

# UC Irvine

## UC Irvine Previously Published Works

### Title

Multi-disciplinary summit on genetics services for women with gynecologic cancers: A Society of Gynecologic Oncology White Paper.

### Permalink

<https://escholarship.org/uc/item/39d8c0b3>

### Journal

Gynecologic oncology, 146(2)

### ISSN

0090-8258

### Authors

Randall, Leslie M  
Pothuri, Bhavana  
Swisher, Elizabeth M  
[et al.](#)

### Publication Date

2017-08-01

### DOI

10.1016/j.ygyno.2017.06.002

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Contents lists available at ScienceDirect

## Gynecologic Oncology

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)

Society Position Statements/White Papers

## Multi-disciplinary summit on genetics services for women with gynecologic cancers: A Society of Gynecologic Oncology White Paper



Leslie M. Randall <sup>a,\*</sup>, Bhavana Pothuri <sup>b</sup>, Elizabeth M. Swisher <sup>c</sup>, John P. Diaz <sup>d</sup>, Adam Buchanan <sup>e</sup>, Catherine T. Witkop <sup>f</sup>, C. Bethan Powell <sup>g</sup>, Ellen Blair Smith <sup>h</sup>, Mark E. Robson <sup>i</sup>, Jeff Boyd <sup>d,j</sup>, Robert L. Coleman <sup>k</sup>, Karen Lu <sup>k</sup>

<sup>a</sup> University of California Irvine, Irvine, CA, United States<sup>b</sup> New York University Langone Medical Center, New York, NY, United States<sup>c</sup> University of Washington, Seattle, WA, United States<sup>d</sup> Miami Cancer Institute, Miami, FL, United States<sup>e</sup> Geisinger Health System, Danville, PA, United States<sup>f</sup> Uniformed Services University of the Health Sciences, Bethesda, MD, United States<sup>g</sup> Northern California Kaiser Permanente Gynecologic Oncology, San Francisco, CA, United States<sup>h</sup> Texas Oncology, P.A., Austin, TX, United States<sup>i</sup> Memorial Sloan-Kettering Cancer Center, New York, NY, United States<sup>j</sup> Florida International University, Miami, FL, United States<sup>k</sup> University of Texas MD Anderson Cancer Center, Houston, TX, United States

## HIGHLIGHTS

- The Society of Gynecologic Oncology convened a multidisciplinary Genetics Summit.
- The benefits and challenges of genetic risk assessment were discussed.
- Minimum standards for genetic risk assessment are suggested.
- Suggestions for further research and educational efforts are communicated.

## ARTICLE INFO

## Article history:

Received 19 April 2017

Received in revised form 25 May 2017

Accepted 1 June 2017

Available online 7 June 2017

## ABSTRACT

**Objective.** To assess current practice, advise minimum standards, and identify educational gaps relevant to genetic screening, counseling, and testing of women affected by gynecologic cancers.

**Methods.** The Society of Gynecologic Oncology (SGO) organized a multidisciplinary summit that included representatives from the American College of Obstetricians and Gynecologists (ACOG), the American Society Clinical Oncology (ASCO), the National Society of Genetic Counselors (NSGC), and patient advocacy groups, BrightPink and Facing our Risk of Cancer Empowered (FORCE). Three subject areas were discussed: care delivery models for genetic testing, barriers to genetic testing, and educational opportunities for providers of genetic testing.

**Results.** The group endorsed current SGO, National Comprehensive Cancer Network (NCCN), and NSGC genetic testing guidelines for women affected with ovarian, tubal, peritoneal cancers, or DNA mismatch repair deficient endometrial cancer. Three main areas of unmet need were identified: timely and universal genetic testing for women with ovarian, fallopian tube, and peritoneal cancers; education regarding minimum standards for genetic counseling and testing; and barriers to implementation of testing of both affected individuals as well as cascade testing of family members. Consensus building among all stakeholders resulted in an action plan to address gaps in education of gynecologic oncology providers and delivery of cancer genetics care.

© 2017 Published by Elsevier Inc.

\* Corresponding author at: University of California Irvine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, 333 City Blvd. W., 92868, Orange, CA, United States.

E-mail address: [lrاندall@uci.edu](mailto:lrاندall@uci.edu) (L.M. Randall).

## 1. Introduction

The discipline of cancer genetics developed outside the scope of gynecologic oncology practice, complicating the integration of genetic counseling and testing into gynecologic cancer care. Several aspects of

clinical practice confounding this problem include: the perceived low prevalence of genetic mutations in women with gynecologic cancers; the historic lack of cancer management changes based on genetic test results; the cost of testing; and the complex and rapidly changing recommendations on whom to test and how to test. When testing for *BRCA1*, *BRCA2*, and Lynch syndrome first became available in the 1990s, genetic testing was generally reserved for women affected with gynecologic cancers who had early-onset cancers or suspicious family histories [1]. In a seminal publication in 2005, the United States Preventive Services Task Force stated that benefits of *BRCA1* and *BRCA2* testing outweighed potential harm and “strongly recommended” that genetic services should be offered to at risk individuals, while identifying a wider net of eligibility criteria, which would identify up to 2% of adult American women [2]. Within a few years, the NCCN updated their genetic testing guidelines to include offering *BRCA1* and *BRCA2* testing to all women with ovarian, tubal or peritoneal cancers (collectively termed ovarian cancer) regardless of age or family history. The SGO subsequently issued Position and Clinical Practice Statements supporting this recommendation [3,4]. The NSGC has voiced similar support [5]. Despite this consensus, genetic testing rates for women with ovarian cancer remain consistently low at 20–30% in many centers [6,7], equally concerning is the racial disparity among those women who are tested, and suboptimal access to testing in underserved populations [8,9]. The recent US Food and Drug Administration (FDA) approvals of the first poly-ribose ADP polymerase (PARP) inhibitors, olaparib and rucaparib, for the treatment of women with *BRCA*-mutated ovarian cancer, plus reports of immunotherapy efficacy in colorectal and endometrial cancers with microsatellite instability (MSI) consistent with Lynch syndrome create a new level of urgency to integrate genetic testing into clinical practice as knowledge of genetic status may impact treatment decisions [10–15].

In order to better understand the barriers to and to promote improved uptake of genetic testing in gynecologic cancer patients, the SGO convened a summit of expert stakeholders, including multi-disciplinary health professionals and community advocates. The purpose of this white paper is to communicate the consensus of the summit participants and the position of the SGO on the complex and evolving subject of cancer genetic testing in the context of care delivery, provider education, and integration of effort among stakeholders.

### 1.1. The importance of genetic testing in cancer care delivery

Gynecologic oncologists are uniquely positioned to identify women and families affected by cancer-associated germline genetic mutations. Diagnosis of mutations that cause hereditary breast and ovarian cancer or Lynch syndrome has been designated as a high priority public health measure by the Centers for Disease Control and Prevention [16] and is promoted by publicly led cancer risk advocacy groups such as BrightPink and FORCE. Although a high-risk cancer susceptibility mutation is optimally identified before cancer is diagnosed, identifying causative mutations in women with cancer informs tumor biology, prognosis, treatment decisions, clinical trial enrollment, risk assessment and prevention of subsequent malignancies, and cancer risk and prevention for blood relatives. Responsive to President Barack Obama's 2015 announcement that encouraged development of biomarker-based, “precision” medicine in all diseases, the most common causes of genetic predisposition to gynecologic cancers, hereditary breast and ovarian cancer (HBOC) and Lynch syndromes, as models for precision medicine in gynecologic oncology [17,18].

Approximately 15–20% of ovarian cancer patients are *BRCA1* or *BRCA2* mutation carriers [19,20]. These mutations increase a woman's lifetime ovarian cancer risk on average up to 40% for *BRCA1* carriers and 20% for *BRCA2* carriers. The study of *BRCA*-mutated ovarian cancer has stimulated important progress in the field of tumor biology. *BRCA1* and *BRCA2* are critical proteins in the homologous recombination DNA repair pathway. Following classic tumor suppressor gene

kinetics, *BRCA1*- and *BRCA2*-induced carcinogenesis result from a “second hit” somatic mutation(s) in the normal allele, leading to loss of *BRCA* function [21] and homologous DNA recombination deficiency (HRD). This HRD state, though carcinogenic, can paradoxically confer sensitivity to platinum and other DNA-damaging cytotoxics, as well as PARP inhibitors [22,23]. Several studies have reported better prognosis for women with *BRCA*-mutated ovarian cancer, especially *BRCA2*, possibly secondary to the improved platinum response [22–27]. Other genes in the HR pathway such as *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, and *BARD1*, may also influence ovarian cancer risk and biology [28–30]. With the increasing number of cancer susceptibility genes identified, multiplex testing of many cancer susceptibility genes has become increasingly attractive as a cost and time efficient testing strategy.

The most common cause of hereditary endometrial cancer, and a less common cause of hereditary ovarian cancer, are mutations in the genes associated with Lynch syndrome, a highly penetrant, autosomal dominant condition caused by mutations in one or more DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2* or by *EPCAM* deletions [31]. With Lynch syndrome, a woman's lifetime risk of endometrial, ovarian and colon cancer by age 70 is 40%, 7–10%, and 40%, respectively [32]. Approximately 7–12% of women with synchronous uterine and ovarian primaries have Lynch syndrome [33,34]. In a large prospective study of endometrial cancers collected by the Gynecologic Oncology Group, GOG 210, the microsatellite instability (MSI) phenotype characteristic of Lynch-associated cancers, which can also be driven by non-heritable epigenetic silencing of *MLH1*, was associated with poor prognostic factors such as lympho-vascular space invasion and higher grade histology [35]. This phenotype might also have therapeutic implications secondary to a higher mutational load and subsequent increased number of neoepitopes. MSI-unstable colorectal cancers have shown improved response to immunotherapy using checkpoint inhibitors [14]. Early results are promising that endometrial and ovarian cancers with MSI may exhibit similar sensitivity to this therapeutic approach that warrants further study [15].

### 1.2. Which patients should be offered genetic testing?

Guidelines regarding which gynecologic cancer patients should be considered for genetic testing are available from multiple sources and are listed in Table 1. Each of the convened stakeholders in this summit has independently created or jointly contributed to recommendations for identifying HBOC and Lynch syndrome-affected patients, followed by recommendations for more rare syndromes. Collectively, these guidelines are less complex than those issued for testing in the unaffected (by cancer) population, and thus, should be more easily applied in clinical practice.

As listed in Table 1, stakeholders agreed that all women with invasive epithelial ovarian, tubal, and peritoneal cancer at minimum be offered *BRCA* germline testing, and all women with endometrial cancer undergo either molecular tumor screening followed by genetic testing for Lynch syndrome, or primary referral for genetic testing based on age at diagnosis, family history or modified, revised Bethesda criteria [3–5,36,37]. In addition, Fig. 1 refers to the guidelines reported in the joint ACOG/SGO Practice Bulletin for evaluating women with endometrial cancer for the presence of Lynch syndrome [31,38]. (Fig. 1) In contrast to HBOC and Lynch syndromes, Cowden and Peutz-Jeghers are rare cancer susceptibility phenotypes but remain important because female mutation carriers might present with gynecologic malignancy as their index cancer (Table 1) [36]. Once mutation carriers are identified, counseling and testing of blood relatives should be initiated.

### 1.3. How is testing performed?

Genetic risk assessment starts with a detailed family history [39], even in those who already meet testing criteria, since some women might be best served by testing for multiple genes or syndromes. If eligible, the patient is approached with the option of testing. The

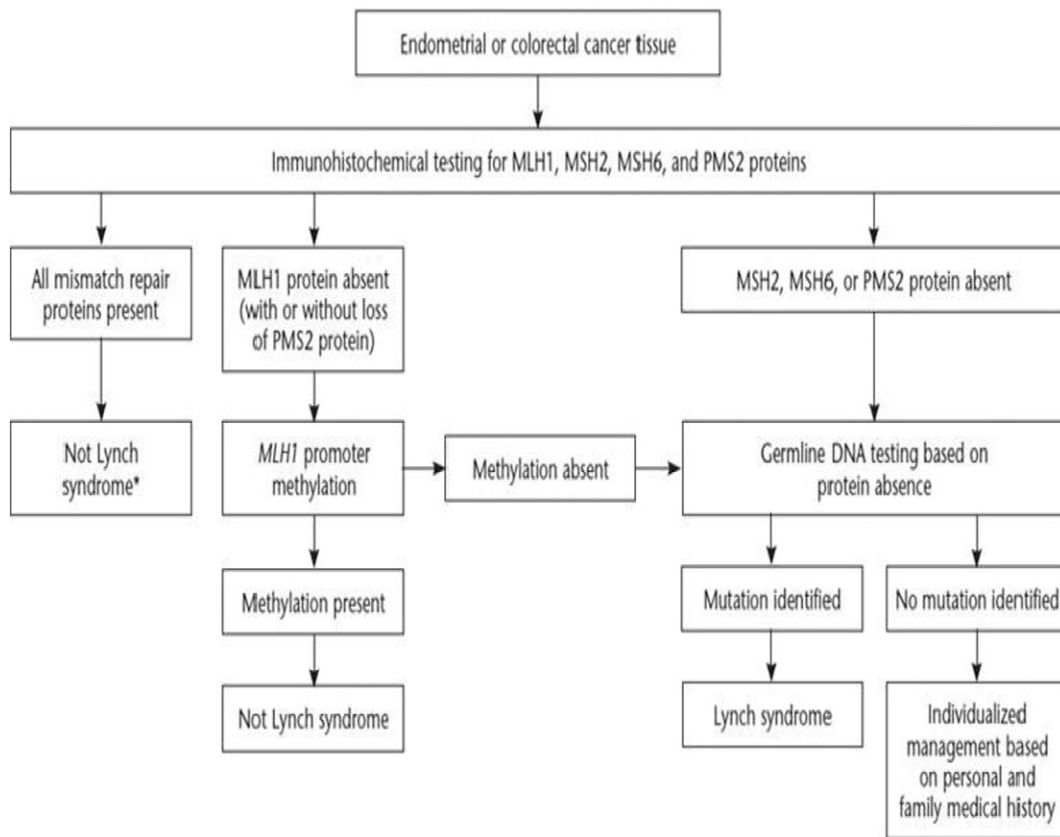
**Table 1**  
Summary of societal recommendations on genetic assessment in women with ovarian and uterine cancers.

Stakeholder	Date(s) issued	Ovarian cancer recommendations	Uterine cancer recommendations
Society of Gynecologic Oncology (SGO)	2014	Genetic counseling and testing for all ovarian, fallopian tube, peritoneal cancers [3]	Joint ACOG/SGO recommendations: Tumor testing for MSI/MMR IHC on any endometrial or colorectal tumor from a woman at risk for Lynch syndrome by focused personal and family medical history, or all endometrial cancers age < 60. Germline testing for marker expression loss on tumor tissue [37]. <ul style="list-style-type: none"> <li>• Endometrial cancer age &lt; 50</li> <li>• Endometrial cancer dx at age ≥ 50 if there is a FDR with colorectal or endometrial cancer at any age</li> <li>• Synchronous or metachronous colorectal or endometrial cancer in the same person</li> <li>• Endometrial cancer showing mismatch repair deficiency on tumor screening</li> <li>• Endometrial cancer and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in close relatives</li> <li>• Epithelial endometrial cancer and two additional Cowden syndrome criteria (Table 4) in the same person [6]</li> </ul>
American College of Obstetricians and Gynecologists (ACOG)	2009	Patients with greater than an approximate 20–25% chance of having a mutation [35]	
National Society of Genetic Counselors (NSGC) [Joint with the American College of Medical Genetics and Genomics (ACMG)]	2014	Single case of ovarian, fallopian tube, or peritoneal cancer present in the patient or a first degree relative [6]	

operational aspects of testing depend upon the practice environment and available resources to perform pre-test counseling, obtain insurance authorization for counseling and/or testing, collect samples and retrieve results, and finally to follow through with post-test counseling. When an inherited genetic mutation is identified, cascade testing introduces additional challenges, but planning for this testing can begin early in the risk assessment process and should include notification of and provision of information about how relatives may pursue testing. In addition to the aforementioned barriers, summit stakeholders sought to understand and harmonize delivery of care models and the types of tests ordered.

1.4. Delivery care models

Models of care delivery define the logistics of executing each step in the counseling and testing pathway. The most traditional and comprehensive model provides testing in conjunction with in-person genetic counseling, both pre- and post-testing, by a dedicated genetic counselor. Alternative service delivery models, as described by the NSGC Service Delivery Model Task Force, include provision of counseling by a genetic counselor via telephone, tele-video (tele-genetics), or in a group setting [40]. Little research has been undertaken to document the success or failure of current or alternative care models in



**Fig. 1.** Immunohistochemistry-based tumor testing for mismatch repair gene expression to assess for the possibility of Lynch syndrome. \*The scenario in which all four mismatch proteins does not rule out Lynch syndrome is the situation in which a deleterious mutation allows the production of a full-length but nonfunctional mismatch protein. Given this possibility, in the setting of a very high clinical suspicion of Lynch syndrome and normal immunohistochemical testing results, the tumor can be further evaluated by microsatellite instability testing. Reprinted with permission from Gynecologic Oncology [31].

gynecologic cancer, but several summit participants had queried their institutions under quality improvement initiatives [6]. They reported testing rates, influenced by maturity of initiatives, ranging from 25 to 80%, with many under 40%. Summit attendees discussed the multifactorial nature of low testing rates, and concurred that the most common obstacles appeared to be lack of availability of (or meaningful access to) an appropriately trained genetics professional, insufficient provider awareness of available genetics professionals, inconvenience and cost to patients of making separate visits with genetics professionals, and lack of operational infrastructure to track lengthy insurance pre-authorization processes for counseling and testing.

The traditional prenatal genetic testing model that includes detailed pre-test and post-test counseling by an appropriately trained genetics professional was identified as the ideal, though not always practical, strategy in cancer genetics. Professionals provide salient pre-test information to patients not limited to the disclosure of the test being performed with its intent and accuracy. Additionally, they inform the patient regarding implications of a negative test, a deleterious mutation, or a variant of uncertain significance (VUS) which is a structural difference in the gene with a yet undetermined effect on the gene's function [41]. This approach works well in many settings, as evidenced by short time to cancer genetic counseling appointments reported in several cancer centers [42]. However, cancer genetics expertise is not evenly distributed in the U.S., with cancer genetic counselors tending to cluster in urban areas and academic centers [42,43]. Moreover, though having certified genetic counselors perform pre- and post-test counseling is desirable, other clinicians with significant training in genetics may be able to provide comparable pre- and post-test counseling [41]. This may reduce barriers with regard to access of genetics counselors and delays in testing especially in more remote areas. Therefore, research to investigate models for training and delivering high-quality care efficiently, particularly in settings without ready access to trained genetic counselors, is critical.

One alternative pathway is for the oncologist to perform genetic testing at the point of care. This model has the benefit of streamlining testing, removing referral delays and inconsistencies, and allowing women to be counseled by their current provider. However, it adds the burdens of increased time and specialized training to oncology practice. Physician-directed testing is considered particularly acceptable by summit participants when ovarian cancer patients are being considered for PARP inhibitor therapy. Several ongoing clinical trials and the recent approval of additional PARP inhibitors expand the indications to include earlier treatment settings and somatic mutations. Therefore, the therapeutic incentive for at least *BRCA1* and *BRCA2* testing in ovarian cancer patients has already increased. Streamlined genetic testing could aide in universal testing, but, importantly, it does not obviate the need for adequate counseling, appropriate test selection, or discussion of cascade testing. Summit attendees believed that it is acceptable for the oncologist to conduct this counseling with appropriate training and selective utilization of additional support from genetics professionals.

If the provider can provide adequate pre-test counseling but is not qualified to provide informative post-test counseling, he/she should have a mechanism to access these services for tested patients. The provider should also acknowledge the increased complexity of panel testing for many genes. In the absence of a local cancer genetics professional, early research has shown the efficacy of genetic counseling via telephone conversation [44–48] and telemedicine via live videoconferencing [49]. Other service delivery models discussed among the summit attendees included group counseling instead of individual counseling and online counseling in real time or by previously prepared materials. Research evaluating the comparative and cost effectiveness of these alternate service delivery models, including factors such as patient-centered behavioral and psychosocial outcomes and insurance reimbursement, remains critical.

Despite these challenges, the summit attendees unanimously agreed that genetic testing of cancer-affected individuals who meet testing criteria is so fundamental to oncologic care, that physicians, payers,

and institutions should provide patients access to counseling and testing. To establish a minimum guideline, summit attendees made a unanimous recommendation that directed genetic counseling and, at least, germline testing for *BRCA* mutations in women with invasive epithelial ovarian, tubal, or peritoneal carcinomas, should be offered soon after initial diagnosis. However, as discussed below, comprehensive identification of hereditary ovarian cancer risk requires the assessment of at least 11 genes, so multiplex testing is likely the most efficient and cost-effective way to identify hereditary ovarian cancer risk. Furthermore, it was agreed upon that women with endometrial cancer should also be offered genetic risk assessment either through initial tumor testing or referral to genetics based on the modified, revised Bethesda criteria for Lynch syndrome. Though the intent of the group was to develop consensus regarding optimal genetics care delivery models, it was apparent that variability in resources by regions and practices will likely dictate different strategies to improve access to genetic counseling and testing.

### 1.5. Which test should be performed?

Until 2013, when the US Supreme Court issued the landmark verdict prohibiting patents on specific human DNA sequences in the case of *Association for Molecular Pathologists v. Myriad Genetics, Inc.*, testing options for *BRCA1* and *BRCA2* were limited [50]. Following this decision, there was an emergence of new companies offering similar Sanger-sequencing genetic tests as Myriad, but also many companies offering testing by multi-gene and next-generation sequencing (NGS) methods. The overwhelming, and nearly overnight, increase in testing options has complicated the testing landscape. It was apparent to summit attendees that these rapid changes have produced a need for clarity regarding the utility of various tests for clinical care.

The first challenge regarding testing discussed by the group was the distinction between germline and tumor, or somatic, testing. Germline mutations are those present in germ cells at conception and are heritable by future generations. This is in contrast to somatic mutations that occur after fertilization and are only perpetuated through mitosis within a specific cell lineage or neoplasm [51]. Mutations in *BRCA1* and *BRCA2* or in DNA mismatch repair genes associated with Lynch syndrome can manifest as germline, somatic, or both. Germline and somatic mutations may confer a similar molecular phenotype, such as MSI associated with mutations in DNA mismatch repair genes. The important distinction is that somatic mutations are not present in the germline and cannot be passed to future generations. Most mutations identified in normal tissue testing, such as blood or saliva, are germline in origin, though rare subclonal somatic mutations can sometimes be detected [52]. Tumor testing identifies both somatic and germline mutations. When a mutation is identified on tumor testing that may be heritable, confirmation of its presence in a paired blood or other non-tumor sample from the patient can confirm whether it is present in the germline. Therefore, when tumor sequencing is ordered, pre-test counseling at a minimum should inform patients of the possibility of discovering heritable mutations. In the case of PARP inhibition, both germline and somatic *BRCA1* and *BRCA2* mutations have been shown to predict drug efficacy. Current United States FDA drug approvals of PARP inhibitors include olaparib for germline *BRCA1* and *BRCA2* mutation carriers [10] and rucaparib for both germline and somatic *BRCA1* and *BRCA2* mutations [12,13].

The second testing issue addressed by the panel was the indications for and implications of germline multiplex, or panel, testing. Following the discovery of *BRCA1* and *BRCA2*, it was apparent that these two genes were not responsible for all familial cases of breast and ovarian cancer, and though non-*BRCA* mutations are individually rare, collectively they account for an estimated 6–10% of inherited high grade serous ovarian cancer [28]. Hereditary gynecological cancer panel testing is designed to detect mutations in a menu of genes that might contribute to incident cases of ovarian cancer, endometrial cancer, or both. Therefore, panel testing may be particularly useful in women

with significant family history who have previously tested negative for germline *BRCA1* and *BRCA2* mutations or those who test negative for mutations in Lynch syndrome genes. In addition, panel testing facilitates more robust identification of women at increased risk of ovarian cancer who could potentially benefit from risk-reducing surgery. Although less is known about the exact penetrance of mutations in non-*BRCA* hereditary ovarian cancer genes, a recent NCCN Guideline revision lists *RAD51C*, *RAD51D*, and *BRIP1* mutations, in addition to *BRCA1*, *BRCA2*, and Lynch gene mutations, as candidates for risk-reducing surgery at age 45–50 [53]. In this update, risk was not considered increased for *ATM*, *CDH1*, *CHEK2*, or *NF1* mutations, and remains uncertain for *NBN* and *PALB2* mutations. Panel testing has the disadvantages of a higher rate of VUS results that are confusing to patients and families and do not currently inform treatment or risk management decisions [54,55] and of finding deleterious mutations in unexpected genes. The likelihood of VUS results increases with the number of genes on a panel test, varies by laboratory, and can be as high as 25–41% [56,57].

Next-generation sequencing (NGS) has become the standard sequencing strategy for most laboratory genetic testing. These platforms can analyze millions of base pairs simultaneously by massively parallel sequencing, in contrast to the traditional base-by-base technique of the Sanger sequencing method, reducing the time and cost of analysis [58]. NGS has facilitated multi-gene testing, allowing the addition of genes with minimal increased costs. The limitations of NGS include difficulty detecting certain mutation types (i.e., genomic rearrangements), large amounts of computational data necessitating formal bioinformatics analysis, and high start-up costs to run the platform. Use of NGS, however, does not imply inaccurate or less definitive mutational analysis provided appropriate laboratory validation has been conducted, and should not be considered “investigational” as claimed by some insurance carriers.

Providers of genetic testing face the challenge of knowing which tests are most accurate, interpretable, and cost-effective. Panel testing is available through many commercial vendors and in the laboratory research setting [59]. Currently, most guidance is provided by commercial entities. At times, third-party payers will dictate which testing modality will be covered for the patient, but most of these decisions will be made by the clinician who is ordering the testing. The choice of test is complex but important because many payers will limit coverage to a single genetic test for a patient, preventing the provider from ordering, for example, testing for other susceptibility genes when *BRCA1* and *BRCA2* testing does not identify a mutation. With this in mind, the cost of the multi-gene panel tests decreasing, and increasing numbers of genes implicated in cancer susceptibility, panel tests are increasingly being utilized for frontline cancer susceptibility testing.

The FDA responded to the need for unbiased, evidence-based guidance to consumers of laboratory-developed tests (LDTs) inclusive of cancer-associated genetic testing. A Notification to Congress initiated this movement in July 2014, which was followed by a series of Draft Guidance documents for public comment that is still ongoing [60,61]. The central goal of this initiative is to provide oversight of genetic testing assays as regulated devices. Although this initiative was intended to help clinicians identify the assays that are acceptably accurate, there exists the possibility of impeding progress by increasing the financial and regulatory burdens of development, especially for smaller laboratories. ASCO supports a risk-based approach to proposed FDA regulation, where genetic tests that identify cancer susceptibility would be classified as high-risk testing, in a way that does not impede innovation or patient access [39].

### 1.6. Barriers to genetic testing in the clinical setting

A subgroup of the Summit was charged with examining the reasons for low uptake of genetic testing despite strong recommendations from national professional societies. Research addressing this topic is lacking, necessitating discussion based on experience rather than data. This subgroup included members from different practice settings (academic

plus large and small private practices) and engaged all stakeholders including patient advocates. They identified multiple factors of concern: lack of physician awareness of, or time, to fully assess family history, lack of patient acceptance, delays and/or denials by third party payers, variable availability of genetic counseling professionals, lack of reimbursement for genetics professionals, and racially and culturally disparate and/or underinsured populations (Table 2). Some providers may be concerned that there is a psychologically negative effect of being “labeled” as a mutation carrier, although most studies and experience refute this assertion [62–67]. In fact, most women and their families are empowered by informative results. For women worried about health insurance coverage and other health care discrimination should they be identified as mutation carriers, protection is guaranteed by a Federal law, the Genetic Information Non-Discrimination Act (GINA). As these debates persist, the science has advanced at a rapid pace to include access to multigene panels and NGS testing modalities, which can increase the sensitivity and speed of genetic testing, but also add time and complexity to counseling.

### 1.7. Gaps and obstacles associated with cascade testing

Despite the potential life-saving impact of cascade testing, challenges often arise in the execution of this two-stage process which requires the affected patient to inform family members of their mutational status and then for the family member(s) to act upon that information. In most practices, responsibility for the first step is delegated to the affected patient. This might result in communication obstacles such as lack of ability or desire to inform relatives secondary to the physical and emotional burden of cancer, strained dynamics between the patient and her relatives, and/or ambivalent communication of the information to her relatives. In addition, a guilty sentiment about possibly passing a mutation on to one's children might exist. Therefore, non-judgmental, practical resources to understand the meaning of positive results is likely an under recognized need for mutation carriers.

If the affected woman does indeed successfully communicate the results and recommendation for cascade testing to her relatives, each relative must then process the information and, if desired, seek out counseling or further information. In this phase, cancer-affected mutation carriers might encounter an unexpected response, depending on

**Table 2**

Barriers to the provision of genetic counseling and testing services to cancer patients with proposed solutions.

Barrier(s)	Proposed solutions
Provider-mediated	
Lack of awareness of testing benefit	Provider education, reinforcement of societal recommendations
Lack of time during patient encounter	
Concerns over cost	
Perception that information detrimental to patient well-being	
Payor-associated	
Lack of reimbursement for genetic counseling services	Payment reform
Lack of reimbursement for genetic tests	
System-associated	
Lengthy authorization processes	Research into optimal operational processes
Lack of infrastructure/staff to process authorizations	
Lack of tracking mechanisms to monitor execution of physician orders for testing	
Patient-associated	
Misunderstanding of counseling/testing intent	Public education through public and professional societal advocacy Payment reform
Disinterest in results	
Fear of social or financial discrimination	
Racial disparities in testing due to education and access	

gender as well as social, cultural, educational, and economic factors, inadequate shared decision making with primary care or women's health care provider, variable access to care, and concern that follow-on care will not be accessible. Although there may be significant fear, suspicion and prejudice surrounding genetic testing in all populations, minority populations have unique challenges and involvement of community leaders, churches, and social networking may serve to breach these barriers.

Mutation carriers identified by cascade testing can then enter the "high-risk" pipeline, gaining access to targeted screening, risk-reducing medications and surgeries, and/or clinical trials. Therefore, cascade testing has the potential to reduce the incidence and mortality of cancer in the at-risk population, significantly expanding the value of genetic testing. Ultimately, all summit members agreed that prevention is the best method of eradicating cancer and that it is time for our federal and state legislatures to recognize the importance of genetic risk assessment and improve our laws to facilitate it. The SGO and other societies represented at this Summit are committed to educating our legislators about our patients' needs.

### 1.8. How can we improve this process?

Women's health and primary care providers need to be educated about cascade testing so they can engage in effective shared decision making with the relative who presents to discuss testing. If the provider does not have sufficient knowledge, training, or expertise to help the relative understand the risks and next steps or to elicit the patient's values and preferences, a referral to genetic counseling should be made. Approaches to improve provider efficacy may include an online cascade testing toolkit or a publication (e.g. Committee Opinion) that outlines the role of, and recommendations for, the women's health or primary care provider. Furthermore, to facilitate understanding of the information, standardized notification templates, for both the patient letter and provider of relative letter, can be developed and included in a cascade testing tool kit. This tool kit should be available online and updated as needed.

Providers can investigate alternative approaches to notification. If allowed in the relevant state, consent and contact information for relatives can be obtained from the patient and notification letters sent directly to the relative. If not allowed, integrating cascade testing into survivorship planning and re-addressing the issue with the patient at a later date may give the patient sufficient time and perspective to consider relative notification. These initiatives challenge the regulations of the Health Information Portability and Accountability Act (HIPAA) and might require due diligence prior to implementation.

A novel approach to promoting cascade testing is to engage advocacy groups in the education and support of individuals identified as having an inherited cancer predisposition. Reliance on these public organizations can present risks of incorrect information and poorly informed decision making with serious health and psychological consequences. Select advocacy groups such as Bright Pink and FORCE are professional organizations with medical advisory boards that include thought leaders in the field. They have approachable and evidence-based information that improves patient understanding of what it means to carry a mutation and have their family tested. This model might be complementary to physician-led or even counselor-led education because it allows patients to obtain and process information at their own pace and in alignment with their values. To facilitate education and allay fears of relatives, contact information for advocacy groups should be made available to relatives at the time of notification (including websites for known advocacy groups). Providing a community for the relative will allow for resources and a peer group to help process the information.

Information sharing between health care providers might facilitate cascade testing, but privacy and consent issues are paramount in any

communication, and secure registries may offer a future way to facilitate cascade testing.

### 1.9. Education and Training

Lack of provider education and training is a modifiable barrier in providing genetic risk assessment. Two central educational mechanisms serve current SGO members in practice—the SGO and the ABOG through the Maintenance of Certification (MOC) process. Future members of the SGO in training are currently governed by the standards of ABOG Gynecologic Oncology Committee, but the Accreditation Council of Graduate Medical Education (ACGME) will soon assume this responsibility and authority. Summit attendees affirmed the importance of incorporating educational objectives for cancer genetic risk assessment of affected and unaffected individuals as early as medical student education, and then graduate medical education through the American Professors of Obstetrics and Gynecology (APGO) and the Council on Resident Education in Obstetrics and Gynecology (CREOG).

Current learning objectives for gynecologic oncology fellows published in the ABOG Guide to Learning in Gynecologic Oncology are comprehensive in terms of medical knowledge, but curriculum changes will be necessary to comply with ACGME's Core Competencies model by the start of the 2017 academic year. In the core competency model, medical knowledge joins patient care, professionalism, interpersonal communication, practice-based learning (personal improvement) and system-based practice (system-based improvement) as required aspects of content mastery. Cancer genetics is an ideal problem for application of this competency model, especially given the need to effectively communicate complex results such as VUS, potentially false negative results, and options for cascade testing in addition to the quality- and system-based nature of care.

Summit stakeholders created a list of educational priorities. In addition to formal training and assessment just discussed, SGO educational leaders identified an electronic-based toolkit as the most valuable option for provider use in the clinic. This toolkit is currently available at <https://www.sgo.org/genetics/genetics-toolkit>.

## 2. Consensus Statement

Summit stakeholders concluded that the following items were minimum standards for the provision of genetics cancer care in women with ovarian or uterine cancer:

- All women with epithelial ovarian, tubal, or peritoneal cancer should be offered and strongly encouraged to have genetic testing for hereditary ovarian cancer risk.
- Women diagnosed with an inherited genetic mutation associated with HBOC syndrome should be referred for management of other associated cancer risks including breast cancer surveillance and their blood relatives should be offered cascade testing.
- Multigene panel testing is acceptable for detection of hereditary ovarian or endometrial cancer risk. Genetics expertise, including that exercised by an adequately-trained oncologist, and patient preferences should help determine the most appropriate test.
- Pre- and post-test counseling by a trained cancer genetics professional is optimal but not available in all practice settings. Increasing access to genetic testing is an important priority to balance with resource availability. Online resources for locating genetic counselors are [www.nsgc.org](http://www.nsgc.org), [www.findgeneticcounselor.com](http://www.findgeneticcounselor.com), and <https://www.cancer.gov/about-cancer/causes-prevention/genetics/directory>
- Gynecologic oncology providers who choose to order testing themselves should be able to interpret test results (positive, negative and VUS), apply results to care, be prepared to initiate cascade testing, recognize situations in which they require input from genetics professionals, and identify genetics with which professionals they can consult when indicated.

- Stakeholders strongly agreed that more research on alternate service delivery models for genetic counseling is needed.
- Gynecologic oncology care providers should be proficient in the SGO/ACOG joint recommendations for Lynch syndrome assessment in women with endometrial cancer [36]. In response, one of three suggested approaches to endometrial cancer testing is clinically appropriate and should be consistently utilized:
  - Genetic testing of women who meet the revised Bethesda 2004 screening criteria modified to include endometrial cancer in addition to colon cancer.
  - Tumor testing with MSI or immunohistochemistry of MMR proteins of all endometrial cancers in patients irrespective of age of diagnosis, or
  - Tumor testing with MSI or immunohistochemistry of MMR proteins of all endometrial cancers in patients diagnosed before age 60 years.
- Women diagnosed with an inherited genetic mutation associated with Lynch syndrome should be referred for management of non-gynecologic associated cancer risks including colorectal cancer surveillance and their blood relatives should be offered cascade testing.
- The agenda for continued research in this area should be directed toward the meaningful implementation of genetic testing in affected women. Summit stakeholders support the development of CMS policies allowing reimbursement for genetic counseling services, the engagement of third party payers in the assurance of genetic testing, including multiplex, in appropriately selected cancer patients, and the involvement of knowledgeable patient advocacy groups in the ongoing education of the public and medical professionals as the field of cancer genetics continues to evolve.

### 3. Joint Genetics Summit Participants

#### 3.1. SGO

Lee-may Chen, MD  
 Elizabeth Swisher, MD  
 Ellen Smith, MD  
 Noah Kauff, MD  
 Angeles Alvarez-Secord, MD  
 Deborah Armstrong, MD  
 Monica Jones, MD  
 Leslie Randall, MD  
 Bhavana Pothuri, MD  
 John P. Diaz, MD  
 C. Bethan Powell, MD  
 Jeff Boyd, PhD  
 Robert Coleman, MD  
 Karen Lu, MD

#### 3.2. ACOG

Christopher Zahn, MD  
 Nancy O'Reilly, MHS  
 Catherine Witkop, MD

#### 3.3. ASCO

Mark Robson, MD

#### 3.4. NSGC

Meghan Carey  
 John Richardson  
 Joy Larsen Haidle, MS, CGC  
 Leigha Senter, MS, CGC  
 Adam Buchanan, MS, MPH3, LGC

#### 3.5. NCCN

Mary Daly, MD, PhD

#### 3.6. Genetic Counselors

City of Hope  
 Jeff Weitzel, MD  
 Kathleen Blazer, EdD, MS, LCGC  
 Gayle Patel, CGC

#### 3.7. FORCE

Sue Friedman

#### 3.8. Bright Pink

Sarah Storey

### References

- [1] B.M. Norquist, K.P. Pennington, K.J. Agnew, M.I. Harrell, C.C. Pennil, M.K. Lee, et al., Characteristics of women with ovarian carcinoma who have BRCA1 and BRCA2 mutations not identified by clinical testing, *Gynecol. Oncol.* 128 (2013) 483–487.
- [2] U.S. Preventive Services Task Force, Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement, *Ann. Intern. Med.* 143 (5) (2005 Sep 6) 355–361 (Review. Erratum in: *Ann Intern Med.* 2005 Oct 4;143(7):547. PubMed PMID: 16144894).
- [3] SGO Position Statement, Genetic testing for gynecologic cancer, <https://www.sgo.org/newsroom/position-statements-2/genetic-testing-for-gynecologic-cancer/> October 2014.
- [4] J.M. Lancaster, C.B. Powell, L.M. Chen, D.L. Richardson, S.G.O.C.P. Committee, Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions, *Gynecol. Oncol.* 136 (2015) 3–7.
- [5] H. Hampel, R.L. Bennett, A. Buchanan, R. Pearlman, G.L. Wiesner, Guideline development group, American college of medical genetics and genomics professional practice and guidelines committee and national society of genetic counselors practice guidelines committee. A practice guideline from the American college of medical genetics and genomics and the national society of genetic counselors: referral indications for cancer predisposition assessment, *Genet. Med.* 17 (1) (2015 Jan) 70–87.
- [6] L.A. Meyer, M.E. Anderson, R.A. Lacour, A. Suri, M.S. Daniels, D.L. Urbauer, et al., Evaluating women with ovarian cancer for BRCA1 and BRCA2 mutations: missed opportunities, *Obstet. Gynecol.* 115 (2010) 945–952.
- [7] K.A. Metcalfe, I. Fan, J. McLaughlin, H.A. Risch, B. Rosen, J. Murphy, et al., Uptake of clinical genetic testing for ovarian cancer in Ontario: a population-based study, *Gynecol. Oncol.* 112 (2009) 68–72.
- [8] D.E. Levy, S.D. Byfield, C.B. Comstock, J.E. Garber, S. Syngal, W.H. Crown, et al., Underutilization of BRCA1/2 testing to guide breast cancer treatment: black and Hispanic women particularly at risk, *Genet. Med.* 13 (2011) 349–355.
- [9] T. Pal, D. Bonner, D. Cragun, A.N. Monteiro, C. Phelan, L. Servais, et al., A high frequency of BRCA mutations in young black women with breast cancer residing in Florida, *Cancer* 121 (23) (Dec 1 2015) 4173–4180.
- [10] B. Kaufman, R. Shapira-Frommer, R.K. Schmutzler, M.W. Audeh, M. Friedlander, J. Balmana, et al., Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation, *J. Clin. Oncol.* 33 (2015) 244–250.
- [11] Food and Drug Administration Approved Drugs, Olaparib, <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm427598.htm>.
- [12] E.M. Swisher, K.K. Lin, A.M. Oza, C.L. Scott, H. Giordano, J. Sun, G.E. Konecny, R.L. Coleman, A.V. Tinker, D.M. O'Malley, R.S. Kristeleit, L. Ma, Bell-McGuinn KM, J.D. Brenton, J.M. Cragun, A. Oaknin, I. Ray-Coquard, M.I. Harrell, E. Mann, S.H. Kaufmann, A. Floquet, A. Leary, T.C. Harding, S. Goble, L. Maloney, J. Isaacson, A.R. Allen, L. Rolfe, R. Yelensky, M. Raponi, McNeish IA, Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial, *Lancet Oncol.* 18 (1) (2017 Jan) 75–87. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533873.htm> (Accessed 1.14.17).
- [13] D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, et al., PD-1 blockade in tumors with mismatch-repair deficiency, *N. Engl. J. Med.* 372 (2015 Jun 25) 2509–2520.
- [14] A.N. Fader, L.A. Diaz, D.K. Armstrong, E.J. Tanner, J. Uram, A. Eyring, et al., Preliminary results of a phase II study: PD-1 blockade in mismatch repair-deficient, recurrent or persistent endometrial cancer, Late Breaking Abstract 3, SGO 47th Annual Meeting on Women's Cancer, San Diego, CA, 2016.
- [15] CDC, Office of Public Health Genomics - genomic tests and family history by levels of evidence, <http://www.cdc.gov/genomics/gtesting/tier.htm> 2014.
- [16] The Precision Medicine Initiative, <https://www.whitehouse.gov/precision-medicine>.
- [17] F.S. Collins, H. Varmus, A new initiative on precision medicine, *N. Engl. J. Med.* 372 (2015) 793–795.
- [18] A. Antoniou, P.D. Pharoah, S. Narod, H.A. Risch, J.E. Eyfjord, J.L. Hopper, et al., Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations



- detected in case series unselected for family history: a combined analysis of 22 studies, *Am. J. Hum. Genet.* 72 (2003) 1117–1130.
- [20] T. Pal, J. Permeth-Wey, J.A. Betts, J.P. Krischer, J. Fiorica, H. Arango, et al., BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases, *Cancer* 104 (2005) 2807–2816.
- [21] P.L. Welch, M.C. King, BRCA1 and BRCA2 and the genetics of breast and ovarian cancer, *Hum. Mol. Genet.* 10 (2001) 705–713.
- [22] P.A. Konstantinopoulos, D. Spentzos, B.Y. Karlan, T. Taniguchi, E. Fountzilas, N. Francoeur, D.A. Levine, S.A. Cannistra, Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer, *J. Clin. Oncol.* 28 (22) (2010 Aug 1) 3555–3561.
- [23] J. Ledermann, P. Harter, C. Gourley, M. Friedlander, I. Vergote, G. Rustin, et al., Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial, *Lancet Oncol.* 15 (2014) 852–861.
- [24] F.J. Candido-dos-Reis, H. Song, E.L. Goode, J.M. Cunningham, B.L. Fridley, M.C. Larson, et al., Germline mutation in BRCA1 or BRCA2 and ten-year survival for women diagnosed with epithelial ovarian cancer, *Clin. Cancer Res.* 21 (2015) 652–657.
- [25] J.R. McLaughlin, B. Rosen, J. Moody, T. Pal, I. Fan, P.A. Shaw, et al., Long-term ovarian cancer survival associated with mutation in BRCA1 or BRCA2, *J. Natl. Cancer Inst.* 105 (2013) 141–148.
- [26] J.L. Lesnock, K.M. Darcy, C. Tian, J.A. Deloia, M.M. Thrall, C. Zahn, et al., BRCA1 expression and improved survival in ovarian cancer patients treated with intraperitoneal cisplatin and paclitaxel: a gynecologic oncology group study, *Br. J. Cancer* 108 (2013) 1231–1237.
- [27] B.S. Norquist, M.F. Brady, M.I. Harrell, T. Walsh, M.K. Lee, S.I. Gulsuner, et al., Mutations in homologous recombination genes and response to treatment in GOG 218: an NRG Oncology study, Abstract 1, SGO 47th Annual Meeting on Women's Cancer, San Diego, CA, 2016.
- [28] K.P. Pennington, E.M. Swisher, Hereditary ovarian cancer: beyond the usual suspects, *Gynecol. Oncol.* 124 (2012) 347–353.
- [29] T. Walsh, S. Casadei, M.K. Lee, C.C. Pennil, A.S. Nord, A.M. Thornton, et al., Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing, *Proc. Natl. Acad. Sci. U. S. A.* 108 (2011) 18032–18037.
- [30] B.M. Norquist, M.I. Harrell, M.F. Brady, T. Walsh, M.K. Lee, S. Gulsuner, et al., Inherited mutations in women with ovarian carcinoma, *JAMA Oncol.* 30 (2015 Dec) 1–9.
- [31] L.M. Randall, B. Pothuri, The genetic prediction of risk for gynecologic cancers, *Gynecol. Oncol.* 141 (1) (2016 Apr) 10–16.
- [32] K.H. Lu, M. Dinh, W. Kohlmann, P. Watson, J. Green, S. Syngal, P. Bandipalliam, L.M. Chen, B. Allen, P. Conrad, J. Terdiman, C. Sun, M. Daniels, T. Burke, D.M. Gershenson, H. Lynch, P. Lynch, R.R. Broaddus, Gynecologic cancer as a “sentinel cancer” for women with hereditary nonpolyposis colorectal cancer syndrome, *Obstet. Gynecol.* 105 (3) (2005 Mar) 569–574.
- [33] P.T. Soliman, R.R. Broaddus, K.M. Schmeler, M.S. Daniels, D. Gonzalez, B.M. Slomovitz, D.M. Gershenson, K.H. Lu, Women with synchronous primary cancers of the endometrium and ovary: do they have Lynch syndrome? *J. Clin. Oncol.* 23 (36) (2005 Dec 20) 9344–9350.
- [34] C.S. Walsh, A. Blum, A. Walts, R. Alsabeh, H. Tran, H.P. Koeffler, B.Y. Karlan, Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening, *Gynecol. Oncol.* 116 (3) (2010 Mar) 516–521.
- [35] D.S. McMeekin, D.L. Tritchler, D.E. Cohn, D.G. Mutch, H.A. Lankes, M.A. Geller, M.A. Powell, F.J. Backes, L.M. Landrum, R. Zaino, R.D. Broaddus, N. Ramirez, F. Gao, S. Ali, K.M. Darcy, M.L. Pearl, P.A. DiSilvestro, S.B. Lele, P.J. Goodfellow, Clinicopathologic significance of mismatch repair defects in endometrial cancer: an NRG oncology/gynecologic oncology group study, *J. Clin. Oncol.* 20 (2016 Jun).
- [36] Committee opinion no. 634, Hereditary cancer syndromes and risk assessment, *Obstet. Gynecol.* 125 (2015) 1538–1543.
- [37] A. Umar, C.R. Boland, J.P. Terdiman, S. Syngal, A. de la Chapelle, J. Ruschoff, et al., Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability, *J. Natl. Cancer Inst.* 96 (2004) 261–268.
- [38] Committee on Practice Bulletins-Gynecology Society of Gynecologic Oncology, ACOG practice bulletin no. 147: Lynch syndrome, *Obstet. Gynecol.* 124 (2014) 1042–1054.
- [39] M.E. Wood, P. Kadlubeck, T.H. Pham, D.S. Wollins, K.H. Lu, J.N. Weitzel, M.N. Neuss, K.S. Hughes, Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology quality oncology practice initiative, *J. Clin. Oncol.* 32 (8) (2014 Mar 10) 824–829.
- [40] S.A. Cohen, M.L. Marvin, B.D. Riley, H.S. Vig, J.A. Rousseau, S.L. Gustafson, Identification of genetic counseling service delivery models in practice: a report from the NSCC Service Delivery Model Task Force, *J. Genet. Couns.* 22 (2013) 411–421.
- [41] M.E. Robson, A.R. Bradbury, B. Arun, S.M. Domchek, J.M. Ford, H.L. Hampel, S.M. Lipkin, S. Syngal, D.S. Wollins, N.M. Lindor, American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility, *J. Clin. Oncol.* 33 (31) (2015 Nov 1) 3660–3667.
- [42] S. Knapke, J.L. Haidle, R. Nagy, S. Pirzadeh-Miller, The current state of cancer genetic counseling access and availability, *Genet. Med.* 18 (4) (Apr 2015) 410–412.
- [43] U.S. Department of Health & Human Services, Coverage and reimbursement of genetic tests and services: report of the secretary's advisory committee on genetics, health, and society, [http://oba.od.nih.gov/oba/sacghs/reports/CR\\_report.pdf](http://oba.od.nih.gov/oba/sacghs/reports/CR_report.pdf) 2006.
- [44] M.D. Schwartz, et al., Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer, *J. Clin. Oncol.* 32 (2014) 618–626.
- [45] R. Sutphen, B. Davila, H. Shappell, T. Holtje, S. Vadaparampil, S. Friedman, et al., Real world experience with cancer genetic counseling via telephone, *Familial Cancer* 9 (2010) 681–689.
- [46] M.D. Schwartz, H.B. Valdimarsdottir, B.N. Peshkin, J. Mandelblatt, R. Nusbaum, A.T. Huang, et al., Randomized noninferiority trial of telephone versus in-person genetic counseling for hereditary breast and ovarian cancer, *J. Clin. Oncol.* 32 (2014) 618–626.
- [47] B.N. Peshkin, S. Kelly, R.H. Nusbaum, M. Similuk, DeMarco TA, G.W. Hooker, et al., Patient perceptions of telephone vs. in-person BRCA1/BRCA2 genetic counseling, *J. Genet. Couns.* 25 (3) (Jun 2015) 472–482.
- [48] A.H. Buchanan, S.K. Datta, C.S. Skinner, G.P. Hollowell, H.F. Beresford, T. Freeland, et al., Randomized trial of telegenetics vs. in-person cancer genetic counseling: cost, patient satisfaction and attendance, *J. Genet. Couns.* 24 (2015) 961–970.
- [49] E.M. Ziliacis, B. Meiser, E.A. Lobb, P.J. Kelly, K. Barlow-Stewart, J.A. Kirk, et al., Are videoconferenced consultations as effective as face-to-face consultations for hereditary breast and ovarian cancer genetic counseling? *Genet. Med.* 13 (2011) 933–941.
- [50] Supreme Court of the United States, Syllabus Association for molecular pathology et al. v. Myriad Genetics, Inc., et al, [http://www.supremecourt.gov/opinions/12pdf/12-398\\_1b7d.pdf](http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf) (Accessed 10/5/15).
- [51] A.J.F.M.J. Griffiths, D.T. Suzuki, et al., *An Introduction to Genetic Analysis*, 7th ed. W.H. Freeman, New York, 2000.
- [52] De, S. Somatic mosaicism in healthy human tissues. *Trends Genet.*, Volume 27(6): 217–223.
- [53] NCCN, Clinical practice guidelines in Oncology (NCCN Guidelines®) genetic/familial high-risk assessment: breast and ovarian. version 2.2017 – December 7, 2016, NCCN.org.
- [54] H. LaDuca, A.J. Stuenkel, J.S. Dolinsky, S. Keiles, S. Tandy, T. Pesaran, et al., Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients, *Genet. Med.* 16 (2014) 830–837.
- [55] N. Tung, C. Battelli, B. Allen, R. Kaldate, S. Bhatnagar, K. Bowles, et al., Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel, *Cancer* 121 (2015) 25–33.
- [56] H. LaDuca, A.J. Stuenkel, J.S. Dolinsky, S. Keiles, S. Tandy, T. Pesaran, E. Chen, C.L. Gau, E. Palmaer, K. Shoaipour, D. Shah, V. Speare, S. Gandomi, E. Chao, Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients, *Genet. Med.* 16 (11) (2014 Nov) 830–837.
- [57] N. Tung, C. Battelli, B. Allen, R. Kaldate, S. Bhatnagar, K. Bowles, K. Timms, J.E. Garber, C. Herold, L. Ellisen, J. Krejdovsky, K. DeLeonardis, K. Sedgwick, K. Soltis, B. Roa, R.J. Wenstrup, A.R. Hartman, Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel, *Cancer* 121 (1) (2015 Jan 1) 25–33.
- [58] E.C. Berglund, A. Kiialainen, A.C. Syvanen, Next-generation sequencing technologies and applications for human genetic history and forensics, *Investig. Genet.* 2 (2011) 23.
- [59] C.S. Walsh, Two decades beyond BRCA1/2: homologous recombination, hereditary cancer risk and a target for ovarian cancer therapy, *Gynecol. Oncol.* 137 (2) (2015 May) 343–350.
- [60] Food and Drug Administration, DHHS, letter to Committee on Health, Education, Labor and Pensions Chairman Tom Harkin, <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf>.
- [61] Food and Drug Administration, Laboratory developed tests, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm>.
- [62] I. van Oostrom, H. Meijers-Heijboer, L.N. Lodder, H.J. Duivenvoorden, A.R. van Gool, C. Seynaeve, et al., Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study, *J. Clin. Oncol.* 21 (2003) 3867–3874.
- [63] M.D. Schwartz, B.N. Peshkin, C. Hughes, D. Main, C. Isaacs, C. Lerman, Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample, *J. Clin. Oncol.* 20 (2002) 514–520.
- [64] J.G. Reichelt, P. Moller, K. Heimdal, A.A. Dahl, Psychological and cancer-specific distress at 18 months post-testing in women with demonstrated BRCA1 mutations for hereditary breast/ovarian cancer, *Familial Cancer* 7 (2008) 245–254.
- [65] J.T. Heshka, C. Palleischi, H. Howley, B. Wilson, P.S. Wells, A systematic review of perceived risks, psychological and behavioral impacts of genetic testing, *Genet. Med.* 10 (2008) 19–32.
- [66] J.G. Hamilton, M. Lobel, A. Moyer, Emotional distress following genetic testing for hereditary breast and ovarian cancer: a meta-analytic review, *Health Psychol.* 28 (2009) 510–518.
- [67] R. Manchanda, K. Loggenberg, S. Sanderson, M. Burnell, J. Wardle, S. Gessler, et al., Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial, *J. Natl. Cancer Inst.* 107 (2015) 379.