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Submitted Electronically Via: GTR@od.nih.gov

July 9, 2010

NIH GTR RFI Comments
National Institutes of Health, Office of Science Policy
6705 Rockledge Dr., Room 750
Bethesda, MD 20892

RE: NIH Genetic Testing Registry Request for Information Comments

Dear Dr. Collins:

The American Society of Clinical Oncology (ASCO), with more than 28,000 members worldwide, is the leading medical society for physicians involved in cancer treatment and research. ASCO is committed to advancing the education of oncologists and other oncology professionals, to ensuring that evidence-based practices for prevention, diagnosis and treatment of cancer are available to all Americans, to advocating for policies that provide high-quality cancer care, and to supporting rigorous clinical and translational research that inform cancer policy. We appreciate the opportunity to provide comments on the National Institutes of Health plan to develop a Genetic Testing Registry (GTR).

As providers of genetic risk assessment to patients and families affected by cancer, it is the role of oncologists and other healthcare providers to offer genetic tests in a manner that is safe and clinically appropriate. In our 2003 and 2009 policy statements on cancer genetics testing, ASCO stated that federal regulation of genetic tests was insufficient and recommended additional oversight of laboratories that provide testing for genetic cancer risks. Given the potential impact of genetic tests for cancer risk on patients, consumers, and families, the federal regulatory framework must be strengthened to ensure that tests results form a reliable foundation for medical decision making. The 2009 statement is attached here for your reference.

ASCO's call for increased federal oversight of genetic testing echoes the recommendations set out in the Secretary's Advisory Committee on Genetics, Health, and Society's (SACGHS) 2008 report on the oversight of genetic testing. ASCO supports the recommendation made by SACGHS in this report, and reiterated in its more recent 2010 report, for the establishment of a mandatory registry for genetic and other laboratory-developed tests that would include information about the analytic validity, clinical validity and clinical

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utility of genetic tests, and be publicly available online. As a centralized information resource, a registry could help to inform the decisions of health care professionals, patients, and others about the quality, accuracy, and reliability of genetic tests and testing laboratories. In addition, a registry could facilitate increased federal oversight of genetic testing.

ASCO appreciates the opportunity to comment on this important issue and would welcome the opportunity to provide additional feedback on its development in the future.

Sincerely,

George W. Sledge, Jr., MD
President

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ASCO SPECIAL ARTICLE

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

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INTRODUCTION

As the leading professional organization representing physicians who are involved in cancer treatment and research, the American Society of Clinical Oncology (ASCO) has long recognized the importance of raising awareness among oncologists and other health care providers about the importance of inherited cancer risk in the practice of oncology and cancer prevention. In 1996, ASCO released its first statement on genetic testing, "Statement of the American Society of Clinical Oncology: Genetic Testing for Cancer Susceptibility,"[1] which set forth specific recommendations for oncologists relating to clinical practice and research needs. In 2003, ASCO updated this statement,[2] issuing recommendations related to the education of oncologists and other providers, pre- and post-test counseling by health care professionals, informed consent, regulation of laboratories, access, reimbursement, and protection from genetic discrimination. Since 2003, there have been significant developments in the field of genetics that require health care providers, patients, and other consumers of genetic information to think in new ways about these topics. In response, in October 2008, ASCO's Cancer Prevention and Ethics Committees commissioned an update of ASCO's previous statements on genetic testing that would reflect scientific advances and the evolving regulatory and policy environment. This statement update briefly reviews progress in priority areas identified in ASCO's previous statements and addresses how new developments, including the availability of genetic tests of uncertain clinical utility and direct-to-consumer (DTC) genetic testing, impact the practice of oncology and preventive medicine.

RECENT DEVELOPMENTS IN CANCER GENETICS AND GENOMICS

Emergence of Tests for Low-Penetrance Genetic Variants

Since the first ASCO statement, genetic testing for cancer susceptibility has become an accepted part of oncologic care. Germline testing for inherited predisposition is well established as part of the care of individuals who may be at hereditary risk for cancers of the breast, ovary, colon, stomach, uterus, thyroid, and other primary sites.[3,4] Germline genetic testing is distinct from somatic genetic profiling of cancer tissue to predict prognosis or treatment response. Germline testing involves analysis of DNA from blood or saliva for inherited mutations in specific genes that are associated with the type of cancer seen in the individual or family seeking assessment. When identified, such high-penetrance mutations usually result in a significant alteration in the function of the corresponding gene product and are associated with large increases in cancer risk. Other mutations (eg, *APC*I1307K*, *CHEK2*1100delC*) result in less dramatic increases in risk (intermediate penetrance). The identification of a high-penetrance mutation often justifies an adjustment of clinical care through the modification of surveillance or through preventive surgery. Germline testing for certain high-penetrance predispositions is now part of clinical guidelines and is reimbursed by most third-party payers.[5,6] The impact of intermediate-penetrance mutations on clinical care is less clear.

Although they are clinically relevant, high-penetrance mutations and intermediate-penetrance mutations are uncommon. Most inherited cancer susceptibility arises from a number of DNA sequence variants, each of which, in isolation, confers a limited increase in risk. The genomic locations of a number of these low-penetrance variants (LPVs) have been defined through genome-wide association studies (GWAS). GWAS have identified genetic variations called single nucleotide polymorphisms (SNPs) that, although strongly associated with disease in large case-control studies, are usually not the DNA variations that alter the function of relevant gene products. Instead, the SNPs are located in close proximity to as yet unidentified causative variants. Unlike high- and intermediate-penetrance mutations, SNPs associated with disease risk are generally common (allele frequencies of up to 50% in the populations studied) and confer a modest increase in risk (per-allele odds ratios of < 1.5), although penetrance can vary based on environmental and lifestyle factors. As many as 100 SNPs are currently associated

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with cancer risk.[7] Examples of low-, intermediate-, and high-penetrance genes with mutations and variants associated with increased risk of cancer are listed in Table 1.[8-24]

Several commercial laboratories currently offer genomic risk assessment, a type of genetic testing for SNPs associated with disease risk. In genomic risk assessment, the SNPs in an individual's genomic profile are identified (or genotyped) and translated into absolute risk estimates through the use of various algorithms. To date, no published studies are known to have established whether these algorithms are well calibrated or whether the risk estimates provided through genomic risk assessment are accurate. Because these tests have uncertain clinical validity, they are not currently considered part of standard oncology or preventive care.

Clinical Utility of Genetic Testing

Tests for high-penetrance mutations in appropriate populations have clinical utility, meaning that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes.[25] Genetic tests for intermediate-penetrance mutations and genomic profiles of SNPS linked to LPVs are of uncertain clinical utility because the cancer risk associated with the mutation or SNP is generally too small to form an appropriate basis for clinical decision making. For example, a particular LPV (ie, *rs13281615*) confers a risk of breast cancer equivalent to that of delaying childbearing from age 30 to 35. This level of risk does not warrant changes in recommendations for screening or prevention. However, if not framed appropriately, clinically ambiguous test results could produce unjustified alarm and may lead patients to request unnecessary screening and other preventive care that can cause physical discomfort or harm and increase costs. Alternatively, ambiguous test results or results associated with minimal cancer risk can provide false reassurance that discourages individuals from taking appropriate preventive measures.

Although tests to identify LPVs lack clear clinical utility, some have argued that genomic profiling may be justified on the basis of personal utility.[26,27] According to this construct, genetic tests may benefit individuals by providing deeper self-knowledge and motivation to pursue healthy behaviors even if the results do not inform clinical decision making. However, the theoretical benefits of personal utility must be balanced against the risks that may be associated with clinically ambiguous test results. Oncologists and other health care providers may be asked for advice about testing based on personal utility, even though the lack of clinical utility places this choice outside of traditional medical decision making.

DTC Availability of Genetic Tests

Until recently, genetic tests were only ordered by health care providers who served as intermediaries between individuals and the laboratories performing the tests. As intermediaries, health care providers order the tests, receive the results, communicate and explain the results, and coordinate appropriate follow-up care. Test results and subsequent interactions are documented in the medical record. Provider-mediated testing is subject to the ethical principles and legal obligations that are the hallmarks of provider-patient relationships, including truth-telling and confidentiality.[28,29]

Recently, a number of commercial entities have begun to provide genetic tests and genomic risk profiles directly to consumers, usually through Internet portals.[30] The DTC model allows individuals to obtain tests and receive results directly from the company that provides the test, outside of an established provider-patient relationship. Potentially medically relevant DTC tests include tests with accepted clinical utility (eg, *BRCA1/2* testing) and with uncertain clinical utility (eg, genomic profiling through SNP genotyping). Genetic tests of no medical relevance are also available but are not the focus of this statement.

Considerable concerns exist within the medical community about various aspects of DTC genetic testing. For instance, DTC advertising of tests with established clinical utility may promote inappropriate utilization of health care resources.[31] There are also

Table 1. Examples of Genes With Mutations and Variants Associated With Increased Risk of Cancer

Penetrance	Associated Cancer	Frequency in Population	Relative Risk (to specified age)	Intervention
Genes with high-penetrance mutations				
BRCA1	Breast cancer	1/166 to 1/1,000; 1/82 (AJ)	32 (age 40-49 years)	Mammography, MRI screening, risk-reducing surgery
MSH2	Colorectal cancer	1/5,800	13.1 (by age 30 years); 9.3 (by age 50 years)	Endoscopy, prophylactic colectomy after diagnosis of malignancy
APC	Colorectal adenocarcinoma	1/13,000	19 (L)	Endoscopy, prophylactic colectomy
RET	Medullary thyroid cancer	1/200,000	125 (L)	Prophylactic thyroidectomy
Intermediate-penetrance mutations				
*APC*I1307K*	Colon cancer	6/100 (AJ)	1.5-1.7 (L)	None proven
*CHEK2*1100delC*	Breast cancer	1/100-1/500	1.2-2.5 (L)	None proven
Low-penetrance variants (SNPs)				
rs10505477 at 8q24	Colon cancer; prostate cancer	1/2	1.27 (L) for colon cancer; 1.43 (L) for prostate cancer	None proven
rs13281615 at 8q24	Breast cancer	2/5	1.21 (L)	None proven
rs1219648 at *FGFR*	Breast cancer	2/5	1.23 (L)	None proven

Data adapted.[8-24]
Abbreviations: AJ, Ashkenazi Jews; MRI, magnetic resonance imaging; L, lifetime relative risk; SNPs, single nucleotide polymorphisms.

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concerns regarding the adequacy of counseling and informed consent for tests obtained in this manner. Similarly, there are concerns regarding the safety, effectiveness, and risks associated with DTC provision of tests of uncertain clinical utility. To date, there has been relatively little analysis of the economic, societal, and medical impact of DTC genetic testing. As benefits remain unclear, medical professional societies and other organizations have made recommendations to health care providers, patients, and families about how best to avoid potential harms.[1,2,32-35]

Early studies suggest that consumers of DTC tests anticipate that they will ask health care providers with whom they have ongoing relationships for advice regarding test interpretation and follow-up care.[36] For health care providers, these requests may pose significant challenges. Consumers may have pursued testing without the benefit of pre- or post-test counseling and may be unprepared to receive ambiguous or clinically significant results from tests with established clinical utility.[37] Where clinical utility is uncertain, providers face the added challenge of explaining why test results lack clinical consequences. In addition, tests with uncertain clinical validity are not sufficiently reliable to inform clinical decision making. For example, several reports show that the risk calculations for the same conditions derived from DNA samples from the same individual can yield disparate results when analyzed by different DTC laboratories.[38-41]

THE ROLE OF ONCOLOGISTS AND OTHER HEALTH CARE PROVIDERS

As providers of genetic risk assessment to patients and families affected by cancer, it is the role of oncologists and other health care providers to offer genetic tests in a manner that is safe and clinically appropriate. In its previous statements, ASCO recommended that, outside of a research protocol, genetic testing for cancer susceptibility only be offered when the following three criteria are met: the individual being tested has a personal or family history suggestive of genetic cancer susceptibility; the genetic test can be adequately interpreted; and the test results have accepted clinical utility.[2] These criteria continue to apply for testing of genetic mutations that cause known cancer susceptibility syndromes. However, for genomic variants of low penetrance, the first of these criteria may require modification. For example, it may be appropriate for oncologists and other health care professionals to support genomic profiling for individuals who do not have a family history of cancer, provided clinical utility is established and results can be adequately interpreted. When genetic tests of high or low penetrance are professionally mediated, health care providers should recommend follow-up care that is justified by the risk level associated with test results. Avoiding unnecessary screening and other medical interventions benefits patients and allows health care providers to serve as responsible stewards of medical resources.[42]

For tests that are professionally mediated, health care providers are responsible for coordinating post-test follow-up care for their patients. Individuals who order DTC tests of uncertain clinical utility (quadrant 4 of Fig 1) may also ask their health care providers for help interpreting test results and for access to follow-up care.[36] This poses significant challenges to the providers, who had no role in initiating or recommending the testing. Further compounding the issue, testing laboratories generally seek to disclaim responsibility for the medical uses of DTC tests, including determining the need for post-test follow-up. If individuals approach providers for guidance after obtaining test results of uncertain utility, it is appropriate for the providers to explain the lack of proven usefulness of the test and base medical follow-up recommendations solely on established cancer risk factors, including family history, possible exposures to cancer-causing substances, and behavioral factors, as well as scientifically validated tests for cancer risks.

Recommendation 1

When offering genetic and genomic testing, oncologists and other health care providers should continue to be guided by the criteria set out in ASCO's 2003 statement update. Recommendations for follow-up care should be commensurate with the level of risk associated with the genetic variant tested. In circumstances where DTC tests are of uncertain clinical utility, health care providers asked to advise on

	Tests for Which Clinical Utility Is Accepted	Tests for Which Clinical Utility Is Uncertain
Professionally Mediated	**Quadrant 1** HCP-ordered testing for high-penetrance mutations (eg, *BRCA1/2, MLH1/MSH2*)	**Quadrant 2** HCP-ordered testing for low- to moderate-penetrance mutations (eg, *CHEK2*)
Not Professionally Mediated	**Quadrant 3** DTC testing for high-penetrance mutations (eg, *BRCA1/2, MLH1/MSH2*)	**Quadrant 4** DTC testing for low-penetrance variants of uncertain clinical utility (eg, breast cancer risk SNPs)

Fig 1. Clinical utility of genetic and genomic tests. When considering the future development of germline genetic testing in oncologic care, it is useful to think of tests with regard to their position along two axes. The first axis identifies whether or not the test can be said to have accepted clinical utility. The second axis describes whether the test was obtained through the mediation of a health care provider (HCP) with whom the individual being tested had an ongoing relationship, or through a direct-to-consumer (DTC) channel. To date, most genetic testing for cancer susceptibility can be categorized as professionally mediated and of accepted clinical utility (quadrant 1). As the fields of oncology and genetics continue to progress and become increasingly intertwined, HCPs will need to develop a working knowledge of tests that fall under the other three quadrants.

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or recommend follow-up care should base recommendations on established risk factors.

EDUCATION AND TRAINING

ASCO's educational initiatives in cancer genetics began more than a decade ago and have led to the development of programs and materials intended to provide ASCO members and others with the information needed to deliver high-quality oncology and preventive care.[1,2,43,44] Today, education of oncologists remains a key priority. A 2007 survey of 2,000 ASCO members (data unpublished) demonstrated that ASCO members have a continued desire for education in the area of genetic testing. With the emerging availability of tests that identify genetic variants of uncertain clinical utility, forthcoming programs should explain the methodology of GWAS and highlight existing evidentiary gaps in clinical utility. An important resource for practitioners, evidence-based reviews are conducted by the Evaluation of Genomic Applications in Practice and Prevention working group, an advisory group to the Centers for Disease Control and Prevention.[45]

Because providers other than oncologists may be asked to aid in the interpretation of tests for cancer susceptibility, educational efforts in clinical cancer genetics must reach beyond the oncology community. Providing other health care providers (eg, internists, family practitioners, gynecologists) with information needed to interpret genetic risk assessments for cancer, including genomic profiles of uncertain clinical utility, will benefit patients, particularly as the United States faces an oncology workforce shortage.[46] Oncologists and other health care providers also have a role in educating patients and potential consumers of DTC tests about the promise and limitations of genomic risk profiles.

Recommendation 2

Forthcoming educational efforts by ASCO should focus on increasing preparedness among oncologists and other health care providers to administer genetic tests and to recommend appropriate follow-up care. Educational efforts should also raise awareness about recent advances in cancer genetic testing, including the uses and limitations of genomic profiling in assessing cancer risk. These educational efforts should extend beyond the oncology community to other health care providers, patients, and individuals considering DTC tests.

RESEARCH

As noted in ASCO's previous statements, prospective clinical trials, large registries, and retrospective reviews are the most accurate methods for deriving relative risks of genetic variants and measuring the response to and effectiveness of clinical interventions based on genetic cancer risk assessment. As tests with uncertain clinical utility become commercially available, establishing an evidence base for the clinically responsible use of these tests is vital for patient safety, as well as effectiveness. Wherever possible, genetic tests with uncertain clinical utility should be administered in the context of clinical trials.

Research is also needed to demonstrate the validity and reproducibility of some commercially available tests, particularly for LPVs defined by SNP genotyping.[47] Systematic reviews of genomic variants used in commercial assays show that more than 40% have not been replicated in meta-analyses.[48] Because the algorithms used to convert genotypes into absolute risk estimates are empirically derived, prospective research is needed to confirm the calibration of these estimates and to measure the effectiveness of interventions based on individual genomic profiling. Research should include basic studies of the functional significance of the genetic variants linked to disease risk, as well as prospective, randomized controlled trials of individual genomic markers. At a more translational level, it is important to establish criteria for the technologic assessment of genetic and other diagnostic tests.

It is imperative that future research efforts, such as prospective studies of LPVs, include behavioral and psychosocial end points. Research should focus on the interactions between genetic variants; the interactions between variants and environmental or other nongenetic risk factors (eg, drug exposures as part of pharmacogenomic studies); the predictive accuracy of genomic tests compared with traditional risk markers (eg, family history); the psychosocial factors that influence uptake of genetic tests and follow-up actions; the impact of ambiguous test results on the decision to engage in regular prevention activities or demand additional preventive care; and the impact of genomic information in the setting of health and economic disparities worldwide.[49-52] Studies to promote effective communication of risk information to patients are important given the challenges of explaining the difference between relative and absolute risks and the minor risks associated with LPVs.[50,51] The high demand for multidisciplinary research related to genetic testing is evidenced by recent requests for research on this topic by federal government agencies including the National Institutes of Health, the National Cancer Institute, the Centers for Disease Control and Prevention, and the Agency for Healthcare Research and Quality.[51,52] These research programs should be funded for additional cycles and expanded.[53-56]

Finally, if genetic and genomic tests for cancer risk are going to be offered or justified on the basis of personal utility, an effort should be made to establish an evidence base for these claims. Research should focus on the extent to which personal benefits accrue to individuals who receive tests that have uncertain clinical utility and the appropriate mechanism for measuring personal utility. Establishing an evidence base for personal utility is particularly important for tests that would not be recommended based on clinical utility.[48,51]

Recommendation 3

ASCO recommends that genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials. In addition, ASCO supports increased funding for basic and translational research in clinical cancer genetics, including research to demonstrate the clinical validity and reproducibility of risk estimates based on genomic profiles; prospective clinical studies of variants discovered through GWAS and sequencing of individual genomes; multidisciplinary research with clinical, behavioral, and psychosocial end points; and research to investigate an evidence base for claims of personal utility.

PRE- AND POST-TEST COUNSELING

As in its previous statements, ASCO recommends that genetic testing only be conducted in the setting of pre- and post-test counseling.

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Pretest counseling allows for advance consideration of medical options and the impact test results may have on family members. Post-test counseling provides a valuable opportunity for health care providers to interpret test results, recommend appropriate follow-up, and emphasize the importance of continuing regular prevention activities. Not all DTC testing companies offer counseling, and they may only offer counseling to consumers who pay additional fees. Where counseling is provided, there is some concern that advice offered by counselors employed by testing companies may be biased in favor of testing.[57]

Recommendation 4

ASCO reiterates its recommendation that all genetic testing and genomic risk assessment, including genomic profiling for LPVs of uncertain clinical utility, be conducted in the setting of pre- and post-test counseling by experienced health care professionals. ASCO recommends that DTC testing companies provide pre- and post-test counseling or refer consumers to independent providers of these services.

INFORMED CONSENT

ASCO has consistently underscored the importance of informed consent for genetic testing in its policy statements and other educational offerings. In its 2003 statement update, ASCO outlined the basic elements of informed consent for genetic testing for cancer risk.[2] This established framework remains relevant today, subject to minor updates that address issues raised by the availability of genetic and genomic tests with uncertain clinical utility and DTC tests. These updates are listed in Table 2.

For professionally mediated genetic and genomic tests, health care providers and patients engage in the process of informed consent, often as a component of pre- and post-test counseling. In the absence of genetic counseling by their health care providers, it is necessary for individuals seeking DTC testing to proactively obtain information they need to make informed decisions. The basic elements of consent identified by ASCO can serve as a framework for gathering this information. Awareness of laboratory privacy policies and practices related to data security, laboratory compliance with applicable licensing requirements, the availability and cost of genetic counseling, and the possible use of DNA testing samples in future company research may be relevant to an individual's decision to pursue genetic or genomic testing. Companies offering DTC tests should make this information clearly and easily available to the public, preferably as part of a consent form that must be acknowledged by the individual undergoing testing before testing is completed. Laboratories intending to conduct research using DNA samples submitted for testing should obtain consent to use these samples. The consent form should explain whether and how samples will be identified, stored, and destroyed, and whether genetic risks found through future research will be reported back to individuals who allow their samples to be used. Testing should not be contingent on allowing DNA samples to be used in future research.

Table 2. Basic Elements of Informed Consent for Cancer Susceptibility Testing (modified from American Society of Clinical Oncology 2003 statement[2])

1. Information on the specific genetic mutation(s) or genomic variant(s) being tested, including whether the range of risk associated with the variant will impact medical care
2. Implications of a positive and negative result
3. Possibility that the test will not be informative
4. Options for risk estimation without genetic or genomic testing
5. Risk of passing a genetic variant to children
6. Technical accuracy of the test including, where required by law, licensure of the testing laboratory
7. Fees involved in testing and counseling and, for DTC testing, whether the counselor is employed by the testing company
8. Psychological implications of test results (benefits and risks)
9. Risks and protections against genetic discrimination by employers or insurers
10. Confidentiality issues, including, for DTC testing companies, policies related to privacy and data security
11. Possible use of DNA testing samples in future research
12. Options and limitations of medical surveillance and strategies for prevention after genetic or genomic testing
13. Importance of sharing genetic and genomic test results with at-risk relatives so that they may benefit from this information
14. Plans for follow-up after testing

Abbreviation: DTC, direct to consumer.

Recommendation 5

Patients and health care providers should engage in the informed consent process before cancer susceptibility testing in accordance with the basic elements of consent updated in Table 2. Individuals considering DTC testing are advised to gather information that will help them make informed decisions about pursuing genetic or genomic testing. Testing laboratories should make information about data privacy, data security, laboratory licensure, the availability of genetic counseling or cancer genetic risk assessment, and any potential for future use of DNA samples submitted for testing clearly and easily available to the public.

ACCESS

ASCO has previously called for increased access to genetic testing and coverage of genetic testing services by third-party payers. Considerable progress in this area has been achieved; genetic risk assessment and genetic counseling for most cancer predisposition syndromes are covered by major third-party carriers. ASCO reiterates its call for coverage of genetic and genomic testing services that keeps pace with proven scientific advances in testing and preventive care.[2,44] As data emerge and are replicated, it will be vital to include evidence-based genomic risk profiles and pharmacogenomic tests in existing third-party reimbursement policies. In addition, the importance of making genetic and genomic tests available to populations who have been historically underserved by the US health care system cannot be overstated; without improvements in access, the health disparities faced by these groups will continue to grow. Providing coverage under Medicare and Medicaid for a broader range of genetic testing and related services with demonstrated clinical utility would help minimize gaps in access.[58] The exploration of novel, culturally sensitive approaches may also improve uptake and effectiveness of genetic testing among underserved groups.[59-61]

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Recommendation 6

ASCO supports continued expansion of third-party reimbursement of genetic and genomic tests and preventive care with accepted clinical utility in keeping with the rapid pace of scientific advances. ASCO also recommends that steps be taken to ensure access to testing for historically underserved groups, including increased coverage by Medicare and Medicaid, and the exploration of novel, culturally sensitive approaches to increasing the uptake and effectiveness of testing.

GENETIC DISCRIMINATION

ASCO previously identified genetic discrimination by employers and health insurance companies as a significant barrier to uptake of genetic and genomic testing services and called for federal antidiscrimination protections. In 2008, the signing into law of the Genetic Information Nondiscrimination Act[62] established significant protections against genetic discrimination by employers and health insurers.[63] The Genetic Information Nondiscrimination Act prohibits health insurance carriers from denying coverage because an individual took or refused to take a genetic test, or from denying coverage based on test results, and prohibits employers from using this information as the basis for employment decisions. It is hoped that these protections will ensure that individuals who stand to benefit from genetic tests are not deterred by fears of discrimination based on test results, particularly as genetic testing becomes an increasingly standard part of medical practice. However, it is important for patients to be aware that, at this time, there are no special protections against the use of genetic information to inform the provision of life insurance, disability insurance, or long-term care insurance.[64]

GENETIC PRIVACY

Results from genetic and genomic testing facilitated by health care providers can only be disclosed by health care providers and laboratories in limited circumstances permitted by state and federal privacy laws and regulations, including the Health Insurance Portability and Accountability Act.[65] However, companies that provide genetic tests directly to consumers may not be obligated to comply with these rules and could use or disclose consumers' genetic information in ways that would not be permitted within the traditional health care system.[66] Individuals considering DTC testing should become familiar with the terms of company policies related to privacy and data security, including how genetic information can be shared with outside parties or become part of their medical records. In addition, these individuals should be mindful of potentially misleading claims about the privacy of DTC tests, including that DTC tests have more privacy protections than professionally mediated tests because results do not necessarily become part of a patient's medical record.[34] Misleading claims should be investigated by the Federal Trade Commission (FTC), which has the authority to regulate claims about the risks and benefits of genetic tests, including privacy risks.[34,35,66-68]

Recommendation 7

ASCO recommends that individuals considering genetic testing become familiar with company policies related to privacy and data security. Laboratories providing testing should develop written privacy policies that are easily accessible to individuals considering testing. Any claims about the privacy of DTC testing should be truthful and nonmisleading.

REGULATION OF GENETIC AND GENOMIC TESTS

In its 2003 statement update, ASCO observed that federal regulation of genetic tests was insufficient and recommended additional oversight of laboratories that provide testing for genetic cancer risks. To date, little progress has been made toward increasing oversight of genetic and genomic tests. Given the potential impact of genetic tests for cancer risk on patients, consumers, and families, the federal regulatory framework must be strengthened to ensure that tests results form a reliable foundation for medical decision making.

Most genetic tests and genomic risk profiles are made by individual testing laboratories for in-house use (home brews) and are primarily regulated under the Clinical Laboratory Improvement Amendments (CLIA).[69] Under CLIA, laboratories that provide testing services are required to meet standards for quality, accuracy, and reliability. Beyond these general requirements, the Center for Medicare and Medicaid Services (CMS) can set additional standards for analytic validity and require proficiency testing to establish the accuracy of tests across laboratories. CMS has not established additional requirements for genetic and genomic testing, despite calls from ASCO and other groups.[34,70-72] ASCO continues to support its previous recommendation that all genetic testing laboratories participate in some form of proficiency testing.[2] As noted in ASCO's 2003 statement update, laboratories should, at a minimum, meet the highest available standards for laboratory genetics services established by the certifying or regulating bodies in their home countries. In the United States, this includes successful participation in the College of American Pathologists inspection and American College of Medical Genetics/College of American Pathologists survey program, and state licensing and credentialing of laboratory directors and staff.

The US Food and Drug Administration (FDA) can also regulate genetic and genomic tests but has generally chosen not to exercise its authority.[34] However, recent activities may signal a change in course. In 2007, the FDA released draft guidance that asserted FDA authority over a subset of laboratory tests.[73] More recently, FDA used its authority to remove a cancer diagnostic test from the market based on concerns about its clinical validity.[74] ASCO supports FDA oversight of the safety and effectiveness of genetic and genomic tests. Regulatory standards should be clear and efficient and should not unreasonably hinder scientific development or the delivery of quality oncology and preventive care.[75] Efforts should be made to clarify the roles of the FDA and CMS and avoid duplicative oversight efforts. In addition, FDA and other stakeholders within the Department of Health and Human Services (DHHS) should work with FTC to ensure adequate oversight of advertising claims made by genetic test manufacturers.

In the absence of increased federal oversight, variations in state regulation of genetic and genomic tests have become more apparent. Although most states require laboratories to comply with basic CLIA standards, some impose additional requirements for laboratory certification and licensure that exceed these standards (eg, New York, Washington).[76] Also, according to research originally conducted by the Genetics and Public Policy Institute in 2007 and reviewed by ASCO staff in 2009, although most states permit some form of DTC

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testing, some prohibit it (eg, Alabama, Connecticut, Michigan) or only allow it subject to strict laboratory licensure requirements and marketing restrictions (eg, New York, California).[77] These variations create inconsistent protections for patients and consumers and inconsistent compliance obligations for laboratories and testing companies. The impact of these inconsistencies was evident in the past year, as health officials in New York and California threatened to take enforcement actions against DTC genetic testing companies that failed to meet state-specific laboratory and other requirements.[78,79]

ASCO's call for increased federal oversight of genetic testing echoes the recommendations set out in the Secretary's Advisory Committee on Genetics, Health, and Society's (SACGHS) 2008 report, "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services ("2008 Oversight Report")."[80] In its 2008 Oversight Report, SACGHS called for DHHS to establish a mandatory registry for genetic and other laboratory-developed tests that would include information about the analytic validity, clinical validity, and clinical utility of genetic tests, and be publicly available online. ASCO supports this recommendation and joins several other groups in advocating for the creation of a registry that includes DTC tests.[81,82] As a centralized information resource, a registry could help to inform the decisions of health care professionals, patients, and others about the quality, accuracy, and reliability of genetic tests and testing laboratories. In addition, a registry could facilitate increased federal oversight of genetic testing.

Although DHHS has not yet created a registry, ASCO is hopeful that a renewed call for action by SACGHS will encourage DHHS to carry out this and other recommendations initially proposed in the 2008 Oversight Report. A SACGHS paper on DTC genetic testing, expected in 2010, will suggest that DHHS take specific action steps based on 10 recommendations from the Oversight Report, to address issues raised by DTC tests. In addition to calling for a genetic test registry that includes DTC tests, it is anticipated that the upcoming SACGHS paper will recommend convening an DHHS-FTC task force to develop specific guidelines for advertising, promotion, and claims about DTC tests; identifying gaps in state and federal privacy protections for consumers of DTC tests; and developing an educational initiative specific to DTC tests. ASCO endorses these initiatives as well as the call for greater stakeholder input in rulemaking.[83]

Recommendation 8

ASCO recommends increased oversight by FDA and CMS that sets standards for the accuracy, validity, and quality of genetic tests and testing laboratories. Regulatory standards should be applied in a manner that is clear and efficient and does not unreasonably hinder scientific development or the delivery of quality oncology and preventive care. To facilitate increased oversight, ASCO supports the creation of a mandatory, publicly available registry that requires the manufacturers of genetic tests, including DTC tests, to disclose information about their tests' analytic validity, clinical validity, and clinical utility.

CONCLUSION

The recent emergence of genetic tests that have uncertain clinical utility and the availability of DTC testing require oncologists, other health care providers, patients, and consumers to think in new ways about topics ranging from informed consent to privacy, education, and counseling. ASCO believes that the basic principles established in its prior statements on cancer genetic testing are appropriate, in updated form, to guide the responsible integration of these new genetic and genomic technologies into clinical practice. ASCO remains committed to providing educational opportunities that delineate both the promise and limitations of genetic and genomic testing in the context of clinical oncology and preventive medicine. To keep up with the rapid pace of scientific advancement and changes in the regulatory and policy environment, ASCO will continue to review and update these recommendations periodically.

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