have false reassurance of no hereditary cancer condition in themselves or their families, with subsequent missed hereditary cancer management and lack of appropriate follow-up care[4,44–47]; misunderstanding of various types of genetic results (such as VUS) can occur, with propagation of misinformation in families, potential adverse effects on life insurance or long-term care insurance for mutation carriers, and adverse psychological consequences without preparatory pre-test genetic counselling[44–47]. Furthermore, patients might present to their physicians or genetic counsellors with results of at-home genetic tests, which could then require repeat or confirmatory germline testing, often at a cost to the patient.

Overall, criteria for genetic testing for prostate cancer are tailored to the clinical features, pathological features and family history[7,9]. Genetic testing options have expanded and providers should have an understanding of the benefits and limitations of genetic test options[2,7,9,42]. Close collaboration between health-care providers and genetic counsellors is important for optimal testing and comprehensive recommendations to patients[2,7,9,14,42].

Management of prostate cancer based on germline mutations

Historically, germline testing for cancer predisposition syndromes was performed to inform cancer risk, screening and cancer risk-reduction measures[44]. However, advances in precision medicine have heralded a new era of expanded therapeutic utility of germline testing, which is now highly relevant to prostate cancer[1,2,4–7,9] (TABLE 1). Hereditary cancer management for syndrome-associated cancers including and beyond prostate cancer is also crucial[7,9].

The influence of genetic testing in prostate cancer screening has been of long-standing interest, with emerging data influencing screening approaches[2,7,48]. Updated results from the IMPACT prostate cancer screening trial were reported in 2019 (REF.[48]). This study included men aged 40–69 years, 919 of whom were *BRCA1* carriers, 709 of whom were *BRCA1* non-carriers, 902 of whom were *BRCA2* carriers, and of whom 497 were *BRCA2* non-carriers, who underwent 3 years of screening[48]. Higher prostate cancer incidence was observed among *BRCA2* carriers than non-carriers (19.4 versus 12.0; $P = 0.03$). *BRCA2* carriers were also diagnosed with prostate cancer at a younger age (61 versus 64 years; $P = 0.04$) and were more likely to have clinically significant disease than *BRCA2* non-carriers (77% versus 40%; $P = 0.01$)[48]. Cancer incidences per

1,000 person-years were 19 in *BRCA2* carriers, 12 in *BRCA2* non-carriers, 14 in *BRCA1* carriers and 11 in *BRCA1* non-carriers[48]. Thus, the NCCN Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic (Version 1.2022) guideline recommends that men with *BRCA2* mutations start PSA screening at the age of 40 and that men with *BRCA1* mutations consider the same[9]. The NCCN Prostate Cancer Early Detection Guideline (Version 2.2020) recommends considering shared decision-making for men carrying *BRCA1* or *BRCA2* mutations regarding prostate cancer screening starting at the age of 40 years and to consider annual versus every other year screening[49] (TABLE 1). Initial results from prostate cancer screening in men with pathogenic variants in DNA MMR genes were also reported in the IMPACT study in 2021 (REF.[50]). Among 962 men enrolled, including those carrying and not carrying DNA MMR mutations, prostate cancer incidence (using a PSA threshold of >3.0 ng/ml) was higher in *MSH2* carriers than in *MSH2* non-carriers (4.3% versus 0.5%; $P = 0.011$) and in *MSH6* carriers than in *MSH6* non-carriers (3.0% versus 0%; $P = 0.034$)[50]. The overall positive predictive value of biopsy using a PSA threshold of 3.0 ng/ml was 51.4% (95% CI 34.0–68.6)[50]. To inform further strategies for prostate cancer screening and to encompass other genes now available on prostate cancer multigene panels, recommendations from the Philadelphia Prostate Cancer Consensus Conference 2019 were published for prostate cancer screening based on mutation status and age at diagnosis of prostate cancer in the family[2] (TABLE 1). In these recommendations, agreement to start PSA screening at the age of 40 years or 10 years before the youngest age at prostate cancer diagnosis among men carrying *BRCA2* mutations, and to consider the same in men with *BRCA1, ATM, HOXB13* and DNA MMR mutations is strong[2]. Currently, prophylactic prostatectomy is not indicated for mutation carriers.

Genetically based management of men with early-stage prostate cancer is also evolving regarding active surveillance discussions[51]. In one study, 6 of 11 men with *BRCA2* mutations on active surveillance had significant upgrading of biopsy samples, either scheduled or prompted by serum PSA levels, compared with 283 of 1,200 non-*BRCA2* carriers (adjusted HR 2.74; 95% CI 1.26–5.96, $P = 0.01$)[51]. Surveillance biopsies were performed at 1–2 years after prostate cancer diagnosis based on the cohorts included in the analysis[51]. These early results point to the potential need to include germline test results, particularly for *BRCA2* mutations, in active surveillance discussions; further data are needed for definitive recommendations and current practice is evolving based on expert consensus[2,52].

Prostate cancer is an important urological malignancy with increasing options for precision medicine for men with mCRPC[2,4–7,53–64]. Genetic results are increasingly influencing choice of therapy, such as PARP inhibitors for men with mCRPC with mutations in DNA repair genes, particularly *BRCA1* and/or *BRCA2* (REFS[4–7,53–56,62]). Genetic mutations that influence treatment decisions can be from germline testing or somatic testing and, therefore, might be based on hereditary or acquired genetic mutations, respectively[7].

Initially, data from phase II trials led to FDA designations for PARP inhibitors including olaparib, rucaparib and niraparib for men with mCRPC with germline or somatic alterations in DNA repair genes involved in homologous recombination repair (such as *BRCA1* and *BRCA2*) and DNA damage signalling and checkpoint regulation (for example, *ATM*)[53–55,61,62]. In 2020, the FDA approved two PARP inhibitors, olaparib and rucaparib, for men with mCRPC with specific DNA repair defects on progression after standard lines of therapy[5,6]. PARP inhibitors work by using the concept of 'synthetic lethality', in which the co-ordinated effort of repairing single-strand DNA breaks by PARP1 and double-strand breaks by homologous recombination repair is compromised[62]. In individuals who carry *BRCA1* or *BRCA2* mutations, homologous recombination repair is defective and, therefore, PARP inhibition has clinical activity[62]. Rucaparib was granted accelerated approval for *BRCA1*-mutated or *BRCA2*-mutated mCRPC with previous treatment with androgen receptor-directed therapy and taxane-based chemotherapy based on demonstrated clinical responses in the TRITON2 study[6]. In TRITON2, overall response rates were reported to be 43.5% in men with *BRCA1* or *BRCA2* mutations with measurable disease (95% CI 31.0–56.7%) and PSA response rate was 54.8% (95% CI 45.2–64.1%)[6]. Olaparib was FDA approved for the treatment of mCRPC in men with deleterious or suspected deleterious germline or somatic homologous recombination repair gene mutations who had progressed following previous treatment with enzalutamide or abiraterone based on the PROfound study[5]. Men with *BRCA1* or *BRCA2* or *ATM* (cohort A) or multiple other DNA repair mutations (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*) (cohort B) were randomized to receive olaparib 300 mg twice a day or enzalutamide or abiraterone. Progression-free survival was significantly longer for men in cohort A treated with olaparib than treatment with abiraterone or enzalutamide (median 7.4 versus 3.6 months; $P < 0.001$)[5]. Furthermore, overall survival was also superior for men in cohort A treated with olaparib to those who received abiraterone or enzalutamide (median 19.1 versus 14.7 months, $P = 0.02$)[64]. Multiple PARP inhibitors are being studied for the treatment of prostate cancer[56]. These trials include PARP inhibitors alone or in combination with androgen receptor signalling inhibitors, immune checkpoint inhibitors, chemotherapy or other agents[56].

Immunotherapy with pembrolizumab for prostate cancer is another area of advance in treatment for which assessment of DNA MMR deficiency is performed on tumour tissue, potentially leading to suspicion of Lynch syndrome[7,57,58]. The mechanism of action is complex; agents such as pembrolizumab promote tumour cell death by binding to T cell PD1 receptors and disrupting interaction with PDL1 molecules on tumour cells, enabling immune attack on a tumour[57,63]. In 2017, the FDA approved pembrolizumab for the treatment of all solid tumours, including prostate cancer, that exhibit MMR deficiency and/or exhibit microsatellite instability[57,58]. Approximately 5–10% of prostate cancers

exhibit MMR deficiency and, therefore, a subset of these patients with prostate cancer might be candidates for pembrolizumab[59]. Clinical trials are ongoing and further data are emerging regarding additional biomarkers of response to immune checkpoint inhibitors in men with prostate cancer[58,60]. Pembrolizumab eligibility is based on MMR deficiency or microsatellite instability status determined in tumours, but the somatic genomic analysis results might point to the need to evaluate the germline for Lynch syndrome[39].

NCCN guidelines address precision management of prostate cancer and are regularly updated[7]. The NCCN Prostate Cancer (Version 2.2021) guideline states that for men with mCRPC, alterations in DNA repair genes such as *BRCA1, BRCA2* and *ATM* might indicate PARP inhibitor therapy[7]. This guideline further suggests consideration of MMR deficiency or microsatellite status for pembrolizumab candidacy[7].

Overall, genetic information has become central to management approaches for prostate cancer, with a rising role in determining which precision medicine to choose, early-stage disease management and screening[7,9]. Olaparib and rucaparib are FDA approved for the treatment of men with mCRPC after progression on various standard therapies, and have unique approvals based on a spectrum of germline mutations[5,6]. Thus, genetic testing and genetic counselling need to be considered by urologists and oncologists for appropriate patients during the course of management or treatment.

Genetics care delivery

Traditionally, genetics care delivery has been conducted through genetic counselling by specialist genetics counsellors; however, novel approaches are also being used to improve accessibility and speed.

Genetic counselling. Many patients with prostate cancer or at risk of developing prostate cancer are now increasingly in need of germline testing[2,7,9], necessitating pre-test informed decision-making for germline testing that addresses precision management and screening and encompasses hereditary cancer management. Genetics care delivery can occur through the traditional approach of referral to genetic counselling or, increasingly, by using hybrid approaches to handle the rising volume of patients in need of germline testing and reduce barriers to care[14–17]. Health-care providers and genetic counsellors need to have a working knowledge of hereditary cancer assessment, the nuances of genetic evaluation, and prostate cancer management across the stage and risk spectrum (FIG. 1; BOX 1).

The generally accepted model of genetic counselling can be divided into pre-test counselling (before genetic testing) and post-test counselling (after test results return)[8,10–12] (FIG. 1). The pre-test counselling visit entails gaining knowledge of a patient's personal medical history, family history and previous genetic testing in the family[8,10–12]. A three-generation pedigree, including the patient's medical history, cancers in male and female relatives, and ethnicity, is gathered at the pre-test session. This information is used to assess the patient's risk of carrying a mutation and informs the strategy for germline testing (genes to include, panel to use, etc.) to fully assess for an associated cancer predisposition syndrome[8,10–12]. Some 'red flags' indicating a suspected hereditary cancer syndrome include personal and/or family history of cancers and other clinical features known to be associated with specific genetic syndromes, cancers diagnosed at unusually young ages, multiple blood relatives across generations diagnosed with similar or genetically linked cancers, a personal history of bilateral and/or multiple primary cancers, and an ethnic background known to increase the risk of hereditary cancer (such as Ashkenazi Jewish ancestry)[8–12,28,29].

Genetic counsellors typically have an education-oriented approach to the counselling session that enables the patient to make an informed decision while addressing psychosocial concerns[10]. The pre-test discussion comprises multiple components, including the purpose of testing (precision therapy, surgical decision-making, risk assessment, effect on screening, cascade testing), estimates of cancer risk, risks and benefits of testing, types of test results that could be returned (pathogenic or probable pathogenic variant, VUS, negative), options for multigene panel testing, cost of genetic testing, and psychological counselling and support[8,10–13]. Communication of genetic risk for at-risk individuals also involves a discussion of statistical probabilities for mutation presence and implications for personal and family cancer risk. In the advanced-cancer setting, genetic counsellors need to adapt counselling models towards how genetic testing might inform options for targeted therapy and guide panel testing[2,4,7,14].

Another component of pre-test counselling is discussion of the benefits and limitations of genetic testing[2,8–13]. Benefits of genetic testing include information for medical management, precision therapy options, identification of additional cancer risks to inform screening, and identification of at-risk family members to address cancer risks. Limitations of genetic testing include technical issues (such as the inability to detect certain genetic variants with standard testing technology), limited knowledge of cancer risk or management for some genes, identification of VUS and complex genetic findings[8–13]. The chances of having a VUS reported are increased when an increased number of genes are tested[2,65]. Furthermore, VUS rates are increased in patient populations with diverse race or ethnic backgrounds[65]. Additional considerations include genetic discrimination protections and gaps in protection under the 2008 Genetic Information Nondiscrimination Act (GINA)[66]. The GINA law provides protection related to health insurance and employment discrimination for mutation carriers in most scenarios. The GINA law does not provide protections for military health insurance and employment, life insurance, disability and long-term care insurance[66]. Currently, this law only applies to adults who have been tested; how the law will apply to blood relatives regarding effect on insurance might evolve over time.

In a post-test disclosure session, genetic test results are discussed with the patient along with recommendations. Genetic results are reviewed to enhance understanding of associated medical implications for patients

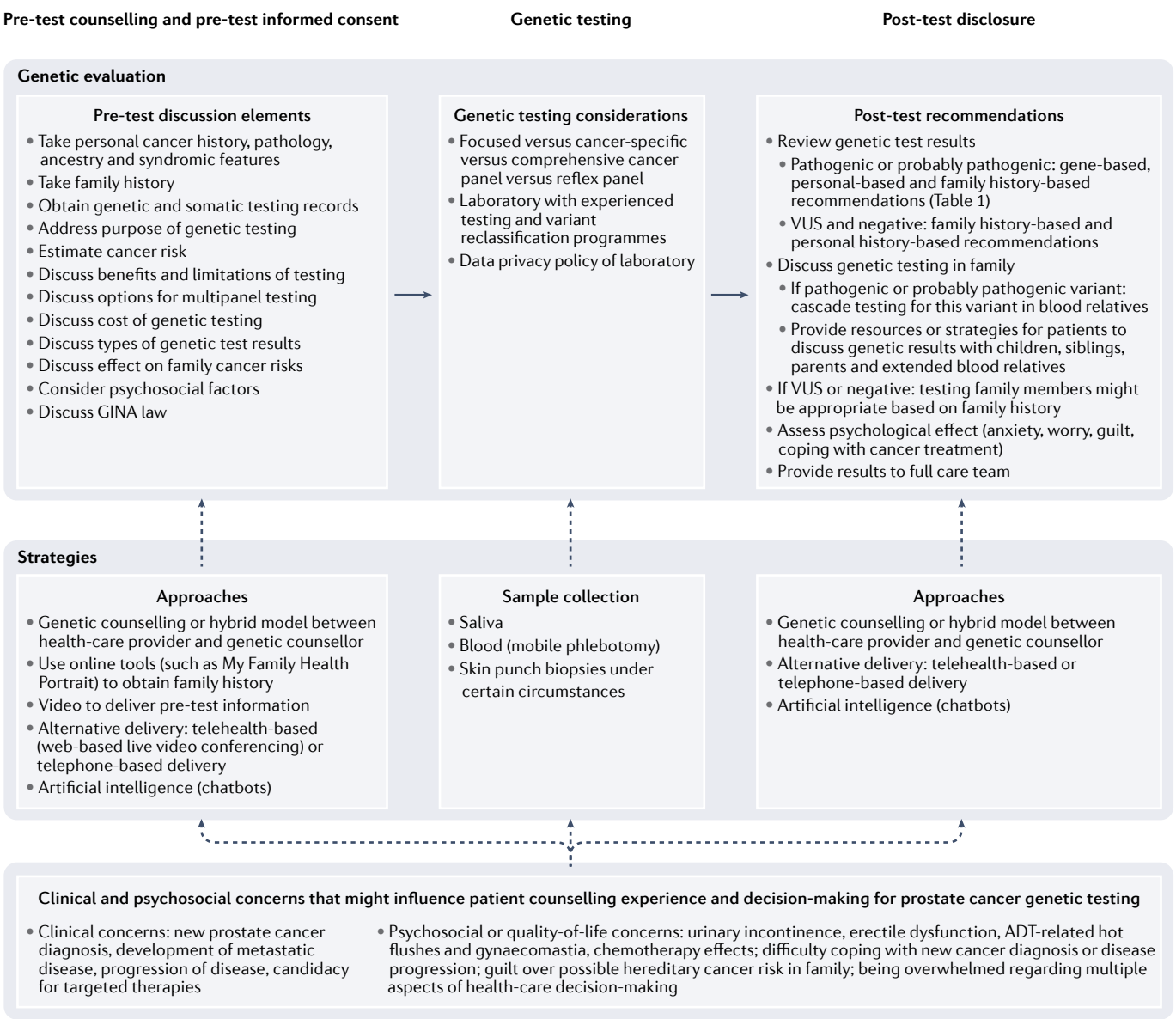

Fig. 1 | **Genetic evaluation process for patients with or at risk of developing prostate cancer.** The process and elements involved in pre-test counselling and informed consent, genetic testing and post-test disclosure. Special considerations in each step in the process and unique clinical and psychosocial concerns that can influence decision-making are shown. ADT, androgen-deprivation therapy; GINA, Genetic Information Nondiscrimination Act; VUS, variants of uncertain significance.

and their family members while also addressing emotional and psychosocial needs[8–13]. Medical management discussion is based on genetic testing results and the patient's specific family history. Pathogenic or probable pathogenic variants can influence medical management for urological malignancies, cancer risk recommendations and cascade testing of blood relatives[2,7,9]. Coordination of cancer screening for mutations can be complex, as multiple cancer risks might need to be addressed. For example, men with *BRCA2* mutations without prostate cancer are usually recommended to start prostate cancer screening at the age of 40 years by their urologist or their primary-care doctor[9]; they are also recommended to have clinical breast examinations by their physician starting at the age of 35 years, discuss pancreatic cancer screening (if a family history of pancreatic cancer exists) with a gastroenterologist and be evaluated by a dermatologist for risk of melanoma[9]. These visits can be coordinated by genetic counsellors, the patient's primary-care doctor or be the responsibility of the patient. Improved support for patients who carry mutations to have multidisciplinary screening is needed.

VUS are also reported in genetic test results; patients need to understand how to interpret these findings. VUS do not affect management at the time of reporting[2,10]. VUS are followed over time by genetic testing laboratories for evidence in support of or against pathogenicity[67,68]. A 2018 retrospective cohort study including over 1 million genetic tests showed that 7.7% of VUS results were reclassified, of which 91.2% were downgraded to benign

or probably benign[68]. Thus, counselling sessions need to provide this information to patients and include plans to recontact patients if VUS reclassification updates occur, to provide revised recommendations as needed. For patients who receive VUS results or totally negative genetic results, referral to genetic counselling might be needed, and, if family cancer history is strong, they might need to receive comprehensive family history-based recommendations or to determine whether additional relatives need germline testing[1,2,4].

Cascade testing in a family of a patient with a pathogenic variant or probable pathogenic variant (mutation) takes co-ordinated effort between a genetic counsellor, the patient, and their family. Once a patient is identified as having a pathogenic variant or probable pathogenic variant, the genetic counsellor typically needs to obtain a release of information from the patient to use this information to guide genetic testing of blood relatives. The patient needs to communicate information of their genetic test results to blood relatives, who then need to contact their local genetics services to make an appointment for genetic counselling and genetic testing. These genetic counselling sessions for relatives will include the genetic results of the proband (original patient), the relative's medical history and family history, discussion of pre-test elements, and optimal testing approach[10]. The relative will next undergo genetic testing and then return for disclosure of results and recommendations based on their test results[10].

Communication of genetic results and recommendations in families can be challenging. Providing resources or strategies for patients to discuss genetic results with children, siblings, parents and extended blood relatives is an important part of genetic counselling[69,70]. Some controversies that genetic counsellors can encounter centre around difficult family dynamics, when family members do not wish to discuss their genetic results with relatives or have little contact with family members[69,70]. In such cases, balancing a patient's autonomy and confidentiality with a duty to warn relatives of the potential genetic risk becomes difficult[69–71]. The American Society of Human Genetics permits a provider to disclose information to a third party only under specific circumstances, such as when encouragement to disclose to family members has failed and a serious risk that is identifiable and can be prevented, treated or reduced by early monitoring exists[71].

In summary, the genetic counselling process encompasses pre-test and post-test sessions, focuses on educating and aiding the patient in choosing appropriate genetic testing, and considers psychosocial concerns that might influence decision-making for genetic testing[8–13]. Genetic test results are not always straightforward as genetic testing technology is limited and guidelines can vary[7,9,10,39]. Results and implications for patients and family members are important to address, along with sharing of results with family members to enable cascade testing[10].

Novel genetics care delivery approaches. In the era of expanded germline testing and precision medicine, the traditional model of referral of all patients to genetic counselling has needed to be adapted for increased access to testing, rapid return of results, and to mitigate the relative shortage of genetic counselling[14–16]. Adaptations to the traditional genetic counselling model have, therefore, been emerging, in which oncologists and urologists are becoming more involved in both pre-test and post-test contexts (FIG. 1; BOX 1). In this hybrid, point-of-care model, the physician performs the pre-test consent and orders genetic testing. When results are returned, they review the results with the patient regarding effect on treatment and then refer a subset of patients to a genetic counsellor to discuss genetic results, provide full recommendations based on personal and family history, and discuss cascade testing or further testing in the family as indicated[14,17]. This approach facilitates rapid return of genetic results, but some complexities in practice need to be considered and addressed proactively (BOX 1). One consideration is the time needed to perform appropriate pre-test informed consent for genetic testing. Multiple elements need to be discussed and understood by patients to make an informed decision for testing[2,7,9,10]. To facilitate pre-test information delivery, videos are being studied in which patients view a genetics education video to understand the genetic testing process and considerations before pursuing genetic testing[72]. Patient-reported outcomes in a male population undergoing prostate cancer germline testing from one study ($n = 127$) revealed that most men (71%) chose a pre-test video compared with genetic counselling (29%) ($P < 0.001$), with no negative effect on patient satisfaction, decisional conflict for genetic testing, cancer genetics knowledge or uptake of genetic testing[72].

In a hybrid model, intake of a three-generation pedigree to accurately determine extent of testing might be challenging in busy clinics. One approach to increase the yield of full family history intake in the pre-test setting includes use of online tools (such as My Family Health Portrait from the Centers for Disease Control and Prevention)[73] into which patients can input family history at home before their appointments. Furthermore, consideration of optimal panels for testing by ordering physicians, such as focused, guideline-based, comprehensive or reflex panels, which cover the patient's medical history, family history and take patient preferences into account, becomes important[2]. In particular, reflex testing might be preferable in hybrid models to enable flexibility for upfront ordering and expanded testing based on full family history information obtained along the care pathway[2]. In the USA, insurance coverage can also be a limiting factor as some policies require the patient to undergo genetic counselling with a certified genetics professional before undergoing genetic testing in order for insurance to cover the cost of testing. Various countries have national or private policies that also need to be followed. Urologists or oncologists seeking to employ hybrid genetics care delivery models in their practices are encouraged to have increased working knowledge of the principles and practice of genetic counselling and genetic testing[2,74]. Finally, proactive development of genetics care delivery and referral criteria between health-care providers and genetic counsellors is encouraged when instituting hybrid models

in practice to streamline pre-test and post-test care and optimize genetic testing[14] (BOX 1; FIG. 1).

To enhance access to genetic counselling, novel technology-based approaches are in use or under development. Telephone-based and telehealth-based (also called telegenetics when in the context of providing web-based video-conferencing genetic consultation) are alternative ways of disseminating genetic counselling[75,76]. More research is needed concerning the use of these approaches in patients with prostate cancer, but previous research in women primarily engaged in genetic counselling for HBOC reported that telephone-based genetic counselling was not inferior to standard genetic counselling for patient-reported outcomes[77,78]. Results of one randomized trial that included 669 women undergoing genetic counselling for HBOC showed the non-inferiority of telephone-based genetic counselling versus in-person genetic counselling for knowledge, satisfaction, decision conflict, distress and quality of life[77]. Results of another study showed that anxiety, cancer-specific distress, perceived personal control, and decisional conflict for genetic testing were not inferior at the 1-year follow-up point between telephone-based counselling and in-person counselling among women undergoing evaluation for HBOC[78]. Web-based telegenetics has also been reported to have high satisfaction rates among patients undergoing genetic counselling and genetic testing[76]. A randomized trial of 130 patients (90% of whom were women) undergoing cancer genetic counselling primarily for HBOC or Lynch syndrome reported no difference in patient satisfaction between telegenetics and in-person genetic counselling ($P = 0.03$)[76]. Key barriers to address include comfort with and access to technology, reimbursement, co-ordination of sample collection for genetic testing, and privacy and ethical issues. In the virtual era of the COVID-19 pandemic, the importance of remote genetics care delivery, such as telegenetic visits, and remote sample collection, such as through mobile phlebotomy, have increased[79,80]. Finally, chatbots are also being studied in genetic education, consent and counselling delivery[81]. A chatbot is a computer programme that simulates human conversations and enables communication of information by messages or voice command[81]. Chatbots have been developed to aid delivery of genetic testing consent, follow-up monitoring and cascade testing of family members, with patients supporting this technology from focus group data[81]. In one study of focus group participants enrolled in a genomics research programme in which chatbots were used, participants were supported using chatbots to consent to genomics research and to interact with health-care providers for recommendations and co-ordination of care, as well as to share genetic information with relatives[81]. Further research is needed among men with prostate cancer regarding utility and satisfaction with genetics care delivery models and tools for male-specific patient-reported outcomes.

Overall, with the rising volume of patients in need of genetic counselling and germline testing, current and future models of genetic counselling need to be adapted to provide responsible delivery of genetic counselling to patients on an individualized basis.

Unique aspects of genetic counselling for men with prostate cancer

With the expansion of genetic testing criteria for prostate cancer[7,9], improved insight is needed in to how men process the pre-test counselling discussion, understand their genetic results and handle the anxiety or guilt of having an inherited genetic mutation. Many men might have high satisfaction with their genetic evaluation experience, but some men may have difficulty with the process. Patients might need additional resources or support to understand their genetic results. For example, results are emerging that report that some men who undergo prostate cancer genetic testing might have limited understanding of VUS[82]. Given that ~30% of men undergoing prostate cancer germline testing will have VUS reported[1,83], this proportion represents a substantial number of men in need of reinforcement of information to enhance understanding of results and to limit propagation of misinformation in families[82].

Furthermore, understanding quality-of-life issues for men dealing with prostate cancer treatment across the stage spectrum is needed when discussing germline testing. Men might be dealing with treatment-related effects, such as urinary incontinence, erectile dysfunction, fatigue, hot flushes, weight gain, gynaecomastia, or loss of libido and/or sexual dysfunction caused by treatments including prostatectomy, radiotherapy, androgen deprivation therapy or chemotherapy[84–86]. Men on active surveillance might fear disease progression and men with biochemical recurrence might fear disease recurrence (FIG. 1). Clinical experience shows that most of the time these issues are not barriers for men to undergo germline testing, but occasionally current quality-of-life issues might make processing genetic information difficult or overwhelming[87]. Difficulty coping with progressive metastatic disease, new development of metastatic disease, or a new diagnosis of prostate cancer with the multitude of treatment or management options could make informed decision-making for germline testing challenging for some men. If men initially decline germline testing, repeated offering of testing to eligible men would be encouraged. Dedicated patient-reported outcomes data in male populations undergoing genetic testing for prostate cancer are needed. A patient-driven registry (PROGRESS Registry) is currently actively recruiting men in the USA who have had prostate cancer-related germline testing to garner patient experiences to support development of resources for men and their families.

Overall, identifying and addressing the clinical, genetic and psychosocial issues for men is important for facilitating decision-making on genetic testing and for supporting men in their cancer treatment and genetic evaluation experience.

Conclusions

Genetic evaluation for men with prostate cancer or at risk of prostate cancer development is a specialized area requiring knowledge of pre-test genetic information, genetic testing options and approaches, complex hereditary cancer syndromes, and unique considerations important for patients and providers to understand.

Genetic counselling, hybrid models, and technology-based approaches are essential to provide access to genetic testing for men and their families. This population of patients deserves dedicated studies of patient-reported outcomes and increased knowledge of genetics contributing to prostate cancer across diverse populations to enhance the genetic evaluation impact and experience for men and their families.

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