JOURNAL OF WOMEN'S HEALTH
Volume 7, Number 5, 1998
Mary Ann Liebert, Inc.

Choices: Biomedical Ethics and Women's Health

# Genetic Testing for *BRCA1* and *BRCA2*: Recommendations of the Stanford Program in Genomics, Ethics, and Society

BARBARA A. KOENIG, Ph.D., HENRY T. GREELY, J.D., LAURA M. McCONNELL, M.P.H., HEATHER L. SILVERBERG, A.B., THOMAS A. RAFFIN, M.D., and THE MEMBERS OF THE BREAST CANCER WORKING GROUP OF THE STANFORD PROGRAM IN GENOMICS, ETHICS, AND SOCIETY

*In the mid 1980s, an interdisciplinary group, the Stanford University Medical Center Committee on Ethics, was formed to meet regularly and address "policy and ethics" topics. The group's publications focused on death and dying, the use of fetal tissue, and animal research at Stanford.* This interdisciplinary group included faculty, staff, and community representatives from over 25 disciplines and specialties. In late 1989, under the leadership of Drs. Thomas Raffin and Ernlé Young, the Stanford Center for Biomedical Ethics (SCBE) was created within Stanford University. Among SCBE's special programs is the Program in Genomics, Ethics, and Society (PGES) that currently is working on: 1) breast cancer, 2) genetic testing for Alzheimer's disease, and 3) how new genetic technologies will transform clinical practice and public health by "individualizing medicine." PGES is directed by Professors Henry Greely, Barbara Koenig, and Thomas Raffin.*

*The knowledge of the human genome and related genetic testing literally may open a "Pandora's box" (as in the original gift of the Greek gods). The comprehensive recommendations of the Stanford Program in Genomics, Ethics, and Society cover the range of issues relevant to the generic issues of genetic testing and specifically testing for* BRCA1 *and* BRCA2. *The PGES's careful, detailed, and thorough evaluation of benefits, burdens, and risks covers the range of ethical, legal, and social issues. The PGES recommendations are a template for future evaluations in this sphere.*

*—Nancy Boucot Cummings, M.D., Series Editor*

Program in Genomics, Ethics, and Society, Stanford University Center for Biomedical Ethics, Palo Alto, California.

*Ruark JE, Raffin TA. Initiating and withdrawing life support: Principles and practice in adult medicine. N Engl J Med 1988;318:25. Thomas JA, Hamm TE Jr, Perkins PL, Raffin TA. Animal research at Stanford University: Principles, policies, and practices. N Engl J Med 1988;318:1630. Greely HT, Hamm T, Johnson R, Price CR, Weingarten R, Raffin T. The ethical use of human fetal tissue in medicine: Stanford University Medical Center Committee on Ethics. N Engl J Med 1989;320:1093.

## ABSTRACT

**Genetic testing for mutations in *BRCA1* and *BRCA2*, which are associated with increased lifetime risk of breast and ovarian cancer, may become the first widely accessible genetic testing for common adult onset diseases. The Stanford Program in Genomics, Ethics, and Society convened a multi-disciplinary Working Group that, in a lengthy process, studied the ethical, legal, and social issues arising from testing. The Working Group concluded that testing for mutations *BRCA1* and *BRCA2* genes is not appropriate for widespread clinical use or population screening, but may be beneficial in some circumstances—for example, in families experiencing multiple cases of cancer. Testing would raise fewer problems if definitive preventive interventions were available for those with the mutations, and if society better protected people with genetic risk of cancer. Even with current limitations, competent adults at high risk may choose to participate in a testing program. Such programs, however, must meet rigorous standards, including genetic counseling, confidentiality, and follow-up care. Health insurance should pay for all components of testing when it is appropriate; governments should take steps to protect people from discrimination and invasions of their privacy, as well as from the offering and advertising of inappropriate testing. We call on governments, researchers, insurers, testing laboratories, healthcare providers, and individuals to take important steps to help ensure that testing for *BRCA1* and *BRCA2* mutations, surely a forerunner of the many forms of genetic testing that will follow, improves people's lives, and does not diminish them.**


## INTRODUCTION

BREAST CANCER IS A CENTRAL CONCERN in women's health. Although it is not the most lethal cancer affecting women, it is one of the most controversial and widely discussed medical issues of our time. The "one in eight" statistic is part of American culture, often quoted yet generally misunderstood. According to statistics from the National Cancer Institute, women have a 12.5% lifetime risk of being diagnosed with invasive breast cancer and a 3.5% lifetime risk of dying from it.[1] In 1998 there will be 178,700 new cases diagnosed and 43,500 deaths from invasive breast cancer; an additional 36,900 cases of ductal carcinoma in situ will be diagnosed.[1] Ovarian cancer, although less feared, will claim 14,500 lives in 1998, and 25,400 new cases will be discovered.[1]

Advances in molecular genetics led in the early 1990s to the identification of a region on chromosome 17 linked to both breast and ovarian cancer susceptibility in high-risk families.[2,3] The first breast cancer gene, designated *BRCA1*, was cloned in 1994.[4] A second breast cancer susceptibility gene, *BRCA2*, was mapped to chromosome 13 in 1994 and cloned in 1995.[5,6]

These discoveries bring great hope for effective prevention, improved treatment, and eventual cure for all breast cancer, but this promise has yet to be realized. Mary-Claire King, Ph.D., credited with identifying the first breast cancer gene, refers to our current state of knowledge as a form of "scientific purgatory"; we can identify some women who are predisposed to breast and ovarian cancer as a consequence of inherited mutations in *BRCA1* and *BRCA2*, but we do not have measures to ameliorate their plight.[7] No medical guidelines for management of a positive test result have been proven effective in preventing cancer, and our society lacks ways to manage and contain the potentially explosive information testing will produce.

Nonetheless, genetic testing for *BRCA1* and *BRCA2* mutations is now commercially available from several sources. The cost for full-sequence analysis of *BRCA1* and *BRCA2* ranges from $2100 to $2400, and analysis for relatives of an individual with an identified mutation is $357–$395. A panel of tests for three specific mutations is offered to individuals of Ashkenazi Jewish descent for $350–$450.[8,9]

Testing for *BRCA1* and *BRCA2* mutations

may become the first widespread use of presymptomatic genetic testing introduced into general medical practice. The laws, policies, and practices that evolve to guide testing programs will provide a model for the multitude of predisposition genetic tests to come. Francis Collins, M.D., Ph.D., director of the National Human Genome Institute, cautions, "If we do this wrong . . . the consequences could be a public outcry . . . from which we will not recover for decades. . . . Genetic discoveries and genetic testing will not be dangerous additions to medicine. They will be very valuable once we understand enough about them. But one fear is that we will commit enough egregious errors . . . that the American public will be totally turned off and will decide . . . that they don't want anything to do with genetic technology. . . . We don't need a genetic thalidomide."[10]

In 1996, the Stanford Program in Genomics, Ethics, and Society (PGES) assembled a multidisciplinary Working Group to address a broad range of questions about our evolving ability to conduct predictive genetic testing for breast and ovarian cancer. The questions we asked were not limited to clinical concerns but encompassed the full range of social, ethical, and legal issues arising from testing, such as government regulation of genetic tests, the social consequences of widespread testing, intellectual property protection, health insurance coverage, and malpractice liability. The recommendations are addressed to healthcare providers, professional organizations, insurance and industry leaders, legislators and other policymakers, and individuals and families contemplating such testing.

## BACKGROUND

Since *BRCA1* was identified, knowledge of cancer genetics has expanded rapidly, with new information or revisions of earlier findings announced regularly. The pace of research complicated the task of the Working Group. Our best estimates of key facts—in particular the frequency of *BRCA1* and *BRCA2* mutations in the general population and the lifetime risk of cancer associated with specific mutations—are subject to constant revision.

The best available estimate is that 5–9% of breast cancers in the general population are hereditary.[11–13] The majority of these cancers are believed to result from germline mutations in dominant, highly penetrant susceptibility genes—primarily *BRCA1* and *BRCA2*—which are thought to account for 80% of hereditary breast cancers.[14] Both genes have been characterized as tumor suppressor genes.[15,16]

*BRCA1* is a large gene, and hundreds of mutations have been identified to date—some are deleterious, some are harmless polymorphisms, and others have unknown significance.[17] The estimated proportion of breast cancers associated with *BRCA1* mutations—defined as those in the general population not selected on the basis of family history, age at onset, or ethnic background—is 5–7% of those diagnosed before age 40 and 1–4% of those diagnosed over age 40.[18,19] Recent data suggest an even lower proportion of early onset breast cancer attributable to *BRCA1*.[20] Early studies, based on people from families at particularly high risk for breast cancer, estimated that 51–73% of women with mutations will develop breast cancer by age 50 and 82–87% by age 70.[21] These estimates are likely to decrease as a broader population is studied.[22] *BRCA1* mutations are thought to be present in well under 1% of the U.S. population.[22]

*BRCA2* is also a large gene, and numerous germline mutations have been detected in high-risk families.[18,23] The percentage of breast cancer cases in the general population associated with *BRCA2* has not been well established, nor has the population-based frequency of mutations been quantified. The risk that *BRCA2* carriers will develop breast cancer has been estimated to be as high as 87% by age 80 in high-risk families[5]—again, a value which may be revised downward once population-based studies are conducted. BRCA2 mutations are thought to be a factor in the development of certain cases of male breast cancer, a relatively rare disease.[5]

Among *BRCA1* and *BRCA2* mutation carriers, the risk of developing ovarian cancer is less understood. Risk, of ovarian cancer associated

MEMBERS OF THE BREAST CANCER WORKING GROUP OF THE STANFORD PROGRAM IN GENOMICS, ETHICS, AND SOCIETY

Diane Beeson, Ph.D., JoAnn Bergoffen, M.D., Paul Billings, M.D., Sandra Blum, Mark Blumling B.A., Susan Campbell, Robert Carlson, M.D., Monica Casper, Ph.D., Nicki Chun, M.S., Lane Conn, M.S., David Cox., M.D., Ph.D., Anne Dembitzer, M.D., Dianna DeVore, Ph.D., Andrea Fishbach, M.S., M.P.H., Joan Fujimura, Ph.D., Bart Giddings, J.D., Mary Goldstein, M.D., Amnon Goldworth, Ph.D., Deborah Gordon, Ph.D., Elisabeth Hansot, Ph.D., H. Geri Horsma, A.B. (Secondary Teaching Credentials), Stefanie Jeffrey, M.D., Kathreen Johnston, M.D., Jonathan Kaplan, Ph.D., Susan Kelly, Ph.D., Howard Klepper, J.D., Ph.D., Sally Lehrman, Barbara Loebel, M.S., M.S.W., Carol Mullen, M.S., Julie Ann Neidich, M.D., Douglas Owens, M.D., Ph.D., Ellen Porzig, Ph.D., Traci Powell, Robert Reich, M.A., Ph.D., Terence Roberts, M.D., Christopher Scott, Robert Siegel, M.D., Ph.D., David Spiegel, M.D., Susan Stefanac, A.B., Alan Stockdale, Ph.D., Frank Stockdale, M.D., Ph.D., Sara Tobin, Ph.D., M.S.W., Robbie Tung, M.S., Ernlé Young, Ph.D. (and the above named authors)

with *BRCA1* was estimated to be 63% by age 70.[24] In a recent analysis of families followed by the Breast Cancer Linkage Consortium, the risk of ovarian cancer associated with *BRCA2* was estimated to be 27% by age 70.[25] However, it is important to note that these may be overestimates due to the fact that research has so far focused on high-risk families.[26] For example, extrapolating from existing data, Whittemore et al. estimate that in the general population, *BRCA1* mutation carriers have a 21.5% risk of developing ovarian cancer by age 70.[22] Large-scale studies are needed to further determine the prevalence of, and risk associated with, disease-related mutations in the general population.

As with many genetic traits, the prevalence of mutations varies among human subgroups. For example, research has indicated that two *BRCA1* mutations, 185delAG and 5382insC, have a cumulative frequency of 1.4% in the Ashkenazi Jewish population.[27,28] Breast cancer under the age of 40 is uncommon, but as many as 20% of Ashkenazi Jewish women with early onset breast cancer carry the 185delAG mutation.[29–32] These mutations are also found outside the Ashkenazi population.[33]

Ten to 20% of families at high risk for breast cancer do not have mutations in either *BRCA1* or *BRCA2*, implying the existence of additional, yet to be discovered, cancer susceptibility genes.[34] In addition, it is not known what role modifying factors have—whether genetic, hormonal, dietary, or environmental—in determining whether a given mutation causes cancer.

## THE WORKING GROUP

The PGES Breast Cancer Working Group included 49 members from a wide variety of fields: medicine, surgery, oncology, genetics, genetic counseling, biochemistry, biology, psychology, psychiatry, sociology, anthropology, philosophy, law, health policy, biomedical ethics, education, economics, journalism, and others. It also included representatives of breast cancer organizations and women with personal experience of the disease. Working Group members were invited based on their involvement in cancer or genetics issues and included faculty and health professionals from Stanford and neighboring institutions. (While several other groups have made recommendations concerning genetic testing for cancer risk, the PGES process and recommendations are unique because the group was not dominated by a particular professional or disciplinary perspective.[35–41] Although representatives of the insurance and biotechnology industries made presentations to Working Group members, a drawback of the group's academic focus was a lack of ongoing participation by individuals from these groups.

The Working Group met every 2 weeks over a period of 15 months. Early meetings consisted of interactive educational sessions designed to create a baseline level of knowledge. Presentations were made by Working Group members and speakers with expertise in such areas as the epidemiology of breast and ovarian cancer,

SYMPOSIUM SPEAKERS

Lori Andrews, J.D., Paul Berg, Ph.D., Barbara Brenner, J.D., Arthur Caplan, Ph.D., Ruth Chadwick, Ph.D., LL.B., Francis Collins, M.D., Ph.D., Troy Duster, Ph.D., Neil Holtzman, M.D., M.P.H., Eric Juengst, Ph.D., Mary Jo Ellis Kahn, M.S.N., R.N., Mary-Claire King, Ph.D., Bartha Knoppers, LL.D., Margaret Lock, Ph.D., Daryl Macer, Ph.D., June Peters, M.S., Nancy Press, Ph.D., Karen Rothenberg, J.D., M.P.A., Mark Skolnick, Ph.D.

clinical treatment and prevention, psychosocial aspects of breast cancer, molecular genetics of *BRCA1* and *BRCA2*, current and future genetic testing technologies, the politics of breast cancer activism, and social and cultural perspectives on genetic testing.

Subgroups were formed to draft chapters of the final report.* Each subgroup made a presentation to and received feedback from the Working Group regarding the major issues they planned to address. As chapters were completed, they were circulated and discussed by the Working Group as a whole. Throughout this process, communication took place via e-mail and fax, so that members who were unable to attend particular meetings had the opportunity to provide input.

Specific recommendations were culled from the chapters and consolidated into an Executive Summary. In November 1996, the Working Group's recommendations were presented in draft form for comment at a day-long symposium in San Francisco, California. This session was held in conjunction with the IIIrd World Congress of the International Association of Bioethics. Symposium speakers received the Working Group's draft recommendations in advance. Feedback from speakers and symposium participants was discussed by the Working Group and considered as final recommendations were developed after the conference. The majority of Working Group members endorsed the full set of recommendations. Minority opinions, where they exist, are noted in footnotes to the recommendations.

Some recommendations express general principles, some suggest policies that could be implemented by healthcare providers or organizations, and some call for legislative or regulatory change. *All recommendations are explicitly based on the state of scientific knowledge—and legal and cultural constraints—current as the Working Group undertook its deliberations. As both science and society change, the recommendations will necessarily need to be modified.*

We concluded that testing for mutations in *BRCA1* and *BRCA2* genes is not an unequivocally beneficial procedure. Genetic testing for *BRCA1* and *BRCA2* mutations, when conducted properly, may be useful for some, but not all, people in high-risk families. For people who lack a strong family history, it is not likely to be useful. For anyone, it involves significant risks and costs. Testing is not appropriate for widespread clinical use or population screening but may be beneficial in some circumstances, for example, in families experiencing multiple cases of cancer. Testing would raise fewer problems if definitive preventive interventions were available for those with the mutations and if society better protected people with a genetic risk of cancer.

Even with current limitations, individuals at high risk may choose to participate in a testing program. Such programs must, however, meet rigorous standards, including genetic counseling, confidentiality, and follow-up care. Health insurance must cover all components of testing. Testing programs that do not meet specified, high standards should not be covered. We call for governments, researchers, insurers, testing laboratories, healthcare providers, and individuals to take important steps to help ensure that testing for *BRCA1* and *BRCA2* mutations, surely a forerunner of the many forms of genetic testing that will follow, improves peoples' lives and does not diminish them.

We lay out our 13 recommendations here, along with their justification. The recommendations deal with:

1. Context for evaluating *BRCA1* and *BRCA2* tests
2. Overall value of the tests
3. Appropriateness of the tests for different groups
4. What must be included in testing programs
5. Need for more research
6. Regulation of tests
7. Need for better education
8. Limits on marketing
9. Paying for testing programs

*Members of the PGES Breast Cancer Working Group have co-authored a book, forthcoming from Cambridge University Press, which provides an in-depth discussion of the recommendations presented here and a full overview of the scientific background, as well as the ethical, legal, and social issues, raised by testing for *BRCA1* and *BRCA2*.

10. Implications for medical malpractice
11. Needed protections in health insurance and employment discrimination
12. Privacy of genetic information
13. Implications of genetic patents

## RECOMMENDATIONS

1. **The potential value of genetic testing must be judged in the context of the meaning of the disease for those affected or threatened, taking into consideration the social, cultural, political, and economic environments of testing, as well as the medical implications.**

The meaning of cancer cannot be found in DNA sequences. Evaluations of new genetic technologies cannot be reduced to questions of technical efficacy. Genetic testing for cancer susceptibility is not just about medicine or science. It is about people's lives and the families and societies in which they live. There are consequences unique to each woman's sense of self, including her view of her own mortality, sexuality, and reproductive potential. Family relationships, ethnicity, and socioeconomic status all influence one's fear of cancer, methods of coping, levels of emotional and financial support, and ability to understand and act on information. The impact of having or fearing cancer not only varies among women but also may change depending on age, experience with the disease, and assessment of risk.

In addition, genetic services are delivered within a social context described by King as shaped by "a paternalistic medical establishment, an opportunistic biotechnology industry and a malevolent insurance industry."[42] Genetic testing will be implemented within those contexts. *BRCA1* and *BRCA2* testing cannot be looked on in isolation; it is part of one very particular approach to health, illness, and death. Individual decisions and public policy about the value of genetic testing must take into consideration all of these contexts.

2. **The effects of genetic testing for *BRCA1* and *BRCA2* mutations are complicated. The tests may have both positive and negative consequences for individuals and families. At our present level of knowledge, the tests should be offered, and taken, only with great care.***

Bioethicist Arthur Caplan, Ph.D., describes the benefit of genetic testing as the acquisition of knowledge, which is viewed, particularly in our culture, as intrinsically valuable. Testing also promises the ability to plan and prepare based on the information gained, the opportunity for increased monitoring and surveillance, the chance for prophylaxis or treatment, and psychological relief.[43] Medical tests are sometimes viewed as inherently benign procedures, where there is little or no risk of harm to the patient. In light of the medical risks and consequences of false-positive and false-negative results, this is rarely true with any medical test. It is definitely not true with genetic testing for cancer susceptibility, but the risks are primarily nonmedical. People who are tested for *BRCA1* or *BRCA2* mutations risk unforeseen psychological consequences, family disruption, and adverse social consequences, such as loss of insurability or employability. Most people, and many healthcare providers, will not necessarily know or appreciate those kinds of risks when considering genetic testing for breast cancer susceptibility.

Currently, even prophylactic medical interventions are limited. Measures of prevention or early detection of cancer available to individuals with an inherited predisposition to breast and ovarian cancer are imperfect and of uncertain efficacy. The benefits of mammography are not clear-cut in younger women, and ovarian cancer cannot be prevented and is particularly difficult to predict at an early, treatable stage. Although recent predictions generated with hypothetical modeling suggest that prophylactic mastectomy might increase life expectancy in women with *BRCA1* and *BRCA2* mutations,[44] there are no empirical studies documenting this. It is known that cancer can oc-

*Although no one strongly objected to this recommendation, some members of the Working Group believe that genetic testing for *BRCA1* and *BRCA2* should be framed in a more positive light.

cur in women following prophylactic oophorectomy and mastectomy, methods of surgical prevention that carry significant costs, both in altered self-image and in impact on life plans.

These risks do not mean that *BRCA1* and *BRCA2* testing is never beneficial or should never be offered or taken. They do mean that testing should be approached cautiously by both clinicians and patients.*

3. **For most people, testing for *BRCA1* and *BRCA2* mutations is not appropriate. For people at high risk for carrying a mutation, as a result of either their family history or their own early onset of disease, testing is an option that should be discussed and that could reasonably be accepted—or declined. For people who are not at high risk for the mutations, the tests provide little, if any, benefit and carry substantial risks. For some particularly vulnerable groups, including children, the mentally incompetent, and fetuses, testing is inappropriate.†**

*High-Risk Families.* Testing may be appropriate for women and men from high-risk families. The predictive significance of the results of genetic testing for *BRCA1* and *BRCA2* in a given individual increases substantially if other family members have been diagnosed with breast or ovarian cancer. Testing may be particularly appropriate for women from high-risk families who are seriously considering prophylactic surgery. We believe "high risk" may be reasonably defined in a number of ways, so long as all definitions require more than one case among near relatives.

*Early Age of Onset.* Testing may also be appropriate for women who have been diagnosed with breast or ovarian cancer at an unusually early age. Although the risk of carrying a mutation is still relatively low, it may be sufficient to justify the potential benefit of instituting screening for ovarian cancer. Screening for breast cancer is routine, regardless of family history or genetic test results, but special procedures to screen for ovarian cancer are not.

*Men.* Men from high-risk families may want to consider testing for several reasons. First, male breast cancer is associated with *BRCA2* mutations. Although the absolute risk is low, the disease is so rare that heightened awareness might lead to earlier detection and treatment. Second, men may wish to be tested in order to make informed reproductive decisions. Finally, men may wish to be tested to provide information for other family members.‡

Outside the groups mentioned, testing should not be encouraged. We believe the value of any information gained is substantially outweighed by the burdens.

*Newly Diagnosed Patients.* Testing should not be encouraged for all women who have been newly diagnosed with breast or ovarian cancer. The percentage of all cases that involve germline mutations is low, and information gained from the test is unlikely to change treatment decisions. A diagnosis of cancer is invariably a shock, and it is not the ideal time for a woman to consider genetic testing. Once taken and the results revealed, a test can never be undone, whereas a decision to test can always be made later.

*Population Screening.* General population screening clearly cannot be justified, given the small number of people with mutations who would be identified, our inability to interpret results outside high-risk families, and the sub-

*Of interest is a recent report suggesting that the uptake of genetic tests for cancer risk has been significantly lower than expected by professionals, perhaps indicating that individuals are exercising the level of caution suggested by the Working Group.[45]

†Our recommendations about the appropriateness of testing are particularly sensitive to changes in medical practice. Should scientists discover ways in which knowledge of genetic risk could significantly aid people in preventing, detecting, or treating breast or ovarian cancer, far more people may reasonably seek testing. For example, if tamoxifen or newer generations of chemoprevention drugs are proven effective in preventing breast cancer in women with *BRCA1* or *BRCA2* mutations, choices about testing might change.

‡Some members of the group dissent from the recommendation concerning men. They argue that the information gained is not useful enough to justify testing for male breast cancer risk or for reproductive decision making. Rather than a father being tested solely to determine the possible status of his children, interested adult children should request testing themselves.

stantial cost involved. A screening program for any ethnically defined population also cannot be justified. For example, if the incidence of *BRCA1* and *BRCA2* mutations is 2% in Ashkenazi Jewish women, 98% of such women screened will have no mutations. Those who test positive but lack a family history of cancer will be faced with making sense of ambiguous information, particularly in light of the uncertain meaning of mutations outside a high-risk family. Screening for a particular mutation, such as 185delAG, would cut the financial cost of screening but increase the false-negative rate for women who have other mutations. Finally, screening ethnically defined populations, even if medically justified, may exacerbate stereotypes linking disease with particular subpopulations. With so few expected benefits, this concern alone argues sufficiently against such a screening program.

*Vulnerable Groups.* Testing is clearly inappropriate for members of certain vulnerable groups. It should not be available to children, with or without parental consent. There is no medical reason for children to be tested for a condition that rarely, if ever, manifests before the second or third decade of life. The potential burdens in altered self-concept and differential treatment in their families are enormous. Psychological relief for parents cannot justify putting the child's interests at risk. Although 18 is not a magical age, it is a reasonable place to draw the line, a point at which adolescents can make informed and autonomous choices about testing for themselves. Likewise, testing should not be available to individuals of any age who lack the capacity to make informed medical decisions. With our current knowledge, no substantial preventive, clinical, or psychological benefit will accrue to them from the test.

Prenatal *BRCA1* and *BRCA2* mutation testing should not be allowed. The importance of particular mutations remains unknown, penetrance of the genetic trait is not 100%, and the age of onset is late. Current treatments can be effective, and it is hoped that the efficacy of breast and ovarian cancer prevention and treatment will improve over the next decades.*

**4. Whenever undertaken, testing should be done by competent professionals who have received specialized training. Testing programs should encompass adequate genetic counseling, informed consent, and multidisciplinary follow-up care, including psychological counseling for the individual and family when appropriate.**

High-risk individuals and families who consider testing should receive care in a setting in which comprehensive services can be provided. Such services include pretest and posttest genetic counseling, surveillance and, once developed, specialized preventive care, and psychological follow-up. Testing should not be offered in settings or via mechanisms (such as submitting blood tests by mail) where these services cannot be assured. Requiring comprehensive services will increase the cost of testing, but without such services, testing programs will be inadequate and may be dangerous. Our society has not generally allowed substandard care just because it is cheaper. These standards could be legislated by the states or the federal government or imposed through health plans, medical clinics, professional organizations, or testing firms.

Genetic counseling is the linchpin of good care, providing patients with the information they need to make an informed choice about testing. Counseling may be provided by a wide variety of health professionals if they have received specialized training in genetic testing and counseling for breast and ovarian cancer risk. Given the nationwide dearth of genetic counselors with specific expertise in cancer risk, continuing education courses must be created for genetic counselors, oncologists, nurse specialists, primary care physicians, surgeons, and others (see Recommendation 7). Access to

*The Working Group split over the issue of prenatal testing. Some believe that its value is so low and the consequences—in abortions, probably almost always of female fetuses—are so grave that it should not be allowed. Others favor a broad right of women to choose to carry or not carry pregnancies to term and to get as much information as possible in making that decision. We all agree, however, that such testing should not be encouraged.

*BRCA1* and *BRCA2* mutation testing should be allowed only through trained professionals who can provide evidence of competence.

Informed consent for *BRCA1* and *BRCA2* mutation testing must encompass information about both medical and nonmedical benefits and risks, including familial and social consequences of choosing to be tested and choosing not to be tested. Genetic testing of an individual necessarily provides some probabilistic information about that person's relatives. Given the inherently familial nature of genetic information, the issue of who should grant consent to testing inevitably arises. We believe the informed consent process should focus on the individual considering testing but strongly encourage the patient to consider the implications of testing for other family members, to discuss the issues with them, and to involve them in the genetic counseling process whenever possible.*

Any program of genetic testing for *BRCA1* and *BRCA2* mutations must include multidisciplinary follow-up care for those who elect to undergo testing and for those who do not. For example, changes in scientific knowledge will be of interest to those who are tested and to those who considered testing in the past but declined. Women who test negative must be informed of the meaning of the results, as well as their continuing general risk of breast and ovarian cancer. Women who have an indeterminate or positive result will need information about their results, services aimed at early detection, and possibly psychological counseling for themselves and family members. Support groups may be particularly useful for providing continuing information and psychological support.

5. **Additional research on the full implications of *BRCA1* and *BRCA2* mutations and testing is crucial. Testing need not be limited solely to research protocols, but all testing programs—whether conducted in a traditional research setting or not—should meet the same high standards and should include a confidential data collection component.†**

The unanswered questions about *BRCA1* and *BRCA2* mutations are many and vital, including their frequency in the general population, the risks conferred by specific mutations, the nature of the cancers associated with them, and the long-term consequences of testing on those who receive it. Most importantly, we do not know enough about how to detect and treat breast and ovarian cancer in women with *BRCA1* and *BRCA2* mutations.

Some groups have recommended that testing be limited to research settings to protect women and families as answers to these fundamental questions are sought. However, both research programs and commercial laboratories can have interests in tension with those of their patients. Although research protocols typically provide substantial protection for participants as a result of federal regulations and the activities of Institutional Review Boards (IRBs), it is possible for them to fall short of acceptable quality standards. This is even more true of commercial testing, which may not have oversight by an independent IRB.

The focus should be on the safety and quality of the program, not on whether the program is called "research." If only those testing programs that meet the standards we recommend (see Recommendation 4) are allowed to proceed, it does not seem warranted to require people to participate exclusively through a research protocol, particularly if geographic or other factors make such participation difficult.

Regardless of the setting, all *BRCA1* and *BRCA2* testing programs should be held to the same high standards. All should have a research component through participation in an

*A minority of the Working Group thought that the unique aspects of genetic information may warrant developing new models of informed consent to allow for family, as opposed to individual, decisions surrounding genetic testing.

†This recommendation was problematic for a minority of Working Group members. These members are in agreement that a research context for genetic testing does not necessarily ensure a high-quality environment. However, restricting testing to traditional research settings is one way to limit the rapid diffusion of *BRCA1* and *BRCA2* tests into medical practice in advance of clear knowledge of the tests' value.

independent, formal registry, established with strong safeguards for patient privacy. This registry should track information about the risks conferred by mutations, the nature of the cancers they generate, the efficacy of detection, prevention, and treatment modalities, and the consequences of testing for those who receive it.

**6. The federal government should regulate the introduction and use of genetic tests for diagnosis, susceptibility, and carrier status.**

The introduction of genetic tests into clinical use has not been adequately regulated. The Food and Drug Administration (FDA) regulates, as medical devices, genetic tests marketed as test kits. It has not, however, chosen to regulate genetic tests provided as clinical laboratory services. We believe that Congress should pass legislation requiring a regulatory scheme to assure that genetic tests are safe and effective. Regulatory authority could be vested in the FDA, in another existing agency with expertise in genetics, or in a newly created agency or regulatory body.*

An ideal scheme should provide regulation of three distinct stages of test development and use: initial research, a phase of preliminary marketing approval, and final approval. First, research must be conducted to show that the proposed genetic test can reliably detect mutations and that those mutations are associated with the occurrence of a disease. Human subjects approval must be obtained, and the research must be carried out under the oversight of an IRB. Once the sensitivity and specificity of the test for a defined population have been validated, preliminary approval for clinical use and marketing would be granted. During this second stage, the test could be delivered only among the defined population and only within a program meeting the standards set forth under Recommendation 4. The laboratory seeking regulatory approval would bear the responsibility of ensuring that the individuals tested and the programs referring patients meet stated criteria. Additional data must be collected concerning the benefits and burdens of both positive and negative test results—not just medical but psychological and social. If safety and efficacy can be proved in all these regards, final approval could be sought.

If this regulatory scheme were currently in effect, it is likely that there would be sufficient evidence to grant preliminary approval for *BRCA1* and *BRCA2* mutation testing in individuals who meet the definition of "high-risk." There does not appear to be enough information about the meaning of mutations outside high-risk populations to justify even preliminary approval for such testing.†

The Clinical Laboratories Improvements Amendments Act of 1988, which sets training and skill requirements for laboratory technicians and provides for quality control procedures to assure the accuracy of tests, should be fully implemented with respect to genetic testing.

**7. Education programs need to be undertaken for people at risk, for the general population, and for healthcare providers. Education programs must reflect the currently understood advantages and disadvantages of testing and make clear that not being tested can be a wise decision. These programs should not be controlled by those with a financial interest in testing.**

Existing cancer education programs for health practitioners should be expanded, and new, well-coordinated programs should be initiated to enable such practitioners to learn

*A similar conclusion was reached by the Federal Task Force on Genetic Testing.[35]

†The Working Group is divided on how this proposed regulatory regimen would be applied to the current state of *BRCA1* and *BRCA2* mutation testing. If such a regulatory regimen were in effect currently, the Working Group agrees that there is sufficient information to grant preliminary approval to the use of *BRCA1* and *BRCA2* mutation testing for people at high risk. The connection between those mutations and high risk of breast and ovarian cancer for such people, although not yet perfectly understood, is clearly substantial. The Working Group is divided as to whether there is now sufficient information to justify preliminary approval for *BRCA1* and *BRCA2* mutation testing of people who are not at high risk. Under our proposed regulatory scheme, such evidence would be required to permit testing of competent adults who were not at high risk. Either because of weighing of the evidence or because of varying views of the importance of autonomy, some of us believe that testing should now be permitted; others believe that the social cost of strict prohibitions is too high.

about and discuss the ethical, legal, social, and medical issues surrounding genetic testing for breast and ovarian cancer susceptibility with their patients. Similarly, existing breast cancer awareness and outreach programs for patients, their families, and other potential consumers should be expanded to include information on genetic testing for hereditary susceptibility to breast and ovarian cancer. Programs to educate policymakers, including legislators, about the ethical, legal, and social implications of genetic testing should be encouraged, as should efforts to educate the public about the work of the Human Genome Project and its possible applications and consequences.

In spite of the great need for education, we believe that programs should not be controlled by those with financial interests in testing. For example, firms providing genetic testing services should not control the content of educational programs about *BRCA1* and *BRCA2* services for either consumers or healthcare providers. However, it would be responsible and laudable for such firms to support educational activities by funding independent programs.

8. **Marketing of genetic tests for *BRCA1* and *BRCA2* mutations should be carefully limited.**

It is easy to imagine an advertisement for *BRCA1* and *BRCA2* mutation testing that preys on women's fear of breast cancer and then offers testing as a solution to this heightened concern. Marketing of genetic tests should be subject to at least the same level of regulation as marketing of pharmaceutical drugs, whether administered by the FDA or another federal agency. Marketing should be restricted to approved uses and include lengthy discussion of potential risks.

9. **Health plans should cover genetic testing for *BRCA1* and *BRCA2* mutations for appropriate plan members through testing programs meeting stated criteria. When genetic testing is covered, the full scope of a comprehensive program must be covered.**

Although much remains to be learned, enough is known about genetic testing for *BRCA1* and *BRCA2* mutations in appropriately selected individuals from high-risk families that it should not be considered experimental for the purposes of health coverage. Although the definition of "high-risk" might reasonably vary among health plans, whatever definition a health plan adopts should be readily available to plan members. Payers should reimburse genetic testing services only when provided within a proper program that includes testing and counseling by health professionals of demonstrated competence, comprehensive follow-up care, and participation in properly planned research on genetic testing for breast or ovarian cancer susceptibility. It is essential that payers should cover not just the cost of the test itself but also the recommended genetic counseling and follow-up services.

Although there is no reason to believe that testing is medically appropriate for people who do not have high-risk genetic backgrounds, payers should cover, at a minimum, genetic education or counseling programs for women concerned about whether genetic testing is appropriate for them.

10. **Given current knowledge of *BRCA1* and *BRCA2* mutations and of breast cancer prevention and treatment, malpractice liability for failing to offer genetic testing should not be used as a reason for healthcare providers to offer such testing broadly. When genetic testing programs are offered, liability considerations should be viewed as a good reason to offer tests only in the context of comprehensive testing and counseling programs. Professional organizations should develop guidelines for whether and when *BRCA1* and *BRCA2* testing is appropriate.**

In healthcare, clinicians' concerns about potential medical malpractice liability for failing to use new technologies have sometimes led to the inappropriate adoption of such technologies. Nonetheless, a concern about medical malpractice is not a sufficient justification for ordering a genetic test for breast or ovarian cancer susceptibility. There is no reason to believe that genetic testing for *BRCA1* and *BRCA2* mutations is or will soon become the standard of care for women. Even if it were accepted as such, the difficulty of proving damages from

failing to provide such testing would greatly limit any liability. On the other hand, harm to patients who were tested inappropriately or without adequate counseling or follow-up may realistically result in medical liability.

Professional organizations and others should continue to draft guidelines that further define the appropriateness of *BRCA1* and *BRCA2* testing for specific groups and describe the characteristics of excellent testing programs. When testing for *BRCA1* and *BRCA2* mutations is offered, the use of genetic counseling in connection with the testing should become part of the professionally and legally recognized standard of care. In providing such counseling, practitioners without substantial knowledge or experience in genetics may well risk violating the standard of care. Finally, access to psychological counseling for those who receive genetic testing should become part of the standard of care.

**11. Federal and state laws should clearly prevent the use of information about genetic testing, such as *BRCA1* and *BRCA2* mutation testing, in health coverage or employment decisions. The fact that a genetic test has been administered should be protected in the same way as the information gained from the test. Governments should study carefully limiting uses of genetic information in other contexts.**

Among the most feared consequences of genetic testing in the United States are its effects on health coverage and employment. It is possible that the Americans with Disabilities Act provides some protection against employment discrimination, but that conclusion is not certain. The federal government should clearly ban employment discrimination based solely on the results of genetic tests or on the fact that such tests have been done. The federal government should also require that the availability or price of health coverage should not be conditioned, limited, or affected by genetic information. Existing federal legislation provides only limited protection. Preferably, such a requirement would be in the context of guaranteed health coverage for all Americans. Before federal legislation is effective or where federal legislation does not reach, states should ban employment and insurance discrimination.

Predictive genetic information may also affect the availability of other forms of insurance, such as disability and life insurance coverage, or may be used in custody and adoption proceedings. Federal and state governments should study limiting such uses of genetic information.*

**12. The privacy of genetic information—and all medical information—should be better protected.**

Privacy legislation must be strengthened as one part of a strategy to limit genetic discrimination. Employers and insurers should be prevented from making decisions based on genetic information by putting health professionals and others who have access to the information under an obligation not to disclose it. Ideally, as genetic information may be indistinguishable from other medical information in patient files, privacy legislation should be broad enough to cover both categories.

Research protocols also must be designed to protect patient privacy. Genetic research may follow the health of many people over a number of years, yielding data widely available to researchers via a computerized database. Confidentiality would be compromised if the database contained personally identifying information or even full background information. Patients should be fully informed of the protections for confidentiality and the risk that it may be breached before they decide whether to participate in research.

*A minority of the Working Group believe that disability and life insurance, which may be essential for a woman to provide a reasonable quality of life to her family, should be included in legislation barring the discriminatory use of genetic information. Substantial efforts should be made to understand the impact of the potential loss of these forms of insurance on high-risk families.

Even within a family, privacy rights should be maintained. Genetic tests reveal information about family members that some people may not want to know and that may impart economic, social, or psychological harm. If a woman does not wish to disclose her genetic status, healthcare professionals have no obligation to warn her family members in order to prevent harm. The potential harm to family members is not immediate, and given the current risks and benefits of genetic information, disclosure against the wishes of an individual undergoing testing cannot be justified. The informed consent process should include discussion of privacy within the family. Practitioners may want to encourage their patients to share information about test results with family members, but they must not take that step themselves without the consent of the person tested.

**13. Congress should consider the possible implications of a patent monopoly resulting from a patent on an important human genetic sequence.**

*BRCA1* and *BRCA2* are the subjects of several patents and patent applications. To the extent they are granted, these patents would give the institutions that employed the "inventors" substantial power to control how genetic testing is conducted and by whom. Some argue that such patents may have a negative impact on research and, thus, are not in the public interest. Others say that gene discoveries are part of nature, not inventions, and thus not morally patentable. Still others argue that patent protection is crucial for encouraging biotechnologic innovation.

The Working Group made no substantive recommendation on the issue of whether particular genetic sequences should be subject to patent protection. It did conclude that patents for genetic discoveries, such as *BRCA1* and *BRCA2*, should not be allowed to be a significant barrier to research. Furthermore, when the federal government is an assignee on a patent application, its agreements with other assignees or coinventors should be public and should protect the public interest in the uses of the invention. Congress should directly examine the full range of issues involved in gene-related patents.

## CONCLUSION

The news that mutations in first one, then a second, gene had been linked to hereditary breast cancer excited many and led people to hope that a new genetic era of prediction, prevention, and treatment for breast cancer was opening. Four years after the successful cloning and sequencing of *BRCA1*, the hopes remain, but they are tempered. They are joined by an increasing realization that the discoveries bring costs as well as benefits. In many respects, these costs are currently more numerous and more significant than the benefits. Commercial availability of tests for genetic susceptibility to a common and dreaded disease puts in stark relief inadequacies in our ability to regulate genetic tests, in legal protections of privacy, in our knowledge of how best to prevent cancer, and in our delivery of clinical genetic services. We urge legislators, healthcare providers, payers, biotechnology industry leaders, and those concerned with the broader societal impact of genetic testing for cancer risk to work together in responding to the challenges such tests brings. *BRCA1* and *BRCA2* tests are among the first genetic tests for susceptibility to common diseases. They surely will not be the last.

## ACKNOWLEDGMENTS

The Working Group would like to express special thanks to Susan Campbell, now deceased, who devoted valuable time at the end of her life to our work. PGES is supported in part by generous funding from SmithKline Beecham Corporation. We also gratefully acknowledge the support of the Arnold and Mabel Beckman Foundation (through the Stanford Program in Molecular and Genetic Medicine) and the Walter and Elise Haas Fund. The recommendations are those of the Working Group and do not necessarily represent the views of SmithKline Beecham Corporation or other funders, nor have they been reviewed or approved as a precondition of publication.

## REFERENCES


1. Ries L, Kosary CL, Hankey BF. SEER cancer statistics review, 1973–1994. NIH Pub. No. 97-2789. National Cancer Institute, 1997:131.
2. Hall JM, Lee MK, Morrow J. Linkage analysis of early onset familial breast cancer to chromosome 17q21. Science 1990;250:1684.
3. Narod SA, Feunteun J, Lynch HT, et al. Familial breast-ovarian cancer locus on chromosome 17q12-23. Lancet 1991;338:82.
4. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66.
5. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, *BRCA2*, to chromosome 13q12-13. Science 1994;265:2088.
6. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene *BRCA2*. Nature 1995;378:789.
7. King MC. The genetics of breast cancer. Genetic testing for breast cancer susceptibility: The science, the ethics, the future. San Francisco, 1996.
8. Myriad Genetics. An overview of *BRC*Analysis testing options. February 12, 1998. <http://www.myriad.com/0health/hlthff.html>.
9. Oncormed. Patient resources. May 20, 1998. http://www.oncormed.com/omed2/patient/patres.htm.
10. Collins FS. Keynote address. Genetic Testing for Breast Cancer Susceptibility: The Science, the Ethics, the Future. San Francisco, November 23, 1996.
11. Lynch H, Lynch J, Conway T, et al. Hereditary breast cancer and family cancer syndromes. World J Surg 1994;18:21.
12. Lynch HT, Watson P, Conway TA, Lynch JF. Natural history and age at onset of hereditary breast cancer. Cancer 1992;69:1404.
13. Black DM. The genetics of breast cancer. Eur J Cancer 1994;30A:1957.
14. Greene MH. Genetics of breast cancer. Mayo Clin Proc 1997;72:54.
15. Futreal PA, Liu Q, Shattuck-Eidens D, et al. *BRCA1* mutations in primary breast and ovarian carcinomas. Science 1994;266:120.
16. Davies K. Breast cancer genes. Further enigmatic variations. Nature 1995;378:762.
17. Couch FJ, Weber BL. Breast cancer information core: Mutations and polymorphisms in the familial early-onset breast cancer (*BRCA1*) gene. Hum Mutat 1996; 8:8.
18. Ford D, Easton DF. The genetics of breast and ovarian cancer. Br J Cancer 1995;72:805.
19. Malone KE, Daling JR, Thompson JD, O'Brien CA, Francisco LV, Ostrander EA. *BRCA1* mutations and breast cancer in the general population: Analyses in women before age 35 years and in women before age 45 years with first-degree family history. JAMA 1998;279:922.
20. Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King MC. Frequency of breast cancer attributable to *BRCA1* in a population-based series of American women. JAMA 1998;279:915.
21. Hill ADK, Doyle JM, McDermott EW. Hereditary breast cancer. Br J Surg 1997;84:1334.
22. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of *BRCA1* mutations in breast cancer and ovarian cancer: Results from three U.S. population-based case control studies. Am J Hum Genet 1997; 60:496.
23. Tonin P, Weber B, Offit K, et al. Frequency of recurrent *BRCA1* and *BRCA2* mutations in Ashkenazi Jewish breast cancer families. Nature Med 1996;2:1179.
24. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. The Breast Cancer Linkage Consortium. Am J Hum Genet 1995;56:265.
25. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676.
26. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. *BRCA1* and *BRCA2*. Cancer Genetics Studies Consortium. JAMA 1997;277:997.
27. Streuwing JP, Abelovich D, Peretz T. The carrier frequency of the *BRCA1* 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals. Nature Genet 1995;11:198.
28. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in *BRCA1* and *BRCA2*. Nat Genet 1996;14:185.
29. FitzGerald MG, MacDonald DJ, Krainer M, et al. Germ-line *BRCA1* mutations in Jewish and non-Jewish women with early-onset breast cancer. N Engl J Med 1996;334:143.
30. Offit K, Gilewski, T, McGuire P. Germline *BRCA1* 185delAG mutations in Jewish women with breast cancer. Lancet 1996;347:1643.
31. Berman DB, Wagner-Costales J, Schultz DC. Two distinct origins of a common *BRCA1* mutation in breast-ovarian cancer families: A genetic study of 15 185delAG-mutation kindreds. Am J Hum Genet 1996;58:1166.
32. Muto M, Cramer DW, Tangir J, Berkowitz R, Mok S. Frequency of the *BRCA1* 185delAG mutation among Jewish women with ovarian cancer and matched population controls. Cancer Res 1996;56:1250.
33. Neuhausen SL, Mazoyer S, Friedman L, et al. Haplotype and phenotype analysis of six recurrent *BRCA1* mutations in 61 families: Results of an international study. Am J Hum Genet 1996;58:271.
34. Kerangueven F, Essioux L, Dib A, Noguchi T, Allione F. Loss of heterozygosity and linkage analysis in breast cancer carcinoma: Indication for a putative third susceptibility gene on the short arm of chromosome 8. Oncogene 1995;10:1023.
35. Holtzman NA, Hilgartner S. Promoting safe and ef-

fective genetic testing in the United States: Final report of the Task Force on Genetic Testing. Washington, DC: National Institutes of Health, 1997.
36. American Society of Clinical Oncology. Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. J Clin Oncol 1996;14:1730.
37. National Action Plan on Breast Cancer. Position paper: Hereditary susceptibility testing for breast cancer. 1996. <http://www.napbc.org/napbc/hspospap.htm>.
38. Wilfond BS, Rothenberg KH, Thomson EJ, et al. Cancer genetic susceptibility testing: Ethical and policy implications for future research and clinical practice. J Law Med Ethics 1997;25:243.
39. National Advisory Council for Human Genome Research. Statement on use of DNA testing for presymptomatic identification of cancer risk. JAMA 1994; 271:785.
40. American Society of Human Genetics. Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition. Am J Hum Genet 1994;55:i.
41. Pinn V, Jackson D. ORWH update: Advisory committee to NIH office passes resolutions. J Women's Health 1996;5:549.
42. King MC. The genetics of breast cancer. Breast Cancer Action Fundraiser. San Francisco, 1996.
43. Caplan AL. Ethical dilemmas in genetic testing and counseling. Genetic Testing for Breast Cancer Susceptibility: The Science, the Ethics, the Future. San Francisco, November 23, 1996.
44. Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis—Effects of prophylactic mastectomy and oophorectomy on life expectancy among women with *BRCA1* or *BRCA2* mutations. N Engl J Med 1997;336:1465.
45. Kolata G. Genetic testing falls short of public embrace. The New York Times, March 27, 1998.

Address reprint requests to:
*Barbara Koenig, Ph.D.*
*Stanford Center for Biomedical Ethics*
*701 Welch Road, Suite 1105*
*Palo Alto, CA 94304*