Gynecologic Oncology 181 (2024) 170–178

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Germline and somatic testing for ovarian Cancer: An SGO clinical practice statement

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HIGHLIGHTS

- Universal genetic testing for patient with ovarian cancer remains underutilized, especially among underserved populations.
- All patients with epithelial ovarian cancer should be offered germline genetic testing.
- Somatic genetic testing of ovarian tumors can identify actionable changes which may influence therapeutic decisions.
- Measurement of homologous recombination deficiency can guide PARP inhibitor therapy in patients with ovarian cancer.
- Mainstreaming genetic counseling may improve genetic testing rates.

ARTICLE INFO

Article history:
Received 29 September 2023
Received in revised form 9 December 2023
Accepted 13 December 2023
Available online xxxx

Keywords:
Genetic screening
Somatic testing
Germline testing
Ovarian cancer

ABSTRACT

Germline and somatic genetic testing have become critical components of care for people with ovarian cancer. The identification of germline and somatic pathogenic variants as well as homologous recombination deficiency can contribute to the prediction of treatment response, prognostic outcome, and suitability for targeted agents (e.g. poly (ADP-ribose) polymerase (PARP) inhibitors). Furthermore, identifying germline pathogenic variants can prompt cascade genetic testing for at-risk relatives. Despite the clinical benefits and consensus recommendations from several organizations calling for universal genetic testing in ovarian cancer, only about one third of patients complete germline or somatic genetic testing. The members of the Society of Gynecologic Oncology (SGO) Clinical Practice Committee have composed this statement to provide an overview of germline and somatic genetic testing for patients with epithelial ovarian cancer, focusing on available testing modalities and options for care delivery.

1. Introduction

A comprehensive, evidence-based approach to germline and somatic genetic testing in people with ovarian cancer is critical due to the high prevalence of pathogenic variants (also referred to as "gene mutations") within this population. Results from this genetic testing hold significant implications for patients and their relatives. Approximately 25% of patients with ovarian cancer (including epithelial ovarian, primary peritoneal and fallopian tube) have a pathogenic variant in a cancer-associated gene on germline assessment [1]. An additional 6–7% of patients have a somatic pathogenic variant on tumor testing and 11–15% of patients' tumors demonstrate homologous recombination deficiency (HRD) through epigenetic silencing of the *BRCA1/2* genes [2,3]. Furthermore, other somatic findings can guide treatment, including expression of folate receptor alpha for mirvetuximab soravtansine [4] and, rarely, *RET and NTRK* gene fusions for RET and TRK inhibitors [5].

The identification of germline and somatic pathogenic variants as well as HRD can contribute to the prediction of treatment response, prognostic outcome, and suitability for targeted agents (e.g. poly (ADP-ribose) polymerase (PARP) inhibitors). Germline genetic testing results can inform risk for other malignancies and prompt cascade testing and cancer risk management for at-risk relatives. Multiple organizations including the Society of Gynecologic Oncology (SGO), American

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https://doi.org/10.1016/j.ygyno.2023.12.010
0090-8258/

Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN), United States Preventive Services Task Force (USPSTF), and American College of Obstetricians and Gynecologists (ACOG) recommend universal germline genetic assessment for all those diagnosed with epithelial ovarian cancer [6–10]. Despite this consensus, only about one third of patients with ovarian cancer complete the requisite germline or somatic genetic testing [8,11–13]. Furthermore, individuals of racial and ethnic minority status and those of lower socioeconomic status have even more pronounced underutilization of recommended genetic services [11,14]. The purpose of this statement is to provide an overview of germline and somatic genetic testing for patients with epithelial ovarian cancer, focusing on available testing modalities and options for care delivery.

2. Germline genetic testing

Germline genetic testing refers to the sequencing of germline DNA which is the the tissue derived from nucleated cells that becomes incorporated into the DNA of every cell in the body [15]. Germline DNA can be extracted from blood, serum, or saliva. The DNA is evaluated for variants, defined as genetic alterations that occur within all cells, including germ cells, such that the modification can be passed to subsequent generations. The majority of deleterious germline genetic alterations are inherited, with de novo genetic alterations being quite rare [16,17].

Testing is performed by clinical laboratories certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA). Genetic testing laboratories often offer several options for germline testing, ranging from single-targeted detection of a known familial pathogenic variant to large multigene panels including dozens of cancer-associated genes. Historically, genetic profiling relied on single-gene testing by gene Sanger DNA sequencing. This sequencing method was limited by cost, depth of coverage, and the ability to analyze only a small number of genes at once. The advent of commercially available next-generation sequencing (NGS) revolutionized patient access to genetic testing. NGS uses massive parallel sequencing to analyze numerous genes in a single assay, resulting in cost-effective, high-throughput, comprehensive sequencing with a high depth of coverage [18]. During the development of these technologies, it was standard practice for the US Patent Office to issue patents on human genes. In 2013, the US Supreme Court unanimously ruled that DNA segments are products of nature and could not be patented as an invention. This ruling invalidated exclusive gene patent rights and resulted in a shift towards affordable use of larger multigene panels, which can identify sequence variants as well as large rearrangements and deletions [19].

The American College of Medical Genetics and Genomics and the Association for Molecular pathology recommend the use of specific terminology to describe variants identified in genes that cause Mendelian disorders. This includes “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” [20]. Variants of uncertain significance (VUS) are classified as such because there is insufficient evidence to determine whether the genetic alteration impacts disease risk and, therefore, this result should not be used for clinical decision-making or medical management [6,7]. VUS reclassification rates reported in the literature range from 8 to 28%, with most being downgraded to likely benign/benign, and fewer being upgraded to likely pathogenic/pathogenic [21–26]. Most genetic testing laboratories report these reclassifications to the ordering provider. Providers should consider establishing a standard practice for periodic monitoring of changes in classification of VUS. Additionally, patients should be educated on publicly available resources including genetic data repositories containing updated information on variant classification (e.g. Clinvar https://www.ncbi.nlm.nih.gov/clinvar/) and resources made available by commercial laboratoires that perform this testing.

Today, there is an ongoing debate challenging the current standard whereby germline genetic testing is limited to those patients with cancer at highest risk for carrying pathogenic variants, with many calling for unrestricted testing among all solid tumor patients [27]. Based on the high incidence of pathogenic variants and implications for treatment and prognosis, the SGO and several other organizations recommended universal germline genetic testing for patients with epithelial ovarian cancer [28]. However, the SGO does not endorse a single clinically available germline testing assay. Providers should select the germline genetic test based on the personal and family history of each patient and their preferences regarding which genes to be included in the evaluation. Insurance coverage of individual tests and affordability for the patient may also guide test selection.

3. Somatic testing

In contrast to germline variants, somatic variants are defined as genetic alterations that are acquiried in certain cells of the body, including tumor cells, and excluding germ cells. Such alterations are spontaneous and non-inheritable. Historically, performing comprehensive tumor sequencing was hindered by cost and technology. More recently, advances in NGS platforms have allowed for high-quality, rapid, and more affordable tumor mutational profiling in the clinical setting. Somatic tumor testing may employ targeted gene panel sequencing (specific genes of interest only), whole exome sequencing (WES) (protein-coding regions of the genome), or whole genome sequencing (WGS) (both coding and non-coding regions). Typically, as more of the genome is sequenced, the sequencing read-depth (the expected coverage on the basis of the number and length of high-quality reads) decreases and cost increases [29]. Depth of sequencing increases the ability to distinguish small point mutations from sequencing errors or normal variants in a gene. In the clinical setting, commercially available tumor tests typically use targeted NGS panels rather than WES or WGS due to cost and ease of interpretation. Some platforms incorporate a matched normal tissue sample to compare with the known tumor sample which can aid in detecting somatic versus germline origin of a pathogenic variant.

Somatic genetic testing of tumors can lead to the discovery of actionable changes which may influence therapeutic decisions. Pathogenic variants in *BRCA1* and *BRCA2*, whether inherited or acquired, are an important cause of HRD and render cells particularly sensitive to PARP inhibitors. HRD can also result from variants in other homologous recombination genes such as *RAD51C* and *RAD51D*, through mechanisms such as epigenetic silencing of homologous recombination genes (including *BRCA1* and *RAD51C* promotor methylation) [30]. In the absence of germline variants, acquired somatic variants in *BRCA1* and *BRCA2* are found in approximately 6–7% of ovarian cancers, and an additional 11–15% may demonstrate homologous recombination deficiency (HRD) through epigenetic silencing of *BRCA* and other HRD genes [2,3].

Comprehensive genomic analysis suggests that homologous recombination is defective in approximately 50% of high grade serous ovarian cancers [31] (see Fig. 1). Furthermore, identifying HRD in the tumor holds implications for treatment (e.g. PARP inhibitor therapy) and, thus, knowledge of HRD status is an important part of the treatment plan for patients with ovarian cancer. There are several commercially available tests aimed at predicting the presence of HRD based on genomic features of the tumor. One such method of determining HRD is to measure genomic instability in the tumor, which is an indicator of past defective homologous recombination DNA repair leading to an accumulation of measurable genetic damage. Rather than analyzing individual genes and their variants (causes of HRD), this somatic tumor analysis measures areas of “genomic scarring” (effects of HRD) including large scale transition state changes, loss of heterozygosity, and telomeric allelic imbalances [32]. A score (also called a “genomic instability score”) can be calculated based on these features and this score has been used as a surrogate marker in clinical trials to determine the likelihood of response to PARP inhibitor therapy. Currently, there is a paucity of literature comparing different methods of HRD assessment

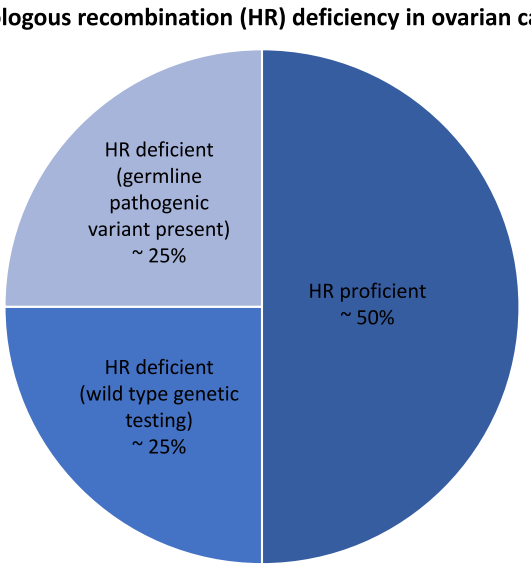

Fig. 1. Homologous recombination (HR) deficiency in ovarian cancer.

and further research is needed examining available genomic and functional assays and the clinical implications of their results [33].

There are many clinically available NGS somatic testing assays, and the SGO does not endorse the use of one over another. A list of commonly available commercial somatic tumor testing platforms is included in Table 1. Many, but not all, of these platforms offer HRD scoring systems and data comprehensively comparing the available platforms are lacking. Information regarding somatic testing is also available via the SGO/Association of Community Cancer Centers (ACCC) Joint Education Collaborative (https://www.sgo.org/practice-management/collaborations/) [34].

In addition to indicators of HRD, tumor sequencing can detect other targetable variants and microsatellite instability or a high tumor mutational burden, which, while relatively rare in ovarian cancer, may support the use of immunotherapy. Future translational research endpoints in gynecologic cancer clinical trials are needed to expand the repertoire of actionable biomarkers.

4. Guidance regarding germline and somatic genetic testing strategies

There are several approaches to genetic assessment, and providers must individually decide which germline testing to use as well as which patients should undergo somatic tumor testing. We have addressed some common areas of interest based on the current literature and the NCCN guidelines for genetic assessment in ovarian cancer [7].

4.1. When is it appropriate to order single-gene vs. multi-gene germline panel testing?

NGS allows for the simultaneous analysis of several genes and the efficacy of this process has resulted in a shift away from single gene assessment (traditionally *BRCA1/2* genetic testing) towards more comprehensive panels that cover larger sets of genes associated with cancer. The benefits of multi-gene panels include: 1) An individual's personal/family history may increase risk for several pathogenic variants, and therefore, multi-gene testing offers the most time- and cost-efficient method of identification with the highest yield of determining the familial variant. 2) Individuals can have pathogenic variants in more than one gene and, therefore, an actionable finding could be missed with limited single gene testing. 3) Pathogenic variants in some autosomal dominant cancer-related genes including *ATM, BRCA1/2, BRIP1, MLH1, MSH2, MSH6, PMS2, EPCAM, MSH3, NBN, PALB2*, and *RAD51C* are also associated with autosomal recessive conditions and, therefore, can have implications for the offspring of families when both parents carry the pathogenic variant [7].

The concerns with adopting multigene panel testing include: 1) Multi-gene panels can include intermediate/moderate risk genes with limited associated data on cancer risk and/or no established guidelines for cancer risk-reduction. 2) As additional genes are added to panels, the risk of detecting a VUS increases. A study of 2984 patients with cancer undergoing an 80-gene germline NGS platform identified a VUS in 47% of patients [35]. This highlights the need for pre-test counseling with patients to comprehensively review the possible outcomes and advantages/disadvantages of large panels. VUS pose a dilemma for patients and providers as the genetic alteration either represents a benign polymorphism or an increased risk for cancer. Furthermore, the interpretation of a VUS can vary between clinical laboratories, adding complexity to clinical counseling. The provider must be prepared to counsel the patient regarding this result and establish a follow-up plan to monitor the VUS for updated classification status. 3) As additional genes are added to panels, the risk of identifying mosaicism (multiple cell lineages with different genotypes within the same individual) and clonal hematopoiesis of indeterminate potential (CHIP) increases. CHIP refers to the presence of clonal populations of hematopoietic stem cells and has been found to be associated with blood cancer and coronary artery disease [36]. Providers must be prepared to counsel patients on these findings and follow-up with the results when indicated. 4) Multi-gene panels often include polygenic risk scores. However, there are significant limitations in interpretation of risk scores and for most tumors, including ovarian, the scores are not yet validated for clinical management. 5) There are several commercially available tests on the market. Providers must consider several factors when selecting a multi-gene panel including the specific genes to be tested on the panel, turnaround time, variant classification, methods of DNA and/or RNA analysis, and cost. Furthermore, some testing laboratories offer financial assistance for family member cascade testing if a pathogenic variant is identified, which may improve the uptake rates of genetic testing among at-risk relatives [7].

4.2. Which patients with ovarian cancer should have somatic tumor testing performed in addition to germline testing?

Some providers prefer to order both germline and somatic testing on all patients with ovarian cancer. An alternative approach is to reserve somatic tumor testing for patients who do not have germline variants (to identify appropriate patients for maintenance PARP inhibitor therapy) or who experience disease recurrence (to identify actionable pathogenic variants which would inform treatment after first line therapy) (see Fig. 2). Somatic tumor testing alone has been proposed as a method to screen all patients with ovarian cancer and then triage those found to have somatic pathogenic variants to genetic counseling and further gremline genetic testing [37]. There are concerns with utilizing somatic testing alone. Sequencing of the tumor only, and not the germline, can miss approximately 10% of clinically actionable germline pathogenic variants [38]. Therefore, while tumor somatic testing can be considered complimentary to germline genetic testing in ovarian cancer, individuals with negative tumor profiling should still undergo germline testing. Additionally, insurance carriers may not pay for the repetition of tumor somatic testing. The tumor's somatic mutational landscape, capabilities of somatic testing, and relevant biomarkers can change over time. Therefore, if the results of somatic testing will not modify the treatment plan, the provider may want to reserve somatic testing for the future.

4.3. How should providers consider HRD testing alone versus comprehensive tumor molecular analysis?

For patients undergoing upfront treatment for ovarian cancer with negative germline genetic testing, somatic tumor testing should, at a

Table 1
Commonly available commercial somatic tumor testing platforms.

Tests	Sequencing Platform	Test features	HRD Score available	Genes Analyzed	Sample requirement	Manufacturer's Reported Turnaround Time	Website
Caris Molecular Intelligence Profile	Illumina	DNA mutations, CNVs, indels, MSI and TMB, karyotype, whole transcriptomic sequencing (fusion analysis, variant transcripts, gene expression), MMR IHC, ER/PR IHC, PD-L1 IHC, FOLR1 IHC. Genomic Scar Score (GSS). HRD testing performed by LOH.	Yes	>700 genes in targeted NGS panel >20,000 genes included in WES	Archival tissue: FFPE block (preferred) or 25 unstained slides with a minimum of 20% cells of malignant origin for DNA and 10% of malignant origin for RNA. Fresh Tissue: 4–6 biopsies with 18-gauge needle or 6–10 biopsies with 22-gauge needle in 10% neutral buffered formalin	10–14 days	https://www.carislifesciences.com/products-and-services/molecular-profiling/testing-menu/
FoundationOne CDx	Illumina	Base substitutions, CNVs, indels, MSI and TMB, selected genomic rearrangements and signatures, FOLR1 IHC, PD-L1 IHC (as add-on test). LOH score (previous available as separate test-FoundationFocus CDx BRCA LOH). HRD testing performed by LOH. FDA approved companion diagnostic test.	Yes	324 genes in targeted NGS panel	Archival tissue: FFPE block +1H&E slide or 10 unstained slides +1H&E slide with a minimum of 20% cells of malignant origin and surface area minimum of 25 mm^2	12 days or less	foundationmedicine.com/test/foundationone-cdx
Myriad MyChoice CDx	Illumina	SNVs, indels, large deletions and duplications in multiple genes related to HRD, Genomic Instability Score. HRD testing determined by multiple measures of genomic instability (LOH, TAI, LST). FDA approved companion diagnostic test	Yes	2 (BRCA1 and BRCA2) and assessment of LOH, TAI and LST across the genome	Archival tissue: FFPE block or 10 unstained slides. Surface area minimum of 25 mm^2	Not reported	https://myriad.com/oncology/mychoice-cdx/
Myriad Precise Tumor	Illumina	SNVs, indels, CNV, fusions, MSI, TMB, HER2/ ER/ PR IHC, PD-L1 (available as add-on test). HRD testing determined by multiple measures of genomic instability (LOH, telomeric-allelic imbalance, large-scale state transition).	Yes	523 genes genes in targeted NGS panel 56 genes included in RNA analysis	Archival tissue: FFPE block with surface area minimum of 25 mm^2 containing at least 40 μm of tumor (40 ng of DNA input) and 20% tumor purity. If only slides are available, one H&E slide +8 additional unstained 5 μm slides with 20–25 mm^2 tumor surface area.	Not reported	https://myriad.com/oncology/precise-tumor/
Tempus xT	Illumina	SNVs, indels, CNVs, rearrangements and fusions, MSI, TMB (PD-L1 IHC, MMR IHC, HRD and Tumor Origin testing available as add-on test).	Yes	648 genes in targeted NGS panel	Archival tissue: FFPE block or 10 unstained slides <6 years old with a minimum of 20% cells of malignant origin and 10% of malignant origin for RNA. Surface area minimum of 25 mm^2. Also requires whole blood.	8–10 days	https://www.tempus.com/oncology/genomic-profiling/

CNV = Copy number variants, MSI = Microsatelite Instability, TMB = tumor mutational burden, MMR = mismatch repair, indels = insertions and deletions, HRD (homologous recombination deficiency), TAI = Telomeric allelic imabalance, LST = large-scale transition state transitions

minimum, include molecular alterations that have immediate treatment implications. This includes BRCA1/2 somatic variants, loss of heterozygosity, and HRD status as these findings can guide the use of PARP inhibitor maintenance therapy [30]. For patients with recurrent ovarian cancer, the tumor molecular analysis should be more comprehensive, including BRCA1/2, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), BRAF, FRα, RET, and NTRK. Many of these tests involve analysis of immunohistochemical stains, copy number alterations, gene fusions products, splice variants and quantification of mutational burden (see Table 1 for availability of these ancillary molecular tests). Additionally, comprehensive tumor molecular analysis may be especially important for patients with ovarian cancers exhibiting more rare histologies where treatment options are more limited or offered only in the setting of a clinical trial [39]. Benefits of using HRD testing alone in the primary setting include: 1) potential cost-effectiveness when compared to comprehensive molecular profiling, and 2) reserving comprehensive molecular testing for future disease recurrence, as new biomarkers may be incorporated into routine clinical care. Benefits of comprehensive molecular testing at the time of disease diagnosis include: 1) identification

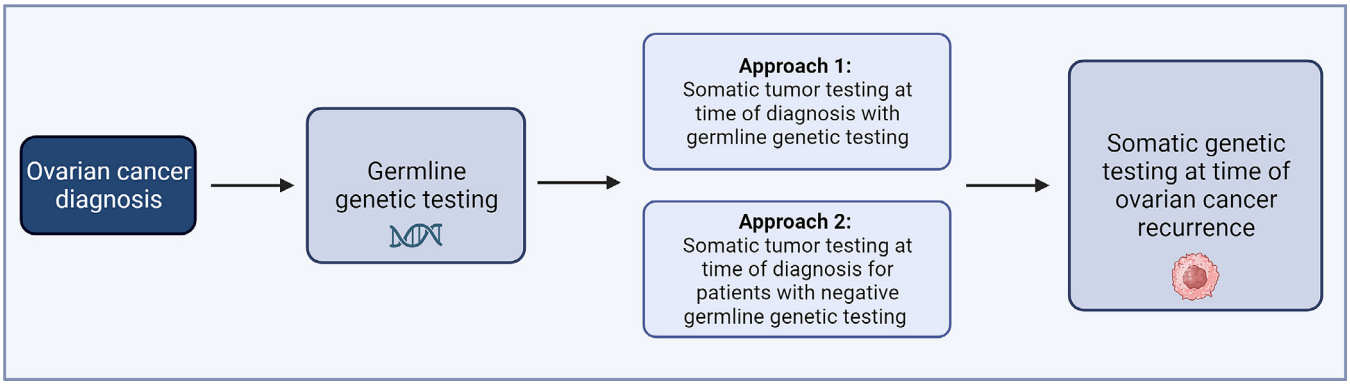

Fig. 2. Algorithm for genetic assessment in ovarian cancer.

of actionable biomarkers which can guide expedient care at the time of disease recurrence, and 2) early identification of individuals who may be appropriate candidates for biomarker-driven clinical trials.

4.4. When is it appropriate to repeat germline genetic testing?

There may be a role for multi-gene panel testing in patients that previously tested negative for a single syndrome. A series of patients who had noninformative testing prior to 2013 found that on retesting with multi-gene panels, 7% of patients were found to have pathogenic variants [40]. Additionally, patients with ovarian cancer and genetic testing limited to *BRCA1/2* can consider retesting as the literature suggests that up to 7% of patients with ovarian cancer will have pathogenic variants in genes other than *BRCA1/2* [41]. For patients with prior germline genetic testing, it is important to evaluate the source of testing and therefore, patients should be encouraged to obtain prior testing results. Commercial companies that offer testing for ancestry and/or general health information directly to consumers often utilize microarray based single nucleotide polymorphism testing. This testing has not been validated for germline cancer-associated pathogenic variants and can have an error rate of up to 40% [42]. Furthermore, these tests often only provide coverage of a small number of founder pathogenic variants. Confirmatory germline genetic testing by a certified clinical laboratory is recommended for all patients with prior direct-to-consumer commercial testing.

4.5. When is it appropriate to repeat somatic genetic testing?

It would be appropriate to repeat somatic tumor testing if new actionable molecular biomarkers with approved therapeutics have become available and were not interrogated at the time of the patient's prior somatic testing. An example of this would be FRα testing to determine eligibility for mirvetuximab sorvatansine in folate receptor alpha over-expressing recurrent ovarian cancer [43]. Understanding that the molecular profile of a tumor may change over time, especially after exposure to multiple lines of treatment, repeat biopsy and tumor profiling may yield novel and helpful information. However, repeat tissue sampling is not always clinically feasible, in which case, repeat somatic testing on archival tissue may be the best option.

5. Disparities and access to genetic testing

Despite the recommendations for universal germline genetic testing in ovarian cancer by multiple organizations, genetic testing remains underutilized, especially among underserved populations [6–10]. This is critical given the significant prevalence of pathogenic variants including *BRCA1/2* across racial and ethnic groups [44]. A recent systematic review and meta-analysis addressing genetic assessment for patients diagnosed with ovarian cancer found that only 39% of patients were referred to genetic counseling and 30% completed genetic testing. Furthermore, rates of genetic counseling and genetic testing differed by race, with genetic counseling completed by 43% of White patients, 24% of Black patients and 23% of Asian patients while genetic testing was completed by 40% of White patients, 26% of Black patients and 14% of Asian patients [11]. The literature suggests that genetic disparities extend beyond germline testing. Huang and colleagues reported that patients with ovarian cancer and Medicaid insurance were less likely to undergo somatic testing compared to those with private insurance [45]. Gamble et al. confirmed this finding and further discovered that the inequity in somatic testing rates has actually widened over time [46]. Similarly, prior research suggests decreased utilization of cancer risk-reducing interventions (e.g. breast screening and risk-reducing surgery), and cascade genetic testing for at-risk relatives among medically underserved populations [14].

The issue of underutilization and disparities in genetic services is complex with several contributors. Frequently cited deficiencies in this process include limited physician appointment time, complexity of genetic counseling and testing referral, and patient uptake/adherence with recommendations for genetic assessment. Potential strategies to address these inequities include emphasizing genetic medicine education, increasing awareness of implicit and explicit bias, and implementing health information technology tools to assist providers with patient communication about topics in genetics. Successful methods to improve genetic testing among patients with ovarian cancer described in the literature include use of telemedicine, embedding genetic counselors in the clinic, and mainstreaming [11]. Mainstreaming is the process whereby genetic counseling and genetic testing are performed by non-genetics specialists, for example, by a member of the gynecologic oncology clinical team, following upskilling in order to consent, order, interpret, and deliver results [47]. Studies of mainstreaming demonstrate rates of successful completion of genetic testing ranging from 86 to 100% [47–50]. Finally, the conceptual framework termed "Traceback" is being evaluated, whereby individuals (alive and deceased) with ovarian cancer and without prior genetic testing are retrospectively identified and genetically tested. Subsequently, information is shared with family members [51–53].

For patients, services that establish trust and address language barriers, concerns about cost, and other social determinants of health that may impede completion of genetic testing must be considered in order to comprehensively address healthcare disparities in this field [54–59]. Finally, although the COVID-19 pandemic has resulted in disruptions to oncology care, the acceleration of telemedicine has expanded access to genetic services with reduced cost and similar patient-reported knowledge, stress, and satisfaction levels [60].

Acknowledging that members of underserved racial and ethnic groups experience pronounced under-recognition of hereditary cancer

syndromes, the American Association for Cancer Research, American Cancer Society, ASCO, and the National Cancer Institute have cited a critical need to improve access to genetic cancer risk assessment and testing for marginalized populations [61]. Further research in the field of cancer genetics disparities is urgently needed. We must also consider the historical and cultural experiences of specific populations to design and implement successful, innovative strategies for addressing barriers to scalable and equitable care.

6. Future directions

There are numerous molecular biomarkers undergoing evaluation for ovarian cancer diagnosis, prognostication, and treatment. Such biomarkers are increasingly incorporated into the evaluation of targeted therapies.

6.1. Cell-Free DNA (cfDNA)

cfDNA is identified in blood, serum, plasma, or saliva and is either released into the blood passively from apoptotic cells or actively secreted. Only a small amount of cfDNA comes from degraded or dying cancer cells, and is referred to as circulating tumor DNA (ctDNA). A recent systematic review noted concordance between pathogenic variants identified in tumor and ctDNA; however tumor heterogeneity is a challenge in assessing for concordance [62]. Specifically, ctDNA has been investigated as a means for early diagnosis and confirmation of ovarian cancer as well as for use in assessment of treatment response and prognosis [63,64]. Further, ctDNA has been used to detect pathogenic variants which have a high concordance with tumor DNA, and can be utilized to support targeted therapies [65]. Lastly, ctDNA has also been used to assess the presence of minimal residual disease in ovarian cancer patients following neoadjuvant chemotherapy and may be utilized in future trials for therapy stratification [66]. Although the majority of studies have investigated ctDNA in blood or plasma, cfDNA has also been identified in other body fluids of patients with ovarian cancer, including ascites and uterine lavage [67,68]. Some available tests report variants that could be germline and others filter out germline variants to more specifically quantify tumor ctDNA. However, currently commercially available assays are not validated for the reporting of germline variants and thus variants detected by ctDNA should be evaluated and confirmed using a CLIA-approved germline assay [7].

6.2. RNA sequencing (RNA-Seq)

Progress in RNA sequencing with NGS technology provides the ability to quantify gene expression and alterations in ovarian cancer cells [69]. RNA-Seq has emerged as a tool to identify gene function and altered pathways in cancer pathogenesis. RNA sequencing has also characterized aberrant genetic pathways in platinum and multi-drug resistant ovarian cancer. While multiple somatic testing platforms offer comprehensive RNA sequencing of tumor specimens, the clinical applicability of the information obtained is not yet clearly understood. Germline RNA-Seq may improve diagnostic yield; one series reported a 9% relative increase in the detection of pathogenic variants when performing simultaneous DNA and RNA sequencing in a clinical context [70].

6.3. Cascade genetic testing

Cascade genetic testing is the process whereby probands (those affected with a germline pathogenic variant) inform their at-risk relatives of variant status [71]. Relatives can have up to 50% risk of harboring the same pathogenic variant, and thus also are eligible for genetic testing. The Centers for Disease Control and Prevention Office of Public Health Genomics has designated cascade genetic testing a tier one genomic application. However, only about a third of eligible relatives complete cascade testing, representing a critical missed opportunity for cancer prevention and early detection, especially for syndromes that increase risk for ovarian cancer [72]. Additionally, the uptake of cascade genetic testing among racial and ethnic monitory groups may be even lower as disparities across genetic medicine have been well documented. Among 8 active trials on clinicaltrials.gov evaluating interventions for cascade testing, 6 (75%) do not include the influence of race, ethnicity, or language on uptake rates of cascade testing as a primary or secondary objective [73]. The literature suggests that a facilitated approach whereby the clinical team or genetic testing laboratory assist the patient in mediating the process of cascade testing may improve relative uptake [72]. Well-designed trials of strategies to improve cascade testing uptake in diverse patient populations are urgently needed.

7. Conclusions

Genetic testing has become integral in the care of ovarian cancer patients. The growing understanding of the burden of germline, somatic and HRD alterations in ovarian cancer has enhanced opportunities for targeted treatment and genetically tailored cancer prevention. However, despite guidelines promoting universal genetic assessment, a testing gap persists in ovarian cancer, as patients are receiving genetic services neither consistently nor equitably [11,14,59]. Several strategies have been proposed to improve access to genetic assessment including mainstreaming of genetic services in the oncology office, embedding genetic counselors, utilization of telemedicine platforms, and traceback programs to identify and genetically test previously diagnosed but unreferred patients with ovarian cancer [11,51]. Based on published literature, mainstreaming yields the highest rates of genetic testing completion, and in practices where this is feasible, clinicians could consider incorporating this practice. Optimizing genetic assessment for patients with ovarian cancer will enhance multiple intersecting aspects of their care. Therefore, individual providers and health care systems must continue to work towards the overarching goal of achieving universal genetic assessment in people with ovarian cancer.

Author contributions

MKF and GMG - As the co-lead authors of this study, Drs. Frey and Gressel wrote key portions of the manuscript and were principally involved in draft revision and organization of the document.

BN, LS, SVB, RU - As study co-authors, Drs. Norquist, Blank, Urban and Ms. Senter wrote and organized several key portions of the manuscript.

Declaration of Competing Interest

Ms. Senter reports personal fees from AstraZeneca and GlaxoSmithKline, outside the submitted work.

Dr. Urban reports personal fees from UpToDate, Inc., Access Hope, and Clinical Care Options, outside the submitted work.

All other authors have nothing to disclose.

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