

Statement of the American Society of Clinical Oncology: Genetic Testing for Cancer Susceptibility

Adopted on February 20, 1996 by the American Society of Clinical Oncology*

As the leading organization of physicians who treat people with cancer, the American Society of Clinical Oncology (ASCO) recognizes that cancer specialists must be fully informed of the range of issues involved in genetic testing for cancer risk. The newly discovered and still developing ability to identify individuals at highest risk for cancer holds the promise of improved prevention and early detection of cancers. It also poses potential medical, psychological, and other personal risks that must be addressed in the context of informed consent for genetic testing. ASCO firmly believes that any physician who offers genetic testing should be aware of, and able to communicate, the benefits and limits of current testing procedures, and the range of prevention and treatment options available to patients and their families. For these reasons, ASCO endorses the following principles:

- ASCO affirms the role of clinical oncologists in documenting a family history of cancer in their patients, providing counseling regarding familial cancer risk and options for prevention and early detection, and recognizing those families for which genetic testing may serve as an aid in counseling.
- To the greatest extent possible, genetic testing for cancer susceptibility should be performed in the setting of long-term outcome studies. ASCO endorses the formulation and implementation of a national cooperative study/registry with appropriate confidentiality to define the clinical significance of mutations in known cancer susceptibility genes.
- ASCO is committed to providing educational opportunities for physicians concerning methods of quantitative cancer risk assessment, genetic testing, and pre- and post-test genetic counseling so that oncologists may more responsibly integrate genetic counseling and testing into the practice of clinical and preventive oncology.
- Oncologists must assure that informed consent has been given by the patient as an integral part of the process

THE American Society of Clinical Oncology (ASCO), a national medical specialty society representing 10,000 cancer specialists involved in patient care and clinical research, recognizes the need for cancer specialists to become aware of the role of inherited genetic alterations in the development of malignancy. The newly discovered and still developing ability to identify subsets of individuals at highest hereditary risk

of genetic predisposition testing, whether such testing is offered on a clinical or research basis.

- ASCO recommends that cancer predisposition testing be offered only when: 1) the person has a strong family history of cancer or very early age of onset of disease; 2) the test can be adequately interpreted; and 3) the results will influence the medical management of the patient or family member. As clinical testing becomes more widely available, the Society encourages oncologists to utilize laboratories committed to the validation of testing methodologies, and to facilitate families' participation in long-term outcome studies.
- ASCO recommends that oncologists include in pre- and post-test counseling discussion of possible risks and benefits of cancer early detection and prevention modalities, which have presumed but unproven efficacy for individuals at the highest hereditary risk for cancer.
- ASCO endorses efforts to strengthen regulatory authority over laboratories that provide cancer predisposition tests that will be utilized to inform clinical decisions. These regulatory requirements should include appropriate oversight of the products used in genetic testing, interlaboratory comparisons of reference samples, as well as quality control mechanisms.
- ASCO endorses all efforts including legislation to prohibit discrimination by insurance companies or employers based on an individual's inherited susceptibility to cancer.
- All individuals at hereditary risk for cancer should have access to appropriate genetic testing and associated medical care, which should be covered by public and private third-party payers.
- ASCO endorses continued support of patient-oriented research to analyze the psychological impact of genetic testing of at-risk populations.

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See Appendix for Subcommittee Member affiliations.

From the American Society of Clinical Oncology.

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**ASCO sincerely appreciates the contributions of the ASCO Subcommittee on Genetic Testing for Cancer Susceptibility, which de-*

voted much time and effort to this project. Chair: Kenneth Offit; and Subcommittee members: Barbara Bowles Biesecker, Randall W. Burt, Ellen Wright Clayton, Judy E. Garber, Mary Jo Ellis Kahn, Allen Lichter, Patrick Lynch, Michael S. Watson, Barbara Lynn Weber, and Samuel A. Wells.

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and treatment options available to patients and their families.

State-of-the-art genetic testing for cancer susceptibility continues to evolve rapidly. Following the localization of genes associated with two common hereditary cancer syndromes, the National Advisory Council for Human Genome Research¹ and the American Society of Human Genetics² issued statements suggesting that clinical use of this information be confined to a research setting. Since these statements were published in 1994, genes associated with inherited susceptibility to common adult malignancies, including those of the breast, ovary, colon, and endocrine organs, have been characterized. Initial reports have documented the most common mutations of these genes and have identified groups that could potentially derive clinical benefit from presymptomatic testing and counseling.³⁻¹³ While important research issues remain, and the need for regulatory assurances of quality of testing is evident, commercial and university-based laboratories have begun to make genetic testing available for some of the recognized syndromes of inherited cancer predisposition.

In response to these developments, ASCO, through its Public Issues Committee, assembled a subcommittee to advise clinical oncologists on the critical issues that must be addressed if these technologies are to be responsibly and effectively translated to the care of their patients with cancer and their families. This statement summarizes the findings and policy recommendations of the Society.

A. Recommendations pertaining to clinical aspects of genetic testing for cancer susceptibility

1) Cancer risk counseling as part of the mission of clinical oncologists

ASCO affirms the role of clinical oncologists in documenting a family history of cancer in their patients, providing counseling regarding familial cancer risk and options for prevention and early detection, and recognizing those families for which genetic testing may serve as an aid in counseling.

Risk assessment based on a family history of cancer and discussion of options for screening and prevention of cancer are basic aspects of preventive oncology. In certain instances, DNA-based testing may serve as a useful adjunct to cancer risk counseling. Because genetic testing raises a host of medical, social, psychological, and ethical issues for patients and their families, it is imperative that these issues be addressed both before and after genetic susceptibility testing for cancer is offered. Genetic

testing should, therefore, be made available to selected patients as part of the preventive oncologic care of families only in conjunction with appropriate patient education, informed consent, support, and counseling. These issues must be addressed by all health care professionals, whether they be oncologists, genetic counselors, medical geneticists, or primary care providers, who plan to offer genetic testing for cancer susceptibility.

2) Educational opportunities for physicians for pre- and post-test counseling

ASCO is committed to providing educational opportunities for physicians on the methods of quantitative cancer risk assessment, genetic testing, and pre- and post-test genetic counseling so that health professionals may more responsibly integrate genetic counseling and testing into the practice of clinical and preventive oncology.

The Society acknowledges that assessment of inherited mutations of cancer predisposition genes will have a significant impact on the practice of clinical and preventive oncology. Cancer specialists will need to address such issues as the risks for secondary cancers and rational treatment strategies for individuals with inherited cancer susceptibilities. In view of the limited number of genetic counselors familiar with cancer care, oncologists will require additional education in molecular genetics, pedigree construction, and Bayesian analysis as well as in the ethical and legal complexities of genetic testing to provide individualized counseling to unaffected members of their patient's families. ASCO is committed to developing courses to educate oncologists, genetic counselors, and other health professionals who will be called upon to provide these services. Until such programs are available, it is prudent and advisable for oncologists to obtain consultation from colleagues with expertise in cancer genetic testing.

3) The need for informed consent

Oncologists must assure that informed consent has been given by the patient as an integral part of the process of genetic predisposition testing, whether such testing is offered on a clinical or research basis.

As new technologies emerge, the investigational nature of the test or treatment is approached with an appropriately high level of concern for informed consent. Even as genetic testing is incorporated into the practice of oncology, the special nature of genetic information requires a continued need for informed consent. The goal of the

Table 1. Basic Elements of Informed Consent for Germline DNA Testing

1. Information on the specific test being performed
2. Implications of a positive and negative result
3. Possibility that the test will not be informative
4. Options for risk estimation without genetic testing
5. Risk of passing a mutation to children
6. Technical accuracy of the test
7. Fees involved in testing and counseling
8. Risks of psychological distress
9. Risks of insurance or employer discrimination
10. Confidentiality issues
11. Options and limitations of medical surveillance and screening following testing

consent process is to include a thorough discussion, as well as written documentation, of the risks, benefits, and limitations of testing by an adequately trained health professional. Such documentation serves as an educational resource as well as a record of the discussion between the parties. The informed consent process is a critical element in pretest genetic counseling.

Discussion of the elements of informed consent, outlined in Table 1, should occur in advance of testing, not when a result is available. Discussion should include: 1) information on the purpose of the test, ie, to determine whether a mutation can be detected in a specific cancer susceptibility gene; 2) what can be learned from both a positive and negative test, including the most recent information on the type and magnitude of health risks associated with a positive test, as well as the risks that may remain even after a negative test; 3) the possibility that no additional risk information will be obtained at the completion of the test; 4) the options for approximation of risk without genetic testing, eg, using empiric risk tables for breast cancer given differing family histories; 5) the risk of passing a mutation on to children; 6) the technical accuracy of the test; 7) the fees involved for both the laboratory test and the associated consultation by the health professional providing pretest education, results disclosure, and follow-up; 8) the risks of psychological distress and family disruption, whether a mutation is found or not found; 9) the risk of employment and/or insurance discrimination following disclosure of genetic test results; 10) the level of confidentiality of results compared with other medical tests and procedures; and 11) the medical options and limited proof of efficacy for surveillance and cancer prevention for individuals with a positive test, as well as the accepted recommendations

for cancer screening even if genetic testing is negative. This latter discussion is important to avoid false security and inadequate surveillance for those whose genetic test may be negative, but who are still at risk based on other genetic factors, age, environment, or other reasons.

The informed consent discussion should emphasize that this process of disclosure serves to make the individual considering testing more fully aware of what is known and what is not known about cancer risk determination and possible means of reducing cancer-associated mortality. Implicit in all discussions of the options for genetic testing is the right of the individual not to be tested.

4) Indications for genetic testing

ASCO recommends that cancer predisposition testing be offered only when: 1) the person has a strong family history of cancer or very early age of onset of disease; 2) the test can be adequately interpreted; and 3) the results will influence the medical management of the patient or family member. As clinical testing becomes more widely available, the Society encourages oncologists to utilize laboratories committed to the validation of testing methodologies, and to facilitate families' participation in long-term outcome studies.

Despite the rapid pace of research in cancer genetics, none of the cancer susceptibility tests currently available are appropriate for screening of asymptomatic individuals in the general population. In the setting of well-defined cancer susceptibility syndromes, however, the identification of a mutation in an affected member of the family can be utilized as a critical baseline in the testing of other family members. A negative test in the setting of a known mutation in a family may provide significant emotional relief as well as allow a decreased frequency of medical surveillance. Despite these benefits, genetic testing also poses several risks. In families where a mutation has been identified, a positive genetic test can create anxiety and may lead to preventive or screening interventions of presumed, but unproven, efficacy. A "false negative" test may result in undue reassurance for an individual at markedly increased cancer risk by virtue of family history, but with a negative result for a particular gene being tested. False negative results may also result from laboratory error. An ambiguous test may result from documentation of a single base pair change or other genetic alteration of unknown clinical significance. For these reasons, ASCO recognizes the need for ongoing research, rigorous quality assurance of genetic testing, and continued medical edu-

Table 2. Three Categories for Consideration for Cancer Predisposition Testing

Group 1	
<i>Tests for families with well-defined hereditary syndromes for which either a positive or negative result will change medical care, and for which genetic testing may be considered part of the standard management of affected families.</i>	
Syndrome	Gene Tested
Familial Adenomatous Polyposis	APC*
Multiple Endocrine Neoplasia 2a, 2b	RET*
Retinoblastoma	RB1
Von Hippel-Lindau Syndrome	VHL
Group 2	
<i>Tests for hereditary syndromes with a high probability of linkage to known cancer susceptibility genes, and for which the medical benefit of the identification of a heterozygote ("carrier") is presumed but not established. The potential clinical value and reliability of the test is based on research studies.</i>	
Syndrome	Gene Tested
Hereditary Non-Polyposis Colon Cancer	MSH2*, MLH1*, PMS1, PMS2
Hereditary Breast Ovarian Syndrome	BRCA1*, BRCA2†
Li-Fraumeni Syndrome	p53*
Group 3	
<i>Tests for individuals without a family history of cancer, in which the significance of the detection of a germline mutation is not clear; or tests for hereditary syndromes for which germline mutations have been identified only in a small number of families, or for which the medical benefit of the identification of a heterozygote ("carrier") is not established.</i>	
Syndrome	Gene Tested
Melanoma, and melanoma associated syndromes	p16*, CDK4
Ataxia Telangiectasia-associated susceptibilities	ATM

*Mutation detection is commercially available, utilizing various methodologies for which sensitivity and specificity may not be known. Commercial availability of a genetic test does not ensure that the test is indicated for routine clinical application (see text Section A.4).

†Risk based on identification of BRCA2 mutations is currently offered only as part of research studies. Pending identification of the spectrum of mutations, the presumed benefits of BRCA2-based counseling are not fully defined.

cation about the interpretation of genetic susceptibility tests (see Sections A.2, B.1, B.4).

In view of the increasing demand for and commercial availability of genetic testing, ASCO recommends that practitioners recognize three categories of indications for genetic testing as listed in Table 2. Tests included in Group 1 are those for families with well-defined hereditary syndromes for which either a positive or negative result will change medical care, and for which genetic testing is now considered part of the standard management of affected families. Group 2 tests are those for hereditary syndromes where the medical benefit of the identification of a "carrier" (heterozygote) is presumed

but not proven. For this category of tests, however, a negative test in the context of a mutation present in the family may have considerable medical and psychological significance, and a positive test may lead to earlier surveillance or consideration of prevention options. Group 3 tests are those for individuals without family histories of cancer, or for syndromes in which germline mutations have been identified only in a small number of families, and for which the medical benefits of the identification of a heterozygote are not apparent.

Oncologists should consider offering genetic testing only for the first two categories described above and listed in Table 2. This should be done only if clinicians are able to provide or make available adequate genetic education and counseling as well as access to preventive and surveillance options. Genetic testing for Group 1 is considered part of the medical management of affected families. Most of the genetic testing for Group 2, including families with hereditary breast, ovarian, and colon cancer, is still in the process of being integrated into standard medical practice and is currently being provided in the context of Institutional Review Board–approved research protocols.

Current criteria defining families with the highest likelihoods of harboring mutations of two common cancer susceptibility genes are listed in Table 3. Even in these settings, when the results of genetic testing are most likely to be of clinical value, oncologists are strongly encouraged to offer family members participation in long-term outcome research, to facilitate such participation (see Section B.4), and to utilize commercial or university-based laboratories committed to the validation of test results (see Section B.1). Such test validation, which is applicable to all three groups listed in Table 2, is necessary to

Table 3. Two Hereditary Cancer Syndromes with High Estimated Probabilities of Mutation Detection in an Affected Family Member

<i>BRCA1 mutations* in Hereditary Breast/Ovarian Syndrome</i>	
Family with > 2 breast cancer cases and one or more cases of ovarian cancer diagnosed at any age	
Family with > 3 breast cancer cases diagnosed before age 50	
Sister pairs with two of the following cancers diagnosed before age 50: two breast cancers; two ovarian cancers; or a breast and ovarian cancer	
<i>MSH2, MLH1, PMS1, PMS2 mutations† in Hereditary non-Polyposis Colorectal Cancer (HNPCC)</i>	
Colorectal carcinoma in three individuals one of whom is the first degree relative of the other two, with two generations affected and one of the cases diagnosed before age 50	

*Prior probability of a BRCA1 mutation estimated to be > 10%.^{5,7}

†Linkage to 2p and 3p has been shown in the majority of families meeting these "Amsterdam" criteria for HNPCC. Uterine cancer, and possibly other tumor types, are also features of HNPCC.^{3,4}

refine estimates of the sensitivity and specificity of tests. Long-term outcome studies are necessary to confirm predicted age-specific risks (penetrance) of mutations, and to document the effectiveness of counseling and prevention/early diagnosis interventions. Genetic testing for Group 3 is considered research with unknown clinical implications and should not be offered in a clinical setting. The results of studies of mutation frequencies in individuals without a family history of cancer will provide information needed to extend counseling beyond high-risk families. Principal investigators of research studies addressing these issues should consider applying for a Certificate of Confidentiality¹⁴ as one means to seek to protect genetic data acquired in the course of these studies.

Commercial availability of a new genetic test in any of the three groups does not ensure that the test is indicated for clinical application.

5) Medical management after testing and counseling

ASCO recommends that oncologists include in pre- and post-test counseling discussion of possible risks and benefits of cancer early detection and prevention modalities, which have presumed but unproven efficacy for individuals at the highest hereditary risk for cancer.

Building upon the discussion necessary for informed consent, clinical oncologists should be prepared to offer family members individualized options for cancer screening utilizing radiographic, biochemical, endoscopic, or direct physical examination, as well as discussion of the option for prophylactic surgery (eg, mastectomy, oophorectomy, colectomy, thyroidectomy) in individuals with a known mutation of a cancer predisposition gene. While prophylactic surgery is an accepted part of the management of some cancer predisposition syndromes (eg, familial adenomatous polyposis, multiple endocrine neoplasia 2a), discussion of these options should be highly individualized in other syndromes (eg, hereditary breast/ovarian cancer). In these circumstances, long-term follow up trials will be necessary to demonstrate efficacy in high-risk groups (see Section B.4). The Society endorses the development of guidelines based on current expert opinion regarding the medical management of individuals found to carry cancer predisposing mutations. These guidelines should include the age of initiation and frequency of cancer detection procedures. Discussions with patients, however, should also emphasize the critical research needed to document the efficacy of cancer screening and prevention in carriers of mutated cancer susceptibility genes.

B. Recommendations relating to policy implications of cancer genetic testing

1) Regulation of genetic testing

ASCO endorses efforts to strengthen regulatory authority over laboratories that provide cancer predisposition tests that will be utilized to inform clinical decisions. These regulatory requirements should include appropriate oversight of the products used in genetic testing, interlaboratory comparisons of reference samples, as well as quality control mechanisms.

The rapid evolution of genetic testing technologies and the speed of human genome research have outpaced the development of quality assurance (QA) and quality control (QC) methods for molecular diagnostics. In this field, laboratories commonly make their own reagents. At a national level, these reagents and procedures are regulated under the Clinical Laboratory Improvement Act (CLIA) 1988 regulations. As they apply to genetic testing, with the possible exception of cytogenetics, the CLIA regulations provide a minimum and insufficient level of oversight. Several states are now developing stricter controls over cancer genetic testing to fill a perceived void. Professional societies such as the American College of Medical Genetics (ACMG) and the College of American Pathologists (CAP) have become actively involved in developing inspection and interlaboratory comparison programs utilizing highly trained inspectors and detailed checklists of items specific to QA/QC in the molecular diagnostic laboratory. The only recognized board that certifies individuals specifically in human molecular genetic testing is the American Board of Medical Genetics (ABMG). Laboratories should meet the standards for laboratory genetics services established by the ACMG.¹⁵ ASCO supports efforts to establish specific federal policies under CLIA to assure the quality of laboratories providing genetic tests.

Thus, ASCO recommends that oncologists planning to offer these services carefully assess a laboratory's ability to provide accurate, state-of-the-art genetic predisposition testing to at-risk families. In addition to basic CLIA requirements, available measures of laboratory competence include successful participation in the ACMG/CAP inspection and survey program, appropriate state licensing, and credentialing of laboratory directors and staff by the ABMG.

2) Genetic discrimination

ASCO endorses all efforts including legislation to prohibit discrimination by insurance companies or

employers based on an individual's inherited susceptibility to cancer.

All Americans, regardless of health status or genetic predisposition to disease, should be guaranteed comprehensive and affordable health insurance. Insurance reform is necessary to ensure that pre-existing conditions or disease susceptibilities are not used as the basis for insurance restriction and exclusions, and that risk pools are large and diverse enough to maintain reasonable premium rates for people with chronic conditions. In the absence of these much-needed reforms, health care providers should explicitly include as part of the informed consent process for genetic testing a discussion of the potential for genetic discrimination (see Section A.3).

3) Coverage of services

All individuals at hereditary risk for cancer should have access to appropriate genetic testing and associated medical care, which should be covered by public and private third-party payers.

It is important that genetic testing and resulting preventive or screening modalities be made available and accessible to everyone. To facilitate medically appropriate interventions, public and private third-party payers should reimburse all items and services related to cancer genetic testing, counseling, and preventive oncology management when recommended by qualified health care professionals directly involved in the care of the individual being tested. Reimbursement should reflect both the professional and technical resources required to provide these services, including the laboratory costs, interpretation of the results, physician visits related to testing and patient counseling, education, and associated medical management. Reimbursement should be provided for prophylactic surgical procedures for children or adults at highest genetic risk who elect this option after full counseling and careful deliberation. If coverage is to be truly accessible given concerns about genetic discrimination, insurers must not exclude individuals and/or their family members from

affordable health care coverage if claims are submitted for genetic evaluation for a family history of cancer.

4) Critical research needs

To the greatest extent possible, genetic testing for cancer susceptibility should be performed in the setting of long-term outcome studies. ASCO endorses the formulation and implementation of a national cooperative study/registry with appropriate confidentiality to define the clinical significance of mutations in known cancer susceptibility genes.

Because of the lack of data on the efficacy of preventive and early detection measures in populations at the highest genetic risk for cancer, long-term follow-up of individuals being tested is essential. There is a critical need for research addressing the environmental and pharmacological modulation of expression of cancer susceptibility genes, so that lifestyle or chemopreventive options may be developed for high-risk families. In addition, there is a need for longitudinal follow-up of families post-testing, to analyze the medical significance of mutations of cancer predisposition genes, and to facilitate genotype-phenotype and other correlations. ASCO supports the formulation and implementation of a national cooperative study/registry addressed to these issues. Such a study/registry should be easily accessible to practicing oncologists, surgeons, and other health professionals caring for families with cancer. As part of this effort, ASCO encourages the development of a model long-term follow-up protocol, with full informed consent, that can be used as a resource for local Institutional Review Boards.

ASCO endorses continued support of patient-oriented research to analyze the psychological impact of genetic testing of at-risk populations.

The Society endorses participation by oncologists in consortia developed to measure the psychological and behavioral impact of DNA-based risk assessment. Clinical trials should also measure the effectiveness of different strategies of counseling and support.

APPENDIX

ASCO Public Issues Committee, Subcommittee on Genetic Testing for Cancer Susceptibility

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*The Subcommittee members marked with an asterisk differ on the language in Section A.4. of the statement. It is their view that genetic testing for breast cancer susceptibility should not be offered outside the context of hypothesis-driven research approved by institutional review boards. These members fully support the concept of a national registry/protocol to meet these needs, and agree with the other important priorities and issues outlined in the statement.

†Dr Weber serves on an advisory board to, and has engaged in collaborative research with, Myriad Genetic Laboratories, Inc, which is in the business of marketing genetic susceptibility tests. As compensation, Dr Weber has received and continues to receive from the company consulting fees and stock options.

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