

Statement of The American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition

Summary of Recommendations

The identification of the gene associated with early-onset breast and ovarian cancer, known as *BRCA1*, has profound implications for the presymptomatic assessment and monitoring of the heritable cancer risks in some individuals and families. This gene may be responsible for ~5% of breast cancer cases.

- Once direct and reliable testing for *BRCA1* mutations is available, it may be offered to members of specific types of families with strong breast-ovarian cancer histories. While the cancer risks associated with different *BRCA1* mutations are being determined, testing should initially be offered and performed on an investigational basis by appropriately trained health care professionals who have a therapeutic relationship with the patient and are fully aware of the genetic, clinical, and psychological implications of testing, as well as of the limitations of existing test procedures. Until then, it is recommended that linkage analysis be offered to selected high-risk families, if it will provide for more refined counseling than is currently available from family history alone.
- Further research is needed to determine optimal monitoring and preventive strategies (surgical or chemo-prophylactic), to assure their efficacy.
- It is premature to offer population screening, until the risks associated with specific *BRCA1* mutations are determined and the best strategies for monitoring and prevention are accurately assessed.
- Public and professional education is vital in developing a responsible approach to genetic testing.

Introduction

The imminent isolation of the breast-ovarian cancer susceptibility gene known as *BRCA1* (Miki et al. 1994), and the future isolation of other breast cancer predisposition genes, such as *BRCA2* (Wooster et al. 1994), raises important questions regarding genetic testing in high-risk fami-

lies, as well as the more far-reaching question of general population screening. The availability of the gene for cystic fibrosis (CF) and the discovery that abnormally high levels of maternal serum alpha-fetoprotein (MSAFP) are predictive of adverse pregnancy outcomes have focused attention on genetic screening and have prompted The American Society of Human Genetics (ASHG) to issue guidelines. In the case of CF, it was recommended that carrier testing be offered to individuals with a family history of CF and be provided only by knowledgeable health care professionals, after appropriate education and counseling. Caution about offering CF carrier screening to the general population was recommended. For both the CF and the MSAFP tests, the need for educational programs for patients and health care providers, accompanied by counseling programs, was emphasized. Other important considerations for testing were quality control and the assurance of confidentiality and fully informed consent (American Society of Human Genetics Ad Hoc Committee 1987; American Society of Human Genetics Ad Hoc Committee on Cystic Fibrosis Carrier Screening 1992). Currently, compliance with existing federal regulations is required of all laboratories offering genetic testing, in order to assure the quality of the laboratories performing these tests (Andrews et al. 1994). All such caveats and considerations are directly applicable to the issue of genetic testing for heritable cancers.

Cancer results from a cascade of genetic changes in a single cell, all of which may be required for malignant conversion. Different changes, or combinations of changes, may result in different types of cancer. This complexity necessitates extreme caution in risk assessment. Some cancers do, however, have a major genetic susceptibility component, making those strategies already developed for genetic testing in other diseases applicable to cancer. Molecular genetics approaches have resulted in the localization and subsequent isolation a breast-ovarian cancer susceptibility gene (*BRCA1*) on chromosome 17q21 (Hall et al. 1990; Narod et al. 1991; Easton et al. 1993; Miki et al. 1994). Current data from multiplex breast cancer families, used to locate the *BRCA1* locus, indicate that women who have inherited a mutant *BRCA1* allele have risks of breast cancer >50% before age 50 years and >80% by age 70 years (Hall et al. 1992; Easton et al. 1993). A second breast cancer predisposition locus, *BRCA2*, has recently been mapped to human chromosome 13q12-13 (Wooster et al. 1994).

Initial studies suggest that interest in genetic testing for breast and ovarian cancer susceptibility is likely to be very

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great (Lerman et al. 1994). In the few families already studied, counselors have been concerned about issues raised in testing (Biesecker et al. 1993; King et al. 1993). In order to assure maximum benefit and minimal risk when testing for *BRCA1* mutations becomes available, it should be approached in a well-considered manner through appropriate investigative studies. These would assess the reliability, sensitivity, and predictive value of testing, as well as the safety and efficacy of monitoring procedures and preventive strategies (surgical and/or chemo-prophylactic) in women with positive test results. In addition, adequate programs for education and counseling must be researched and developed. Such a careful approach is needed to assure the safe and effective management of individuals requesting genetic testing for predisposition to cancer. In the interim, the utilization of existing clinical geneticists to provide these services offers the best approach for maximizing the benefit and minimizing the potential harm associated with testing.

Cancer Risk Associated with Mutations in Predisposing Genes

Specific mutations in the *APC* gene are associated with both a range of colon cancer risks and the severity of polyposis (Spirio et al. 1993). The situation may be analogous for *BRCA1*. Penetrance estimates for those large families appropriate for the initial linkage analysis may not reflect the full range of risk conferred by germ-line *BRCA1* mutations. Further information on gene-environment interactions may also be critical for accurate risk assessment. The possible existence of additional, as yet unidentified, breast cancer predisposition genes in families negative for *BRCA1* alterations must be considered in assessing risk.

High-Risk Families

Direct detection of *BRCA1* mutations is likely to be available soon. The immediate potential for the beneficial effects of DNA testing is in those women with positive family histories of breast cancer. For this reason, it is recommended that testing be offered to such women, on an investigational basis, as soon as it is available. Such a test would reduce anxiety and prevent unnecessary prophylactic surgery in women found not to carry a germ-line *BRCA1* mutation, and it could identify those who would, it is hoped, comply with and therefore benefit most from currently recommended monitoring procedures (Lerman and Croyle 1994). Until direct detection of *BRCA1* mutations in women from appropriate high-risk families is possible, linkage analysis is recommended, if it would provide a greater likelihood of identifying those with an elevated cancer risk than would family history alone. Access to available investigational protocols for long-term monitor-

ing should be facilitated for all participants in any genetic testing program.

Women in high-risk families should be informed about the risks, benefits, and limitations of predictive testing and about the uncertainty about the effectiveness of current monitoring and prophylactic interventions, which may include mammography, physical examination, pelvic ultrasound, and new technologies presently under evaluation. As yet, no proved methods of primary prevention for breast or ovarian cancer exist. Prophylactic mastectomy or oophorectomy may be effective, but the results of systematic long-term follow-up to determine the frequency of cancer in residual tissue or in other organs are not available. Research to evaluate the efficacy and risks of monitoring and prevention strategies is essential to determine if genetic testing translates into reduction of morbidity and mortality for breast and ovarian cancer and to determine if specific management approaches have adverse outcomes. The possibility of widespread use of costly, unproved prevention or surveillance strategies is of particular concern.

Genetic counseling should be provided by a health care professional who has a therapeutic relationship with the patient and/or family, to insure the availability of a permanent source of accurate information that is not limited by the duration of research funding. Predictive testing should always be provided on a voluntary basis and should be conducted only in women who have been fully informed in an effective manner and who consent to testing.

Adult women from families in which *BRCA1* or *BRCA2* is segregating and who do not themselves carry the altered gene should be counseled that they still face the risks of sporadic breast and ovarian cancer in the general population and should be encouraged to follow age-appropriate surveillance measures.

Population-based Screening

Until we know the probability that a particular mutation will occur in cancer, the efficacy and safety of follow-up interventions, and the reliability of the test, mass screening for *BRCA1* mutations is not recommended. If preliminary data suggest that screening for one or more common mutations is reliable and would result in a reduction of morbidity and mortality in individuals harboring such mutations, pilot studies should be conducted to determine the efficacy of such screening. However, if screening is initiated prematurely (i.e., before its effectiveness in decreasing mortality and morbidity is known), it could result in inaccurate predictions of individual risks of developing cancer.

Education

The importance of education for those at high risk, for health professionals, and for the lay public cannot be overstated. People who have inherited altered *BRCA1* alleles

must be informed of the risks and benefits of genetic testing for cancer risk.

During the stage at which a new genetic technology is initially transferred into clinical practice, information about the precision, specificity, and risks of testing will inevitably be limited, and counseling usually will be provided through tertiary referral centers with established genetics programs. Clinical geneticists are uniquely qualified to obtain the most reliable information available, to provide a source of continuing information, and to communicate complex ideas and uncertainty in a way that is helpful to the patient. As the uncertainties surrounding testing are resolved and as testing becomes more widely available, primary care providers will necessarily absorb a larger part of this responsibility. These providers will ultimately control the flow of requests for testing and will have to use appropriate judgment in addressing many of the as-yet-unanswered questions. It is recommended that a major educational initiative be developed to educate providers with no previous experience in genetic testing. Providers are best approached through established continuing-education pathways, including professional society meetings, journal articles, and symposia oriented around diseases or specialties.

Additional issues related to genetic testing—such as quality control, ethical and legal safeguards, obtaining informed consent, and confidentiality—have been discussed elsewhere (Andrews et al. 1994). An integrated approach by geneticists, oncologists, and consumer organizations with special interest in cancer will provide an effective means of educating lawmakers at both federal and state levels about the nature and scope of problems associated with presymptomatic testing for breast cancer. Participation by these groups in the advisory process is needed if these issues—as well as those directly related to testing, counseling, and surveillance and prevention—are to be addressed appropriately. It is recommended that interested members of the lay public, representing the ethnic and cultural backgrounds of the research participants, be involved in testing programs. These concerns are highly relevant not only to testing for *BRCA1*, but to genetic testing in general.

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References

- American Society of Human Genetics Ad Hoc Committee (1987) ASHG policy statement for maternal serum alpha-fetoprotein screening programs and quality control for laboratories performing maternal serum and amniotic fluid alpha-fetoprotein assays. *Am J Hum Genet* 40:75–82
- American Society of Human Genetics Ad Hoc Committee on Cystic Fibrosis Carrier Screening (1992) Statement of The American Society of Human Genetics on cystic fibrosis carrier screening. *Am J Hum Genet* 51:1443–1444
- Andrews LB, Fullerton JE, Holtzman NA, Motulsky AG (eds) (1994) Assessing genetic risk: implications for health and social policy. National Academy Press, Washington, D.C.
- Biesecker BB, Boehnke M, Calzone K, Markel DS, Garber JE, Collins F, Weber BL (1993) Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. *JAMA* 269:1970–1974
- Easton DF, Bishop T, Ford D, Crockford GP, the Breast Cancer Linkage Consortium (1993) Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Am J Hum Genet* 52:678–701
- Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250:1684–1689
- King MC, Rowell S, Love SM (1993) Inherited breast and ovarian cancer: what are the risks? what are the choices? *JAMA* 269:1975–1980
- Lerman C, Croyle R (1994) Psychological issues in genetic testing for breast cancer susceptibility. *Arch Intern Med* 154:609–616
- Lerman C, Daly M, Masny A, Balshem A (1994) Attitudes about

- genetic testing for breast-ovarian cancer susceptibility. *J Clin Oncol* 12:843-850
- Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, et al (1994) Isolation of BRCA1, the 17q-linked breast and ovarian cancer susceptibility gene. *Science* 266:66-71
- Narod S, Feunteun J, Lynch HT, Watson P, Conway T, Lynch J, Lenoir GM (1991) Familial breast-ovarian cancer locus on chromosome 17q12-q23. *Lancet* 338:82-83
- National Advisory Council for Human Genome Research (1994) Statement on use of DNA testing for presymptomatic identification of cancer risk. *JAMA* 271:785
- Spirio L, Olschwang S, Groden J, Robertson M, Samowitz W, Joslyn G, Gelbert L, et al (1993) Alleles of the APC gene: an attenuated form of familial polyposis. *Cell* 75:951-957
- Wooster R, Neuhausen SL, Mangion J, Quirk Y, Ford D, Collins N, Nguyen K, et al (1994) Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 265:2088-2090