

## American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

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### ABSTRACT

The American Society of Clinical Oncology (ASCO) has long affirmed that the recognition and management of individuals with an inherited susceptibility to cancer are core elements of oncology care. ASCO released its first statement on genetic testing in 1996 and updated that statement in 2003 and 2010 in response to developments in the field. In 2014, the Cancer Prevention and Ethics Committees of ASCO commissioned another update to reflect the impact of advances in this area on oncology practice. In particular, there was an interest in addressing the opportunities and challenges arising from the application of massively parallel sequencing—also known as next-generation sequencing—to cancer susceptibility testing. This technology introduces a new level of complexity into the practice of cancer risk assessment and management, requiring renewed effort on the part of ASCO to ensure that those providing care to patients with cancer receive the necessary education to use this new technology in the most effective, beneficial manner. The purpose of this statement is to explore the challenges of new and emerging technologies in cancer genetics and provide recommendations to ensure their optimal deployment in oncology practice. Specifically, the statement makes recommendations in the following areas: germline implications of somatic mutation profiling, multigene panel testing for cancer susceptibility, quality assurance in genetic testing, education of oncology professionals, and access to cancer genetic services.

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### INTRODUCTION

The American Society of Clinical Oncology (ASCO) is the leading medical professional oncology society committed to conquering cancer through research, education, prevention, and delivery of high-quality patient care. ASCO has long affirmed that the recognition and management of individuals with an inherited susceptibility to cancer are core elements of oncology care. ASCO released its first statement on genetic testing in 1996<sup>1</sup> and updated that statement in 2003 and 2010 in response to developments in the field of clinical cancer genetics.<sup>2,3</sup> In 2014, the Cancer Prevention and Ethics Committees of ASCO commissioned another update to reflect the impact of advances in this area on oncology practice. In particular, ASCO wished to address the opportunities and challenges arising from the application of massively parallel sequencing—also known as next-generation sequencing (NGS)—to cancer susceptibility testing.

NGS is a powerful technology that permits the characterization of large amounts of DNA sequence much quicker and at lower cost than traditional Sanger sequencing.<sup>4-6</sup> The ability to affordably sequence panels of genes, exomes, and even whole genomes presents an enormous opportunity, and investigators in all fields of medicine are exploring how to best use this new tool to improve patient outcomes.<sup>7</sup> In oncology, NGS makes it feasible to catalog the DNA sequence variations within a patient's cancer (ie, somatic mutation profiling), with the goal of defining therapeutic targets and thereby improving patient outcomes through the application of specific therapies directed at those targets. NGS can facilitate the identification of inherited susceptibility to cancer (and other diseases) either in the course of somatic mutation profiling or through direct germline multigene (multiplex) panel testing. These applications of NGS challenge existing paradigms of counseling and testing for inherited susceptibility and raise important questions regarding

the optimal approach to incidental germline findings, the appropriate use of multigene panel testing, and the most effective way to ensure the quality of NGS when used in clinical oncology.<sup>8,9</sup> The novel technology also introduces a new level of complexity into the practice of cancer risk assessment and management, requiring renewed effort on the part of ASCO to ensure that those providing care to patients with cancer receive the necessary education to use this new technology in the most effective, beneficial manner. The purpose of this updated statement is to explore these challenges and provide recommendations to ensure the optimal deployment of these technologies in oncology practice.

#### GERMLINE IMPLICATIONS OF SOMATIC MUTATION PROFILING

*ASCO supports the communication to patients of medically relevant incidental germline findings from somatic mutation profiling conducted in the clinical setting. Only laboratories equipped to provide analytically and clinically valid results should conduct secondary analyses to identify germline variants. Laboratories that are not resourced to provide clinically valid information from secondary analysis of the normal sample in tumor-normal subtractive analyses should only report tumor-associated variants and should not be obligated to seek germline variants. Oncology providers should communicate the potential for incidental and secondary germline information to patients before conducting somatic mutation profiling and should review the potential benefits, limitations, and risks before testing. Providers should carefully ascertain patient preferences regarding the receipt of germline information and allow patients to decline receipt of germline information. This may require referral for additional counseling to help the patient clarify his or her preferences. In the setting of tumor-normal sequencing, laboratories conducting secondary analyses should develop mechanisms to report only somatic results for patients who choose to decline receipt of germline findings. ASCO supports research to determine how to best deliver pretest education, support patient preferences, and understand outcomes of providing incidental and secondary germline information with somatic testing.*

Cancer is a genetic disease, in the sense that the malignant phenotype is profoundly influenced by the pattern of genomic aberrations within the tumor. The vast majority of the DNA sequence of a patient's cancer is identical to the inherited germline sequence. Although some sequence variants found in a patient's cancer will be somatic mutations acquired in the course of tumor development, tumor sequencing will also identify germline sequence variants.<sup>5,6</sup> If tumor sequencing is limited to cancer-related genes, most of the deleterious germline variants found in tumor DNA sequence will be in cancer susceptibility genes, although there are some exceptions (eg, germline mutations in *SMAD3* or *TGFBR1/2* are linked to Loey's-Dietz syndrome, an autosomal-dominant connective tissue disorder that increases the risk of aortic aneurysms, among other features). More comprehensive tumor analysis (eg, whole-exome or whole-genome sequencing) will catalog the full range of germline variation, possibly including predisposition to nononcologic diseases.<sup>8</sup> Because the purpose of tumor profiling is to catalog somatic changes driving the cancer phenotype, the discovery of germline variants is usually incidental to the primary purpose of the test. Nonetheless, one can anticipate that the laboratory may identify such variants and that these may be clinically significant. For example, one can expect that the DNA sequence of triple-negative breast cancers and high-grade serous ovarian cancers will contain

*BRCA1* mutations in a significant number of unselected patient cases, many of which will reflect germline variants. It is not possible to know a priori whether a variant identified in a patient's cancer was inherited or arose in the course of tumor development. Therefore, the oncologist must consider whether a patient with a *BRCA1* mutation in his or her tumor in fact has a germline predisposition. Patients undergoing tumor-only sequencing (and their physicians) should be aware, before testing, of the possibility that tumor profiling may suggest germline susceptibility. They should also understand the extent of the sequencing being undertaken in a particular assay, so they are informed of the range of possible findings (eg, cancer susceptibility only or susceptibility to both cancer and nonmalignant disorders). In the event that tumor-only profiling identifies a pathogenic or likely pathogenic variant in a gene linked to inherited susceptibility to cancer or other diseases, the clinician should be prepared to refer the patient and his or her family for further evaluation, including confirmatory germline testing.

Because the purpose of somatic mutation profiling is to identify driver mutations in the cancer that could serve as treatment targets, several laboratories analyze tumor and normal (ie, nontumor) DNA simultaneously and use informatic techniques to subtract the inherited variants from the tumor sequence. This isolates those variants unique to the cancer. This subtractive approach does not require that the patient's germline sequence be compared with a reference standard and therefore does not identify germline variants without further dedicated analysis. This approach leads to a loss of information, because it masks germline variants that would be noted in tumor-only sequencing, including clearly deleterious mutations in known susceptibility genes. This masking approach should be acceptable when the purpose of the test is to identify clinically relevant somatic variants to guide cancer treatment. Most patients currently undergoing tumor profiling have advanced-stage disease, and the identification of inherited disease susceptibility is unlikely to benefit them (although the information could certainly be useful to their family). However, there is an active debate as to whether there is an obligation to actively seek germline mutations in certain genes in the setting of tumor mutation profiling employing a matched normal sample, even if that information is not germane to the primary purpose of the test.<sup>10,11</sup> Using a taxonomy proposed by the Presidential Commission for the Study of Bioethical Issues,<sup>12</sup> the germline variants discovered during a deliberate analysis of the normal sample would be considered secondary findings (ie, not the primary intent of testing and actively sought based on guidelines), whereas variants discovered in the course of tumor-only sequencing would be considered anticipatable incidental findings. This distinction is of particular importance in oncology, because guidelines asserting an obligation to evaluate germline DNA in tumor-normal sequencing would require that laboratories develop distinct variant detection and curation programs, a significant investment of time and effort that is ancillary to the purpose of somatic testing. Accepting an obligation to actively seek secondary findings in this setting could potentially have a negative effect on cancer care and research by increasing costs and requiring incremental resources for germline analysis.

ASCO has consistently endorsed the use of informed consent for germline genetic testing.<sup>1-3,13</sup> Although traditional pre- and post-test counseling may not be necessary or feasible in the setting of somatic testing where the intent of testing is to identify tumor variants to inform therapeutic options, oncology providers should elicit and

honor patient preferences regarding receipt of incidental and secondary germline findings when laboratories provide these results. Honoring patient preferences requires oncology providers to communicate the potential for incidental and secondary germline information specific to the test being offered, the relevance and potential benefits of this information for patients and their relatives, and the limitations and risks of receiving incidental and secondary germline information. Oncology providers should honor patient requests to decline receipt of incidental and secondary germline information. Education and preference elicitation regarding incidental and secondary germline findings are ideally conducted before testing. In the setting of tumor-normal sequencing, laboratories choosing to conduct secondary analyses should develop mechanisms to report only somatic results for patients who choose to decline receipt of germline findings. Some somatic platforms (eg, tumor-only or paired samples using subtraction methods to categorize somatic mutations) will not provide secondary germline findings. In these scenarios, it is important that providers and patients understand that results do not include germline testing, which would need to be pursued independently if there are personal or family history factors that suggest an inherited predisposition to cancer. However, laboratories conducting tumor-only sequencing may wish to highlight somatic sequence variants that may reflect a germline predisposition (eg, based on allele prevalence or identity with a known founder mutation).

ASCO supports continued deliberation and research to refine and establish standards to promote the clinical benefits and minimize the risks of tumor sequencing for the clinical care of oncology patients and their families. Given the ongoing debate and lack of empiric data to inform current policies, ASCO calls for further research to develop best practices with respect to the delivery of incidental and secondary germline findings and supports research aimed at improving understanding of patient preferences, developing optimal pretest education and support for informed consent, and identifying multilevel outcomes (ie, patient, provider, health care system delivery, and cost) in this area. Continued engagement with multiple stakeholders and additional research will be crucial to refining guidelines and best practices to advance the field of precision medicine to the benefit of patients with cancer and their families.

#### MULTIGENE PANEL TESTING FOR CANCER SUSCEPTIBILITY

*ASCO recognizes that concurrent multigene testing (ie, panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient's personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUSs) in a substantial proportion of patient cases, simply as a result of the multiplicity of genes tested. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history. Because of the current uncertainties and knowledge gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include*

*genes of uncertain clinical utility and genes not suggested by the patient's personal and/or family history. ASCO encourages research to delineate the optimal use of panel-based testing, development of evidence-based practice guidelines as data emerges, and education of providers regarding challenges in the use of these tests.*

Identifying inherited mutations in genes such as *BRCA1*, *BRCA2*, and the genes associated with Lynch syndrome allows for interventions that can significantly reduce the development of cancer and improve survival.<sup>14,15</sup> Testing for mutations in these genes has traditionally been directed by personal or family history. However, targeted capture assays employing NGS technology allow for testing many genes simultaneously, including genes that would not necessarily have been tested using the phenotype-directed approach, as well as genes of less clearly established clinical utility.

The use of germline multiplex or multigene panel testing is rapidly expanding in cancer risk assessment. Potential advantages to such testing include time and cost efficiency, decrease in testing fatigue for patients and providers, efficient use of a single specimen, and comprehensive assessment for cancer susceptibility, particularly in common cancers or individuals without identifiable syndromes.<sup>16</sup> This type of testing may be particularly useful in situations where there are multiple high-penetrance genes associated with a specific cancer, the prevalence of actionable mutations in one of several genes is high, and it is difficult to predict which gene may be mutated on the basis of phenotype or family history. One example of such a situation is Lynch syndrome, when the results of immunohistochemical analysis are not available to direct testing. However, there are a number of questions regarding how to best use panel-based testing.

Over the last two decades, it has become clear that the genetic architecture of inherited predisposition is complex, with the risk of common cancers being influenced by rare variants of high penetrance, rare variants of more modest (and variable) penetrance, and common variants of small effect. So far, there is little consensus as to which genes should be included on panels offered for cancer susceptibility testing (although common variants are rarely included). This heterogeneity presents a number of challenges. All panels include genes that are known to cause autosomal-dominant predisposition syndromes (so-called high-penetrance genes), often including genes that are not necessarily linked to the disease for which the testing is being offered. There is uncertainty regarding the appropriate risk estimates and management strategies for families with unexpected mutations in high-penetrance genes when there is no evidence of the associated syndrome. Most panels also include moderate-penetrance genes. Mutations in these genes increase the risk for the associated cancer by a factor of two to five, with factors such as family cancer history influencing the level of risk. Clinical utility remains the fundamental issue with respect to testing for mutations in moderate-penetrance genes. It is not yet clear whether the management of an individual patient or his or her family should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetrance mutations, and no guidelines exist to assist oncology providers.

Early experience with panel-based testing indicates that a substantial proportion of tests identify a VUS in one or more genes.<sup>16,17</sup> VUSs are alterations in the genetic code that may or may not affect the function of the protein. VUSs are more common in broad-panel

testing both because of the number of genes tested and because of the limited understanding of the range of normal variation in some of these genes. It is usually inappropriate to change the clinical management of a patient based on the finding of a VUS. Unfortunately, there is some evidence that clinicians may overinterpret VUSs and make recommendations that should be reserved for individuals with clearly deleterious mutations.<sup>18</sup>

All of the challenges described here raise the possibility of harm to the individual undergoing panel-based testing, including the potential for inappropriate medical intervention and psychological stress resulting from the incidental identification of a mutation in a gene that was not suggested by family history or from aggressive management of moderate-penetrance mutations (or VUSs) that is not yet supported by evidence. Pretest genetic counseling has been the method by which possible negative outcomes are disclosed to patients undergoing ge-

netic testing and has been a cornerstone recommendation of ASCO since 1996.<sup>1-3,13</sup> The traditional pretest counseling model may be difficult to apply to panel-based testing, however, if the panel includes genes of uncertain clinical utility and genes that are not suggested by the patient's personal or family history. Despite these difficulties, the principle remains intact that individuals undergoing panel-based genetic susceptibility testing should provide educated pretest consent for such testing, as summarized in Table 1. It is important to highlight the purpose of the genetic testing, potential outcomes and implications for the patient and his or her family members, and the cancer risks associated with the genes being tested. Although it is usually infeasible to individually review each of the genes in a panel, it is important to discuss the difference between well-described high-penetrance genes and moderate-penetrance mutations that are less well understood. Because unexpected

**Table 1.** Components of Informed Consent and Pretest Education in Clinical Cancer Genetics

Traditional Pretest Counseling for Susceptibility Testing (purpose of testing)	Pretest Counseling for Multigene Panel Testing (same general components as traditional counseling, with following special considerations)	Pretest Education for Somatic Mutation Profiling With Potential for Incidental Germline Findings (purpose of testing)
Information on specific genetic mutation(s) or genomic variant(s) being tested, including whether range of risk associated with variant will affect medical care	Discussions of specific genes may need to be batched, because it may not be feasible to review each gene individually; high-penetrance syndromes being evaluated should be described (eg, hereditary breast-ovary, Lynch, hereditary diffuse gastric, Li-Fraumeni); patients should be aware of possible detection of high-penetrance mutations not suggested by personal or family history; genes of uncertain clinical utility may need to be described more generally	Discussion of possibility of discovering information relevant to inherited risk and range of possible germline risks that may be identified (differs for targeted sequencing v whole-exome or -genome sequencing); if there will be mandatory search for secondary findings, this should be explained, and option to decline to learn results should be provided
Implications of positive (mutation confirmed to be deleterious), negative (no identified change in genetic sequence), or uncertain (genetic variant of unknown clinical significance) result	Particular attention should be paid to implications of positive results in less well-understood or lesser-penetrance genes and in findings of mutations in genes associated with syndromes not suggested by personal or family history	Criteria that will be used to identify germline variants that would be returned to patient or family should be described
Possibility test will not be informative	Attention should be paid to current high rate of variants of uncertain significance	Emphasis that purpose of test is not to identify germline risk and that dedicated testing directed by personal or family history is available
Risk that children and/or other family members may have inherited genetic condition	Highlight potential reproductive implications to family of mutations in genes linked to recessive disorders (eg, <i>ATM</i> , Fanconi's [ <i>BRCA2</i> , <i>PALB2</i> ], <i>NBN</i> , <i>BLM</i> )	Discussion about how incidental findings may be relevant to family members
Fees involved in testing and counseling; for DTC testing, whether counselor is employed by testing company		
Psychological implications of test results (benefits and risks)		
Risks and protections against genetic discrimination by employers or insurers		
Confidentiality issues, including DTC testing companies and policies related to privacy and data security		
Possible use of DNA samples for future research		
Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing		
Importance of sharing genetic and genomic test results with at-risk relatives so they may benefit from this information		Consider identifying surrogate who could receive incidental results information on behalf of patient in event patient has died or is otherwise unable to receive results
Plans for disclosing test results and providing follow-up		

Abbreviation: DTC, direct to consumer.

positive results are possible, it is important to prepare patients for the possibility of unexpectedly identifying a deleterious mutation in a gene. Some unexpected results, such as a mutation in *TP53* (Li-Fraumeni syndrome) or *CDH1* (hereditary diffuse gastric cancer), may have a significant impact on the patient and his or her family, so it is important that the patient is prepared for this possibility.

There have been a number of studies demonstrating the prevalence of mutations identified by panel-based testing in different clinical scenarios.<sup>16,17,19</sup> There remains an urgent need for more research into the implications of unexpected mutations in high-penetrance genes and mutations in moderate-penetrance genes.<sup>20</sup> Continued research is also necessary to resolve VUSs. There is a dearth of literature regarding how to best counsel patients who may be appropriate candidates for panel testing, and it is important to study the most effective counseling techniques. Until these questions are resolved, it remains appropriate to conduct limited testing for mutations in genes of established clinical utility suggested by the patient's history. Because of the complexities attendant on the interpretation of broad panel-based testing, it is particularly important that providers with particular experience in the assessment of inherited cancer risk be involved in the ordering and interpretation of these tests. There is a significant need at this time for education directed at cancer care providers to ensure the optimal use of these tests.

#### QUALITY ASSURANCE IN GENETIC TESTING

*ASCO recognizes the complexity of the analysis and interpretation of genetic tests. ASCO supports high-quality standards to help providers and patients understand the accuracy, benefits, and limitation of genetic tests from individual laboratories. ASCO believes that current regulation of tests to detect inherited genetic variants is insufficient. Where tests are considered laboratory-developed or commercial tests, ASCO supports a risk-based approach to US Food and Drug Administration (FDA) regulation. High-risk tests used to identify patients who are at increased risk for cancer should be subject to regulatory review. ASCO also recognizes that regulation must be designed in a manner that does not compromise innovation or limit patient access to testing.*

Since 2000, there has been an explosion in new genetic diagnostic tests. There are now more than 1,000 conditions for which germline genetic tests are widely available, with approximately a 10% increase in new genetic test availability every year and a 20% increase in gene-based diagnostic tests, compared with approximately 2% for nongenetic medical tests.

More than 200 genetic tests are currently clinically available to help determine the risk of developing a variety of different cancers. The introduction of massively parallel DNA sequencing has altered the landscape of germline cancer predisposition commercial testing, as well as that of somatic mutation profiling. Laboratories performing these tests face common technical challenges regarding quality metrics for massively parallel DNA panel and whole-genome sequencing and computational classification of variants as benign or pathogenic. The different strategies used by different laboratories to address the technical and interpretative challenges of NGS diagnostics have led to difficulties in interpretation of results by providers and patients, also engendering concerns about needed increased regulation and standardization of procedures of testing laboratories.

Until recently, all laboratories performing constitutional DNA testing for hereditary cancer genes have been regulated under the Center for Medicare and Medicaid Services Clinical Laboratory Improvement Amendment (CLIA) program. However, under CLIA, the nationwide established uniform technical standards vital to the standardized reporting of results of NGS do not exist. Needed technical standards relate to issues including the tissue source of DNA analyzed, the depth of coverage of sequencing, the computational algorithms to call variants as well as insertion and deletion mutations, and the format whereby variants are reported. Interlaboratory variation in these parameters and others may lead different laboratories to report different findings from the same DNA sample. In addition, CLIA requires that laboratories—before releasing test results—establish that non-FDA-regulated tests meet certain performance characteristics regarding analytic validity, but demonstrations of clinical utility and clinical validity are not required. These regulatory aspects may prove particularly problematic when commercial testing is offered for genes whose evidentiary basis as cancer susceptibility genes may be based on limited studies.

The other regulatory pathway for genetic test clearance, including germline DNA testing, is at the federal level through the FDA. For genetic tests, the FDA process includes metrics of accuracy of measurements to determine analytic and clinical validity. Clinical validity means that data exist regarding how accurately a test reflects a patient's clinical status (eg, being at increased risk for cancer).<sup>21</sup> In 2001, the US Department of Health and Human Services Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) recommended that the FDA play a greater role in the review of genetic tests.<sup>22</sup> In 2006, the FDA, the Centers for Disease Control and Prevention, and the Federal Trade Commission issued consumer warnings about claims of certain genetic tests that were being conducted in a CLIA-compliant environment.<sup>23</sup> In addition, questions were raised regarding variability among the CLIA requirements of different states for quality control. In 2010, the FDA notified several genetic testing companies offering direct-to-consumer risk assessment that it intended to regulate their offerings. In 2013, the FDA ordered one such company to stop marketing its test, maintaining that the company had not demonstrated that it had "analytically or clinically validated the [test] for its intended uses"<sup>24</sup> and expressing concern "about the public health consequences of inaccurate results from the [test]."<sup>24</sup>

Since these interactions, the FDA has issued draft guidance regarding its plans to regulate laboratory-developed tests using a risk-based framework.<sup>25</sup> Low-risk tests and those for rare diseases and unmet medical needs would require registration and listing, as well as adverse event reporting. Moderate-risk tests would initially follow this same path but, after 5 years, would change to premarket review. High-risk tests would require premarket review. An increased role for the FDA to regulate germline as well as somatic genetic testing would seek to improve overall quality control of testing laboratories and lead to more integrated standards, such as analysis pipelines for NGS data. However, there are significant concerns that such regulation may impede innovation and limit availability of certain specialty tests. ASCO supports the development of a rapid approval pathway for tests that address an unmet medical need, with the understanding that more than one test should be available before such a need is considered to have been met. ASCO further believes that an exemption for rarity should depend on the frequency of use of the test rather than on the

rate of occurrence of the disease in the general population. This distinction is important, because a widely applied test for a rare condition should be held to a high standard of performance. Moreover, infrequent use of a test by a particular laboratory may negatively affect the reproducibility of the results. The FDA must properly balance the limited data available to determine clinical validity and the need to ensure ongoing analytic validity for rare rests.

The application of NGS to cancer susceptibility testing has led to increased testing of genes of uncertain clinical utility and also to increased detection of VUSs. After the US Supreme Court decision in *Association of Molecular Pathology v. Myriad Genetic Laboratories* invalidated patents on isolated genomic DNA sequences, a number of laboratories began offering cancer susceptibility testing (both single-gene tests and multigene panels). The processes by which different laboratories assure the analytic and clinical validity and clinical utility of the sequence variants identified by their NGS analyses may vary. A uniform regulatory framework that extends beyond the assurance of analytic validity would improve the application of newer sequencing technology to the needs of cancer risk assessment. In the absence of such regulatory efforts, variable methods of interpretation and reporting of the clinical significance and actionability of variants could lead to compromises in patient care. In this regard, ASCO supports efforts to catalog and annotate all genomic variants and to create rigorously curated open-access libraries of the variants for use by all laboratories.

## EDUCATION OF ONCOLOGY PROFESSIONALS

ASCO affirms that the recognition and management of individuals at inherited risk for cancer is a core element of oncology practice. The skills required to provide cancer risk assessment services are not specific to a particular discipline but rather incorporate elements from oncology, medical genetics and genetic counseling, and other disciplines. ASCO recommends continued education of oncologists and other health care professionals in the area of cancer risk assessment and management of individuals with an inherited predisposition to cancer. ASCO recommends specific skills be integrated into oncology training and continuing education (Table 2). Oncology training programs should develop a set of core skills for new trainees and ensure adequate time in training for achieving these skills.

The ability to incorporate genetic information, both germline and somatic, into patient care is an important part of oncology practice. Oncologists are optimally positioned to advise patients regarding the management of their primary cancer and the risk of second malignancies and treatment-related cancers; thus, germline risk assessment is regularly integrated into standard oncology practice. For this reason, the identification and management of individuals at increased hereditary cancer risk are core competencies that have been integrated into oncology training requirements and certification by the Accreditation Council of Graduate Medical Education in its program requirements report,<sup>26</sup> summarized as follows:

- Section IV.A.5 delineates a set of competencies requiring that fellows be able to “competently perform all medical, diagnostic, and surgical procedures considered essential for the area of practice.”
- Section IV.A.5.a).(2).(f) states that “fellows must demonstrate competence specific to cancer prevention and screen-

**Table 2.** Suggested Learning Objectives in Oncology Training and Continuing Education

Objective
Understanding hereditary predisposition to cancer
Polygenic and multifactorial nature of cancer risk
Characteristics of hereditary cancer syndromes that may distinguish them from sporadic cancers
Hereditary cancer risk assessment
Describe elements of pretest consent for cancer susceptibility testing
Collection and interpretation of cancer family history
Genetic testing
Understand genetic testing results, including interpretation of variants of uncertain significance
Understand incidental and secondary findings from somatic tumor profiling
Recognition of major hereditary cancer syndromes
Define characteristic tumor spectrum of known syndromes
Recognize overlapping phenotypes that generate differential diagnosis for hereditary syndromes based on presenting cancer
Identify where multiplex genetic testing strategies may be most efficient and how understanding may change as less typical families are tested
Discuss benefits and limitations of available management strategies
Management of individuals at increased hereditary cancer risk
Apply current recommendations for risk reduction strategies in patients with hereditary cancer syndromes
Review how to use available models for estimating and communicating risk in cancer genetics

ing, including competency in genetic testing for high-risk individuals.”

- Section IV.A.5.b) delineates a set of areas where “fellows must demonstrate knowledge of established and evolving biomedical, clinical, epidemiologic and social-behavioral sciences, as well as the application of this knowledge to patient care.”
- Section IV.A.5.b).(4) states that fellows “must demonstrate knowledge of genetics and developmental biology, including: molecular genetics; prenatal diagnosis; the nature of oncogenes and their products; and cytogenetics.”

In addition, genetics and tumor biology comprise a dedicated content area of the medical oncology examination for both the American Board of Internal Medicine certification and maintenance of certification.

The work of oncologists today requires a level of knowledge about genetics that exceeds what most received during training. For oncologists participating in clinical practice who have completed oncology training, continuing medical education is crucial to maintaining an up-to-date understanding of the complex field of oncology and the changing environment for evaluating and treating neoplastic disease. ASCO and its volunteers have devoted considerable time and effort over the past two decades to helping establish high standards of quality for hereditary cancer genetic counseling and testing. Through policy statements, expert guidelines, and Quality Oncology Practice Initiative measures, ASCO has enabled oncology professionals to responsibly integrate genetic counseling and testing into clinical oncology practice. Oncology providers have demonstrated their interest in and commitment to continuing education on this issue. Over the last two decades, ASCO has developed two editions of an educational

**Table 3.** ASCO Cancer Genetics Educational Offerings

Offering
ASCO University Cancer Genetics Program: launched May 2014; No. of users as of October = 505 <a href="http://university.asco.org/node/2666">http://university.asco.org/node/2666</a>
ASCO University: Genetic Testing in Cancer Three-part activity focuses on genetic testing, particularly regarding breast cancer <a href="http://university.asco.org/genetic-testing-oncology">http://university.asco.org/genetic-testing-oncology</a>
ASCO University: Cancer Genetics Review Self-assessment for all oncology professionals, nurse practitioners, and physician assistants who need to assess their knowledge of cancer genetics <a href="http://university.asco.org/cancer-genetics-review">http://university.asco.org/cancer-genetics-review</a>
ASCO Annual Meeting: Cancer Genetics Track Genetics and Genomics for the Practicing Clinician (ASCO pre-meeting symposium): offered June 2013, June 2014, June 2015 ASCO virtual meeting archives <a href="http://meetinglibrary.asco.org/vm">http://meetinglibrary.asco.org/vm</a>
Abbreviation: ASCO, American Society of Clinical Oncology.

curriculum, has held numerous workshops and symposia, and has fostered a growing number of online education modules through ASCO University (Table 3). These efforts alone have resulted in the education of an estimated 10,000+ oncologists to date.

The cancer genetics education programs of ASCO continue to be robust today. Since 2013, ASCO has conducted an annual intensive 1.5-day course on genetics and genomics for oncology providers. ASCO also provides a comprehensive cancer genetics course through ASCO University, its online education platform. Designed to increase knowledge in the area of hereditary cancer genetics, these programs review the genes for which testing is now available and address how to incorporate such testing into patient care. In addition, they cover the process of genetic testing for common cancer syndromes and teach oncologists how to interpret VUSs. A core objective of the ASCO educational programs in this area is to ensure that providers can appropriately apply genetic testing and cancer screening in these syndromes.

ASCO will continue to provide educational opportunities focused on augmenting the training and ability of oncologists and other health care providers to appropriately use genetic testing, both germline and somatic, for the enhancement of care and follow-up of patients with cancer and their families.

### ACCESS TO CANCER GENETIC SERVICES

*ASCO is committed to ensuring access to high-quality cancer genetic services and supports continued expansion of third-party reimbursement for evidence-based genetic and genomic tests and preventive care in keeping with the rapid pace of scientific advances. In addition, ASCO opposes any payment policies that have the potential to negatively affect the care of patients with cancer by serving as barriers to the appropriate use of genetic testing services. ASCO will continue to advocate for coverage policies that support access to cancer risk assessment and prevention services for individuals who are suspected to be at increased genetic risk.*

Coverage of cancer genetic counseling and testing has improved over the last several years, but some payers still provide

inadequate access to these services. In particular, counseling time, if covered, is often poorly reimbursed.<sup>27</sup> The Affordable Care Act has established a set of essential health benefits, or core services that must be offered by individual and group insurers with no copay. Counseling for *BRCA1/2* mutation testing is considered an essential health benefit for appropriate patients with breast cancer, and the administration has clarified that coverage of the genetic test itself is required.<sup>28</sup> However, coverage of genetic counseling and testing for other cancer syndromes is not required under the Affordable Care Act, leaving this provision up to individual health plans to determine if and how they will cover these services.

In addition to ensuring adequate coverage, ASCO is committed to making sure coverage restrictions are not imposed that limit patient access to cancer genetic services. ASCO has become aware of at least one national payer that will only cover the cost of a genetic test if the indication for that test is approved by “a board-certified Genetic Counselor or a board-eligible or board-certified Clinical Geneticist.”<sup>29</sup> Any policies requiring the use of genetic counselors or physicians who are board eligible or certified in genetics before ordering genetic testing discounts the ability of appropriately trained physicians to adhere to the same guidelines and make proper recommendations for genetic counseling and testing. Moreover, such policies can put undue burden on patients, who already have an established relationship of trust and continuity with their physician provider. Ultimately, these types of policies may increase costs by requiring unnecessary outside referrals for services that could normally be provided within the licensed scope of medical practice. ASCO continues to support pre- and post-testing counseling when a patient is considered to be at risk for a hereditary susceptibility for cancer by a qualified health professional so that patients have the benefit of informed decision making regarding genetic testing. ASCO opposes any activities or requirements that limit the ordering of genetic testing when appropriate by current guidelines.

### DISCUSSION

Since the first ASCO statement in 1996, the assessment of germline cancer susceptibility has been established as a core element of oncology practice. The original purpose of risk assessment was largely to provide information regarding second cancer risk and risk to family members. Now, cancer treatment itself often depends on knowing whether a germline mutation is present. However, as germline information becomes more critical to oncology practice, new technology is introducing greater complexity. The application of NGS to somatic mutation profiling introduces the possibility of incidental or deliberate secondary identification of inherited risk, and cancer care providers must be prepared to address this possibility with their patients. The use of NGS in broad multigene germline panel testing also raises a number of issues that are not addressed well by traditional models of clinical cancer genetics. Whether NGS is being applied for somatic profiling or germline testing, appropriate regulatory structures are necessary to ensure that the testing provided to patients is of appropriate analytic and clinical validity to warrant use in clinical care. Cancer care providers from all backgrounds will need to continue their efforts at education to maximize the benefits to patients of new technologies

such as NGS, and organizations such as ASCO will continue to provide educational support. Providers offering comprehensive cross-disciplinary skill set, and adequate coverage for and reimbursement of genetic testing and counseling are necessary to ensure that patients have access to these services. ASCO is committed to working with all stakeholders, including providers, patients, and policymakers, to ensure that new developments in the field of cancer genetics are deployed effectively so as to maximize the positive impact on patient care.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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