



Health Matrix: The Journal of Law-Medicine

Volume 7 | Issue 1

1997

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George C. Cunningham, M.D.

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Recommended Citation

George C. Cunningham, M.D., *A Public Health Perspective on the Control of Predictive Screening for Breast Cancer*, 7 Health Matrix 31 (1997)

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A PUBLIC HEALTH PERSPECTIVE ON THE CONTROL OF PREDICTIVE SCREENING FOR BREAST CANCER

George C. Cunningham, M.D., M.P.H.[†]

AS A PUBLIC HEALTH PROFESSIONAL, the perspectives that I bring in response to this new and challenging technology encompass two interests: one is disease prevention, and the other is protection of the public. My general approach is best summarized by the philosophy expressed in the title of Neil A. Holtzman's book, *Proceed with Caution*.¹

The definition of the word "proceed" within the public health context allows the public to enjoy the considerable proven benefits of a new technology in a reasonable period of time. Likewise, within this same context, "caution" allows the determination that the benefits of employing technology exceed adverse consequences. Likewise, that the methods used in application of the technology minimize the potentially adverse consequences.

It is clear at the outset, that nature provides no free lunch. Every change in the health care environment has both short and long-term consequences, intended and unintended, anticipated and unanticipated. Additionally, it is also clear that health care will never be static. Change will inevitably occur.

Withholding action in any setting, and particularly in the

[†] B.S., University of San Francisco; M.D., University of California, Los Angeles; M.P.H., University of California, Berkeley. Dr. Cunningham is currently principal investigator of the Pacific Southwest Regional Genetics Network and delegate to the Council of Regional Networks for Genetics Services.

1. NEIL A. HOLTZMAN, *PROCEED WITH CAUTION: PREDICTING GENETIC RISKS IN THE RECOMBINANT DNA ERA* (1989) (supporting the author's premise that caution is necessary in the genetic era).

public health context, is a choice which also has consequences. Thus, our primary task must be to control the rate and direction of change. Denying benefits until every potential adverse consequence is scientifically addressed and knowledge is complete and certain is not morally or pragmatically defensible. Any public health policy must be made on a population basis and therefore cannot be optimal for every individual in the population. The task in public health is to adopt policies which guide these changes in a direction that will produce the greatest good for the greatest number of individuals.

We now have new and important information about the relationship between genes and breast cancer.² This information is a vital contribution to understanding the disease process. However, we are far from having definitive answers. The information is incomplete and generates many questions for which we do not have satisfactory answers.³ This Article will outline my seven-step analysis of the role for federal and/or state public health agencies in responding to this conundrum. To preface my position, I agree with the position espoused by Neil A. Holtzman,⁴ Benjamin S. Wilfond, Kathleen Nolan⁵ and others,

2. See generally Amelia A. Langston et al., *BRCA1 Mutations in a Population-Based Sample of Young Women With Breast Cancer*, 334 NEW ENG. J. MED. 137 (1996) (discussing findings from DNA samples from eighty women enrolled in a population-based study of early-onset breast cancer to assess the spectrum and frequency of germ-line BRCA1 mutations); Richard Wooster et al., *Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12-13*, 265 SCIENCE 2088 (1994) (discussing evidence that suggests that BRCA2 confers a high risk of breast cancer but, unlike BRCA1, does not confer a substantially elevated risk of ovarian cancer); Michael G. FitzGerald et al., *Germ-Line BRCA1 Mutations in Jewish and Non-Jewish Women with Early-Onset Breast Cancer*, 334 NEW ENG. J. MED. 143 (1996) (finding that germ-line BRCA1 mutations can be present in young women with breast cancer who do not belong to families with multiple affected members); Donna Shattuck-Eidens et al., *A Collaborative Survey of 80 Mutations in the BRCA1 Breast and Ovarian Cancer Susceptibility Gene: Implications for Presymptomatic Testing and Screening*, 273 JAMA 535 (1995) (discussing the necessity for more data to be accumulated to address the sensitivity and specificity of a BRCA1 diagnostic testing procedure and to better estimate the age-specific risk for breast and ovarian cancer associated with such mutations).

3. See Francis S. Collins, *BRCA1-Lots of Mutations, Lots of Dilemmas*, 334 NEW ENG. J. MED. 186, 187 (1996) (stating that forthcoming studies regarding the BRCA1 mutation may produce answers as well as citing the need for legislation to forbid the use of genetic information in determining health insurance coverage).

4. HOLTZMAN, *supra* note 1, at 232-37 (arguing that employing scientific justification for testing will limit harms).

5. Benjamin S. Wilfond & Kathleen Nolan, *National Policy Development for the Clinical Application of Genetic Diagnostic Technologies: Lessons From Cystic Fibrosis*, 270 JAMA 2948, 2948-49 (1993) (explaining that appropriate procedural mechanisms should be established at both state and federal levels to prevent the unnecessary confusion, expense, and personal or social

that the decision to screen must be based on scientific evidence.

Above all, it must be determined, based on review of the evidence and consultation with experts, whether the testing technology is sufficiently well validated before it is offered to the public. Screening tests, like drugs, must be "safe and effective" before they can be marketed.

To ensure safety, effectiveness, and necessity, federal and state public health agencies must ensure that screening tests satisfy reasonable criteria.⁶ First, the disorder to be screened must be a significant public problem. Hereditary breast cancer certainly qualifies on this account. In 1995, there were an estimated 185,700 new cases of breast cancer; thirty-one percent of those were new cancers in women. Based on the estimated new cases of breast cancer, there will be approximately 44,560 deaths; this constitutes seventeen percent of total cancer deaths in women. Only lung cancer exceeds breast cancer as a contributor to cancer deaths in women.⁷ In fact, one out of every eight women will be affected by cancer by age ninety-five.⁸

Second, a sufficiently reliable screening test must be made available. To date, screening for hereditary breast cancer has failed to meet this criteria. If the purpose of the test is to answer the question "which individuals in the screened population have a specific mutation?" then the available molecular tests would have a high degree of accuracy. This is because the chance of misidentification of the genetic haplotype is very small. However, mutation identification and the actual expres-

harm likely to result from a completely unrestrained application of developing genetic technologies and that these procedural mechanisms should be based on the evidentiary model).

6. See COMM. FOR THE STUDY OF INBORN ERRORS OF METABOLISM, NATIONAL ACADEMY OF SCIENCES, *GENETIC SCREENING: PROGRAMS, PRINCIPLES, AND RESEARCH* (1975) (providing information about a variety of principles, procedures, and problems connected with genetic screening); Neil A. Holtzman, *Genetic Screening: Criteria and Evaluation-A Message for the Future*, in *GENETIC DISEASE: SCREENING AND MANAGEMENT* 3, 3-10 (Thomas P. Carter & Ann M. Willey eds., 1986) (explaining that criteria for genetic screening can seldom be satisfied; therefore, expansion of screening has been limited).

7. See Sheryl L. Parker et al., *Cancer Statistics, 1996*, 46 *CANCER* 5, 19 (1996) (providing a table which demonstrates women's death-rate from various types of cancer).

8. See AMERICAN CANCER SOCIETY, *CANCER FACTS AND FIGURES-1996*, at 13 (1996) (discussing estimates of total U.S. cancer cases diagnosed in 1996, as well as probabilities for developing invasive cancers at certain ages).

sion of malignancy are not synonymous. Thus, a reliable screening test must be developed.

To develop a reliable screening test, multiple hurdles must be crossed. Over 100 mutations of BRCA1 and dozens of mutations of BRCA2 have been identified. Correlation of these genotypes to phenotypic expression is in progress. To ensure the reliability of these predictions, there must be proper documentation.⁹ Additionally, detection rates are incomplete unless a whole series of genetic studies are included in the test panel. To detect the known forms of hereditary breast cancer likely would require tests for BRCA1, BRCA2, ataxia telangiectasia, HER-2/neu and p53. Even with all of these precautions, many women with cancer-associated mutations still will not be identified.

Presently, studies are in progress which will allow better estimates of screening parameters. For example, the frequency of a false positive or negative result and estimates of positive predictive value must be determined. A hurdle which must be faced in this arena is that the definition of a positive test is confounded by the variable existence or expression of the gene. Finally, even after correctly detecting the presence of a mutation, there is only a probabilistic likelihood of the actual expression of malignancy.¹⁰ In screening terminology, this could be called a false screening positive for the women who have a mutation but are spared by failure of expression, or who have mutations which do not lead to an increased risk of cancer.

Third, there needs to be a clear diagnostic test to separate a true from a false positive. (In the case of testing for the

9. See Ruth Hubbard & R.C. Lewontin, *Pitfalls of Genetic Testing*, 334 NEW ENG. J. MED. 1192, 1192 (1996) (stating that even in the case of so-called simple mendelian variations, the relation between the DNA sequence of a gene and the corresponding phenotype is far from simple). See generally Douglas F. Easton et al., *Breast and Ovarian Cancer Incidence in BRCA1-Mutation Carriers*, 56 AM. J. HUM. GENETICS 265 (1995) (explaining that genetic linkage studies have demonstrated that many families with dominant predisposition to early-onset breast cancer or ovarian cancer are the result of a gene located on chromosome 17q21 although there is significant evidence of heterogeneity of risk between families).

10. See Hubbard & Lewontin, *supra* note 9, at 1193 (stating that the fact that a woman from a "cancer-prone" family tests positive for a cancer-linked DNA variant does not mean that she will definitely have a tumor, even though her lifetime risk of breast cancer may be as high as eighty-five percent, and that of ovarian cancer as high as forty-five percent); Easton et al., *supra* note 9, at 270 (stating that the difference in ovarian cancer risk, between high-risk and low-risk families, may have been exaggerated by the heterogeneity analysis).

presence of a gene that increases susceptibility or risk, this criteria does not apply). Typically, an initial positive screening test can be confirmed by a "gold standard" diagnostic test. At the time of the positive BRCA1 test result, the tested woman may have no malignant cells. Only time and careful surveillance with additional screening, like mammography, ultrasound, and ultimately biopsies, will validate the initial screening as a "true positive." Furthermore, these additional screening mechanisms are not without fault. Whether or not a breast examination and mammography will detect tumors is size related and increases with the age of a woman. Finally, the training and experience of the radiologist is also a variable factor.¹¹ Thus, there is a need for more sensitive methods for the early detection of actual malignancy.

Fourth, there must be effective intervention to prevent or ameliorate the consequences of the disorder. Again, presently there is no clearly effective intervention with hereditary breast cancer. The effectiveness of existing options, such as dietary changes, early detection, tamoxifen, and prophylactic breast and ovarian surgery, is not clearly known or documented.¹²

11. See Craig A. Beam et al., *Variability in the Interpretation of Screening Mammograms by U.S. Radiologists: Findings From a National Sample*, ARCHIVES INTERNAL MED., Jan. 22, 1996, at 209, 213 (stating that current accreditation programs that certify the technical quality of radiographic equipment and images, but not the accuracy of the interpretation given to mammograms, may not be sufficient to help mammography fully realize its potential to reduce breast cancer mortality); Joann G. Elmore et al., *Variability in Radiologists' Interpretations of Mammograms*, 331 NEW ENG. J. MED. 1493, 1498 (1994) (stating that although the efficacy of mammography in screening women for breast cancer is well-documented, radiologists can differ, sometimes substantially, in their interpretations and recommendations for follow-up); Daniel B. Kopans, *The Accuracy of Mammographic Interpretation*, 331 NEW ENG. J. MED. 1521, 1521 (1994) (stating that there is great variation among the expertise of radiologists).

12. See Malcolm M. Bilimoria & Monica Morrow, *The Woman at Increased Risk for Breast Cancer: Evaluation and Management Strategies*, 46 CANCER 263, 263 (1995) (demonstrating the difficulty in evaluating the efficacy of prophylactic mastectomy); Karla Kerlikowski et al., *Should Women with Familial Ovarian Cancer Undergo Prophylactic Oophorectomy*, 80 AM. J. OBSTETRICS & GYNECOLOGY 700, 701 (1992) (evaluating the effectiveness of prophylactic surgery for women with a family history of ovarian cancer); NIH Consensus Development Panel on Ovarian Cancer, *Ovarian Cancer: Screening, Treatment, and Follow-up*, 273 JAMA 491, 491 (1995) (stating that current screening modalities to reduce mortalities from ovarian cancer still leave some uncertainty as to their effectiveness); Joyce A. O'Shaughnessy, *Chemoprevention of Breast Cancer*, 275 JAMA 1349, 1349-53 (1996) (summarizing findings about the incidence of breast cancer, indicators of risk, current treatment options and effectiveness, and the status and direction of research); Mary-Claire King et al., *Inherited Breast and Ovarian Cancer: What Are the Risks? What Are the Choices?*, 269 JAMA 1975, 1979 (1993) (stating that the choices available to women with inherited risk are surveillance and surgery with the Tamoxifen Prevention Trial available for some high-risk women); Kent F.

Fifth, there must be resources, such as facilities and staff available, to provide before and after test counseling, test interpretation, and any other necessary interventions. These resources exist to a limited extent, as illustrated by the fifty-four National Institute of Cancer designated centers. However, these centers need to be clearly identified and organized into an effective follow-up network.¹³

Sixth, both health care providers and the population to be screened must accept the screening system as worthwhile and practical. This does not appear to be a substantial barrier as there already appears to be a general acceptance of susceptibility screening.¹⁴

Last, the screening must be cost beneficial and cost effective. Cost benefit methodologies have been developed for cancer,¹⁵ but need to be applied to specific screening designs. The following statistics illustrate the wide range in cost with

Hoskins et al., *Assessment and Counseling for Women with a Family History of Breast Cancer: A Guide for Clinicians*, 273 JAMA 577, 584 (1995) (stating that there is a need for primary care clinicians to be able to assess familial risk factors for breast cancer, provide individualized risk information, offer counseling to high-risk individuals, and offer surveillance recommendations).

13. See Harry Campbell et al., *The Future of Breast and Ovarian Cancer Clinics: No Longer Just Research-Now a Clinical Need*, 311 BRIT. MED. J. 1584, 1584 (1995) (recommending the development of standardized practices and nationally coordinated research for regional cancer clinics, funded by research agencies, to offer screening, information, and counseling).

14. See D. Gareth Evans, *Genetic Testing for Cancer Predisposition: Need and Demand*, 32 J. MED. GENETICS 161, 161 (1995) (stating that while screening for cancer is not fully accepted, most cancer genetics clinics would offer screening to those at high-risk); Hemasree Chaliki et al., *Women's Receptivity to Testing for a Genetic Susceptibility to Breast Cancer*, 85 AM. J. PUB. HEALTH 1133, 1134 (1995) (indicating that the percentage of women participating in the survey who stated that they would accept the test was remarkably high, considering the threatening nature of a positive result); S. Mohammed et al., *Attitudes to Predictive Testing for BRCA1*, 32 J. MED. GENETICS 140, 140 (1995) (stating that 81% of women surveyed indicated a desire to undertake testing); Hemasree Chaliki et al., *Women's Receptivity to Testing for a Genetic Susceptibility to Breast Cancer*, 85 AM. J. PUB. HEALTH 1133, 1134-35 (1995) (explaining that 90% of approximately one thousand patients are willing to be tested for genetic susceptibility to breast cancer).

15. See Mary S. Baker et al., *Estimating the Treatment Costs of Breast and Lung Cancer*, 29 MED. CARE 40, 41 (1991) (describing a general methodology in which the researcher estimates the costs attributable to the cancer as the difference between the cost of caring for individuals with cancer and the cost of caring for comparable individuals without cancer); Ruth Etzioni et al., *Estimating the Costs Attributable to a Disease with Application to Ovarian Cancer*, 49 J. CLINICAL EPIDEMIOLOGY 95, 95 (1996) (focusing on the methods for estimating the average present value of the medical costs attributable to a disease, and more specifically on handling incomplete or censored cost and survival data and incorporating discounting); Herman Kattlove et al., *Benefits and Costs of Screening and Treatment for Early Breast Cancer: Development of a Basic Benefit Package*, 273 JAMA 142, 142 (1995) (indicating that by choosing which services healthcare professionals provide to specific groups of patients, providers can substantially reduce their expenses and still provide quality health benefits).

various cancer screening mechanisms: The cost of the molecular analysis is between \$150 and \$1600 depending on the particular molecular test employed. Counseling and clinical services range from \$200 to \$300 per patient. A mammography costs approximately \$90 per test. Prophylactic surgery and reconstruction costs range from \$10,000 to \$40,000. Finally, the costs of public and professional education and organization still needs to be determined. Until we have more information on the cost and effectiveness of the individual elements of the screening protocol and intervention, cost benefit and effectiveness cannot be assessed.

Only the government is charged with public protection and provided the tools of law and regulation to enforce its policies. Thus, public health practitioners must educate those who implement law and regulation. The scope of the problem is such that even if ninety percent of health care professionals were familiar with and voluntarily observed the general policy statements and practice guidelines of professional organizations like the American College of Medical Genetics, the American Society of Human Genetics (ASHG),¹⁶ the Working Group on Ethical, Legal, and Social Implications of the Human Genome Project (ELSI), the Hereditary Susceptibility Working Group of the National Action Plan on Breast Cancer,¹⁷ and the National Advisory Council for Human Genome Research,¹⁸ inadequate and premature testing programs would still pose a substantial problem. Likewise, even if most third-party payors voluntarily accepted, without modification, these pronouncements as the standard of care, there would still be a substantial problem

16. American Society of Human Genetics, *Statement of the American Society of Human Genetics on Genetic Testing for Breast and Ovarian Cancer Predisposition*, 55 AM. J. HUM. GENETICS i, i (1994) (emphasizing that it is premature to offer screening until the risks associated with BRCA1 mutations are determined and the best strategies for monitoring and prevention are accurately assessed).

17. American Society of Clinical Oncology, *Statement of the American Society of Clinical Oncology: Genetic Testing for Cancer Susceptibility*, 14 J. CLINICAL ONCOLOGY 1730, 1730 (1996) (recognizing that cancer specialists must be fully informed of the issues associated with genetic testing for cancer risk, the American Society of Clinical Oncology recommends that cancer predisposition testing be offered only in limited circumstances).

18. National Advisory Council for Human Genome Research, *Statement on Use of DNA Testing for Presymptomatic Identification of Cancer Risk*, 271 JAMA 785, 785 (1994) (stating that it is premature to offer testing of either high-risk families or the general population as part of general medical practice until crucial questions have been addressed).

with premature and poorly designed commercial and private testing programs.

The government also has the role of balancing competing interests in order to ensure the best public policy. For example, there are a number of "stake holders" with respect to screening for hereditary breast cancer. These include women, high-risk families, academic researchers, commercial test developers, primary care providers, third-party payers, and genetic specialists. The government must balance all of these interests when adopting a public policy regarding screening for hereditary breast cancer.

George Annas¹⁹ has compared the Medical Model, the Market Model, and the Regulatory Model with respect to an analogous problem; prenatal diagnosis. Under the Medical Model, physician specialty groups decide when a test should and should not be offered. However, the Medical Model has been undermined by the Market Model in the interest of third-party cost containment and the fear of malpractice. The Market Model considers susceptibility testing as a profit-producing product. Third-party payors will, therefore, control when, where, and how testing is offered based on the definitions of medical necessity and cost avoidance. Annas concludes that more government regulation is inevitable. This is consistent with Alexander Morgan Capron's theory of "creative preservation" which he defines as "a positive and original effort to enhance important values and relationships, rather than either a negative (and probably futile) attempt to forestall use of the biomedical technique or a resigned acquiescence in its undesirable changes."²⁰

Based on the above-stated theories, I urge that we support public agencies in the implementation of the consensus recommendation of the genetic community. Thus, our goal is to employ legal means to *limit* the offering of susceptibility testing for hereditary cancer to only those health facilities which

19. See George J. Annas, *Noninvasive Prenatal Diagnostic Technology: Medical Market or Regulatory Model?*, ANNALS N.Y. ACAD. SCI., Sept. 1993, at 262, 264 (comparing three models on role of noninvasive prenatal diagnosis).

20. See Alexander Morgan Capron, *The New Reproductive Possibilities: Seeking a Moral Basis for Concerted Action in a Pluralistic Society*, 12 LAW, MED. & HEALTH CARE 192, 193 (1984).

have been approved.

The inherent authority of a government to impose restrictions on private rights for the sake of public health, welfare, order, or security is defined as police power. In fulfilling governmental responsibilities to protect the physical and mental health as well as the welfare of its citizens, state health agencies have the duty, when presented with facts that identify a serious risk in this regard, to use their police powers even if the action violates certain rights. The police power of a sovereign state is a plenary power which need not be expressly stated.²¹ Consideration of the established facts and knowledge with respect to the societal implications of screening for breast cancer susceptibility identifies a situation where this duty arises. I concur with the position of Angus Clarke that "programmes of population screening for genetic susceptibility to disease should not be introduced, sponsored, managed, or promoted by commercial corporations without strict regulation."²² I therefore propose that the following statutory language be adopted:

Every person and institution must be prohibited from offering or providing tests to analyze genetic material with the intent to determine the presence of genes which are associated with, or are claimed to be associated with, breast cancer, unless the person or institution is approved by the state agency to provide such testing.

Because our society emphasizes the values of liberty and autonomy, the use of the state's police powers is often challenged. Any such regulation which restricts liberty and autonomy must, therefore, be defensible in a court of law. I will try to respond to the arguments that could be brought against such a strict implementation of the state's police powers.

What rights are violated? The highest order of rights are fundamental rights guaranteed in the Constitution, thus, the state bears a heavy burden to justify their violation. Opponents

21. See *Jacobson v. Massachusetts*, 197 U.S. 11, 24-5 (1905) (discussing the powers of the state legislature to protect public health and safety within the context of compulsory vaccination laws).

22. Angus Clarke, *Population Screening for Genetic Susceptibility to Disease*, 311 BRIT. MED. J. 35, 37 (1995) (stating that evaluating such testing should include psychosocial and medical outcomes for both high and low-risk individuals).

of strict regulation of genetic screening may allege that there has been a violation of the Fourteenth Amendment's liberty rights. The argument may be made that the rights of health care providers to provide care is being abridged. Health care providers' right to practice their trade in general, to earn a living, or make a profit are not significantly impaired by genetic screening regulations. Providers are only prevented from taking specific actions regarding genetic screening that they may want to take. However, the rights of health care professionals are in many instances subject to such prohibitions. Numerous examples, such as licensing requirements and business and professional regulations, restrict the actions of health care professionals. Moreover, the statutory language that I propose does not totally prohibit the action, such as laws prohibiting murder and theft. Rather, the proposed language merely requires that certain conditions be satisfied before the genetic screening is permitted. My proposal is, therefore, more analogous to such laws as those which require an operator's license to drive a car.

Let us assume for the sake of argument that a court would accept the right of health care providers to offer a BRCA1 test. Let us also assume that the public's right to obtain a BRCA1 test is legally established. Furthermore, let us assume that both the right to provide and the right to receive a BRCA1 test are fundamental rights. Courts have upheld the constitutionality of state laws which infringe on fundamental rights under the following conditions: first, the state must demonstrate that there is a compelling state interest that is sufficiently strong to justify the law; second, the state must demonstrate that no less intrusive or restrictive measures are available; and finally, the state must demonstrate that the law is reasonably expected to achieve the state's objective.

The language that I have proposed is drafted in a similar manner as a licensing law. There is a body of jurisprudence that validates the legitimacy of state licensing procedures. For state licensing procedures to be adopted, the state must establish that the regulation of that activity, in this case the screening for hereditary breast cancer, is necessary. Thus, the state must cite evidence which demonstrates that in the absence of such regulation there is a real potential for harm to the public.

Unregulated screening for breast cancer genes clearly threatens serious harm to the persons tested, their families, and society in general. The first potential harm is the failure of physicians to be provided with, and/or to communicate to potential testees, sufficient objective and valid information about hereditary breast cancer screening. Testees must be informed of the risks and benefits of testing, as well as the current limitations on our knowledge of the consequences of potential interventions.

Second, unregulated screening of hereditary breast cancer could lead to faulty, or negligent DNA analysis, for example, reporting that the BRCA1 haplotype is present when in actuality it is absent. This inaccurate diagnosis would result in unnecessary mental anguish, unnecessary, risky, costly, and mutilating interventions, and the unnecessary expenditure of public and private funds.

A third and more likely harm that could result from unregulated screening of hereditary breast cancer is the anxiety caused by the probabilistic nature of the association of the test results with clinical disease in the tested woman and in her family. Counseling and interpretation of the test results require special knowledge and skills not universally available in the health care community.²³ Errors of commission and omission could lead to the same kinds of adverse consequences as those discussed above.

Fourth, unregulated testing for heredity breast cancer has the potential to generate paranoia about breast, ovarian, and prostate cancer. This could result in a significant increase in the cost of health care due to an increased frequency of physician visits, mammography, vaginal ultrasound, blood tests, and surgery. Moreover, much of this increased intervention would probably prove to be unnecessary and counterproductive.

23. See Hoskins et al., *supra* note 12, at 582 (stating that DNA-based predictive testing is not commercially available, nor is it available as a service in hospital-based clinical laboratories); Barbara B. Biesecker et al., *Genetic Counseling for Families with Inherited Susceptibility to Breast and Ovarian Cancer*, 269 JAMA 1970, 1970 (1993) (stating that large scale population screening for BRCA1 mutations is likely to become a reality in the next few years, but is currently limited to very rare cases); Henry T. Lynch & Patrice Watson, *Genetic Counselling and Hereditary Breast/Ovarian Cancer*, 339 LANCET 1181, 1181 (1992) (stating that physicians must learn how to interpret molecular genetic and gene linkage findings, and how to provide genetic information and management recommendations to those at high risk).

Finally, unregulated screening for hereditary breast cancer poses the distinct possibility that positive individuals will be subjected to discrimination in employment and insurance in order to avoid these costs. States have compelling interests in preventing these adverse consequences that threaten public health and welfare.

Just as critics of highly regulated screening might argue that their liberty rights are being violated, likewise they also may argue that limiting testing to approved centers or personnel is an unlawful restraint of trade. Though the right to practice a trade or earn a living is not a fundamental right, this objection has been raised against various licensing laws in the past.

The legislative intent of anti-monopoly law is to promote competition so as to (1) ensure a variation in the quality of product or services; and, (2) encourage variation in prices which are desirable to a society of consumers. Alternatively, the legislative purpose might be to protect an individual's right to engage in commerce and be oriented to assist commercial vendors.

The statutory restrictions that I propose do not violate any of these objectives of anti-monopoly law. The law guarantees a minimal quality of services. Variation in quality of health care should not be so excessive as to include substandard services that do more harm than good or that are a threat to public health. The quantity and quality of services will not be limited once the minimum standard is achieved. There is no monopoly unless only one person or one facility is qualified. Thus, choice of vendor is preserved.

With respect to price control, the existence of multiple approved centers will contribute to price competition. However, given the major players in current health care, mainly third-party payors, the state, managed care plans, and insurance companies, there is legal recognition of the concept of price restriction.

Finally, the right of providers to offer testing is not absolute, but is conditioned on meeting certain reasonable and necessary standards. The state has no obligation to any individual to guarantee their right to any particular trade or to economic success at that trade.

Therefore, I argue that restraint of trade as a result of the statutory language that I propose is minimal and insignificant. I further argue that any restraint of trade that may result is justifiable in terms of the greater countervailing state interest in the protection of public health. Finally, if the testing program is organized as a state health agency project, with the providers operating as agents of the state, the providers actually would be exempt from restraint of trade requirements.

In addition to establishing a compelling state interest, the state must demonstrate that there is no less intrusive means of protecting the public that would not require regulation. While public and professional education can be promoted, only a law can provide assurance that suggested standards will be followed. Diagnostic tests are currently regulated by the Food and Drug Administration (FDA). Before marketing the test, the developer must demonstrate to the FDA that the test is safe and effective for the purposes for which it will be marketed. In the case of tests for cancer susceptibility, this will be a time consuming and costly procedure. Moreover, it is not likely that in the immediate future developers will be able to demonstrate that screening mechanisms for hereditary breast cancer are safe and effective. In addition, the FDA does not presently regulate the environment of the clinical services which would be required to avoid the adverse consequences described. Therefore, reliance on FDA regulations would not be a more effective but less intrusive alternative.

The State of California followed this highly regulated model for Maternal Serum Alpha Feto-protein testing. Laboratories were prohibited from testing until the state developed regulations to ensure that the benefits exceeded the risks. A program of professional and public education was developed and implemented. Informed consent was a mandatory requirement. Laboratory testing was limited to qualified and monitored, private laboratories which provided high quality services based on competitive bids. Post-test follow-up was provided in private, state approved, multi-disciplinary centers that were experienced in prenatal diagnosis. Costs were distributed across the whole population by the use of a single participation fee. Data were collected and the program policies were continually evaluated. Based on this public/private approach, women from

California got earlier and better access to high quality testing than women in states where testing was unorganized and unregulated.

I would propose a similar approach for breast cancer screening. General offering of the test to the population of women from California should be prohibited, until, with the help of an expert advisory committee, which includes all of the stakeholders, the Department of Health Services has determined to whom, when, where, and how the test can be provided as a net benefit. I cannot anticipate the results of the deliberations of the advising panel. However, I can speculate on what the regulations would do.

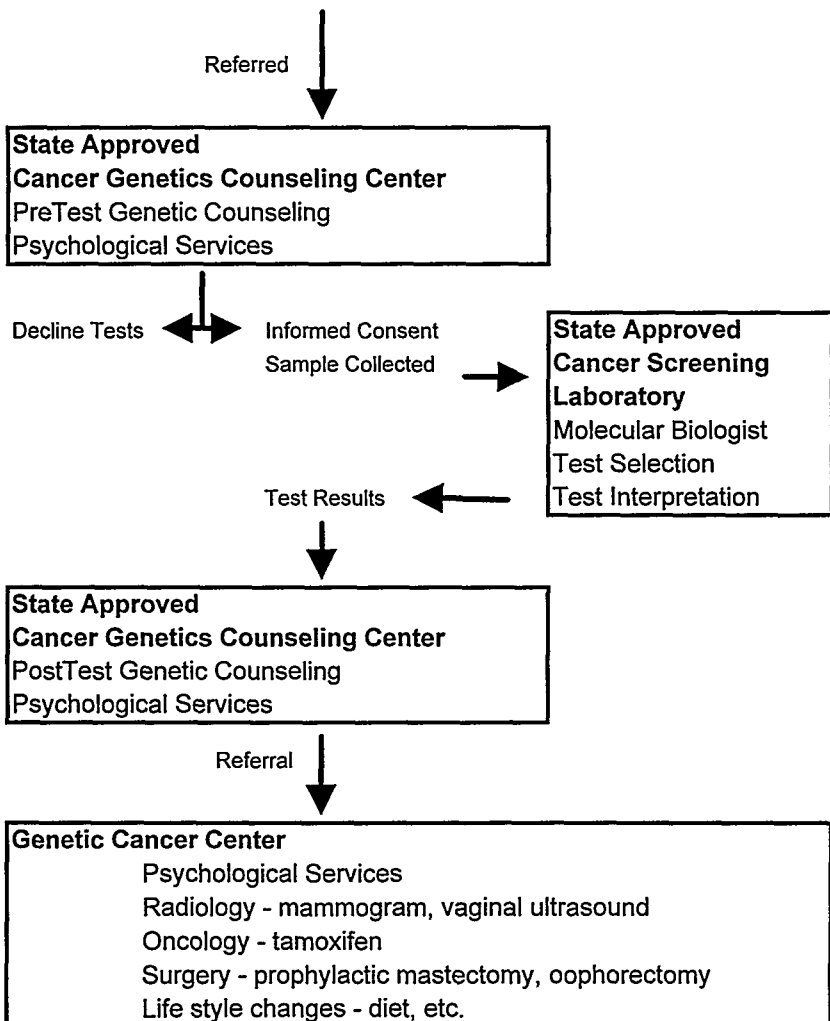
I have diagramed what I perceive to be a general model of a breast cancer screening program in Figure 1. The first task is to develop a method for identifying a high-risk population. Presently, there are several good models for risk assessment which could be implemented.²⁴ Additionally, primary care physicians must be trained in the application of the risk algorithm. If women are identified as being in the high-risk category

24. See Kenneth Offit & Karen Brown, *Quantitating Familial Cancer Risk: A Resource for Clinical Oncologists*, 12 J. CLINICAL ONCOLOGY 1724, 1733 (1994) (stating that multidisciplinary cancer genetic counseling is an emerging resource available to physicians who care for families with common adult malignancies); Mitchell H. Gail et al., *Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who Are Being Examined Annually*, 81 J. NAT'L CANCER INST. 1879, 1879 (1989) (describing a model of relative risks for various combinations of age at menarche, age at first live birth, number of previous biopsies, and number of first-degree relatives with breast cancer as developed from case-control data from the Breast Cancer Detection Demonstration Project); Elizabeth B. Claus et al., *Age at Onset as an Indicator of Familial Risk of Breast Cancer*, 131 AM. J. EPIDEMIOLOGY 961, 972 (1990) (investigating a large population-based, case-control study conducted by the Centers for Disease Control which determined that family and age at onset were the only risk factors strongly associated with familial risk of breast cancer); Diana Eccles et al., *Genetic Epidemiology of Early Onset Breast Cancer*, 31 J. MED. GENETICS 944, 946 (1994) (stating that the parameters of the genetic model were estimated by maximizing the likelihood of the observed phenotypes in families using joint and conditional likelihoods); Deepthi de Silva et al., *Identification of Women at High Genetic Risk of Breast Cancer Through the National Health Service Breast Screening Programme (NHSBSP)*, 32 J. MED. GENETICS 862, 865 (1995) (discussing the first attempt in England at a population-based study to assess the incidence of familial breast cancer and offer genetic counseling for those at greater than twice the age related risk of breast cancer); Elizabeth B. Claus et al., *Genetic Analysis of Breast Cancer in the Cancer and Steroid Hormone Study*, 48 AM. J. HUM. GENETICS 232, 241 (1991) (describing a unique study which determined whether various genetic models fit to an observed data set and then calculated the expected age-specific risk of breast cancer under a given genetic model and compared them with the age-specific risk); David E. Anderson & Michael D. Badzioch, *Risk of Familial Breast Cancer*, 56 CANCER 383, 384 (1985) (discussing a model which develops probabilities of developing breast cancer from three pedigree groups: sisters of patients whose mothers, sisters, or second-degree relatives had previous breast cancer).

ry, they would be referred to approved Breast Cancer Screening Centers. There are several models in this area as well which could be implemented. For example, there are a core of cancer specialty clinics and National Institute for Health recognized cancer centers which could be developed to meet this need. At the Breast Cancer Screening Centers, pre-test counseling would be required to frankly and honestly share the unsatisfactory state of our knowledge about detection rate, sensitivity, specificity, costs, conditional interpretation of risks and known effectiveness of interventions.

Figure 1

Primary Care Selection of High Risk Women



After informed consent, testing would be permitted in quality controlled laboratories directed by a molecular biologist. This molecular biologist would be familiar with the rapidly developing field of mutation and linkage analysis. The laboratory would be prepared to offer cancer-related tests which include BRCA1, BRCA2, p53, HER-2/neu. Post-test counseling would be provided and patients would have additional access to oncologic specialists such as surgeons, radiologists, and oncologists, and mental health professionals. These approved Breast Cancer Screening Centers would also have a research function and would collect data on testing outcomes, intervention decisions, and long-term follow-up and observations.

This scheme has the advantage of providing monitored high quality clinical and laboratory services to a select high-risk population. By organizing data collection, it would contribute to the ultimate resolution of the predictive screening problem. It also addresses the issue of equitable access by providing objective information to all high-risk women. By controlling costs, the technology would no longer be limited to the rich. The scheme also has the benefit of providing a forum, with participation by the women most directly affected, which would debate public policy development rather than blindly adopt policies provided by proprietary programs.

There are several reasons why this model is superior to commercial-based programs. First, commercially based programs have a vested interest in promoting wide-scale testing and, therefore, are less likely to provide complete and objective information about screening. In contrast, regulated programs can insist on adequate public education and consent. Second, commercial third-party payers may develop policies disproportionately weighted toward cost containment rather than high quality care. Therefore, if such a program is approved, it should be mandatory that third-party payers cover the costs for their high-risk eligibles.

The numerous workshops, articles and statements produced by ELSI, The Human Genome Advisory Council, and others in this area are mainly directed toward research pro-

grams, investigators and Institutional Review Boards. Attention must now be directed towards clinical practice.

In the absence of a governmental regulation, premature offering of testing is not only a potential problem, it is highly likely. In fact, two commercial firms, OncorMed and Myriad Genetics Inc.,²⁵ are showing every sign of promotion of testing in the absence of clear guidelines and protocols. These commercial firms have not heeded the recommendations of the genetic experts and concerned women.

Unrestricted marketing of screening for hereditary breast cancer raises issues of equitable access. Will only the affluent have access? Will third-party payors cover the test? In all likelihood, some will and some will not. Likewise, some will cover only laboratory costs, but will not cover the costs of equally important counseling interventions. What is the potential impact on the economics of health care? What are the implications for discrimination by insurers based on membership in high-risk groups, for example, Jewish women, or test results or family history?

A government-regulated program conducted in the private sector, while not able to provide completely satisfactory answers to these questions, has the ability to provide a better response than uncontrolled private provision of testing.

The media can contribute positively or negatively to this problem. By reporting new discoveries they raise expectations. By publicizing the commercial availability of tests, the media can create a demand for testing. However, by carefully reporting the limitations of current testing and knowledge, they can contribute to informed participation by the public in the formation of policy.

Lastly, I would like to speculate on possible future applications of information being developed by the large group of talented people working on this problem. BRCA1 produces a tumor-suppressing protein which might provide a key to screening for nonhereditary forms of breast cancer. Tests for

25. See Rachele Kanigel, *Breast Cancer Test Greeted By Criticism, Concern*, OAKLAND TRIB., Jan. 13, 1996, at A1 (discussing a blood test offered by a Maryland biotechnology company which will locate mutations in the BRCA1 gene); Natalie Angier, *Surprising Role Found for Breast Cancer Gene*, N.Y. TIMES, Mar. 5, 1996, at C1 (stating that Myriad Genetics Inc. has submitted a patent on the gene).

abnormal protein production such as protein truncation appear to be an effective and less costly screening technique.²⁶ Rather than using molecular techniques, we may be able to use a protein transcription translation, biochemical or immunochemical assay, for altered gene product which is more directly related to malignancy. Such a development could replace or supplement the current inadequate screening methods such as self-examination and mammography. It might even lead to more effective therapy.

26. See Pauline A.M. Roest et al., *Protein Truncation Test (PTT) for Rapid Detection of Translation-Terminating Mutations*, 2 HUM. MOLECULAR GENETICS 1719, 1719 (1993) (discussing a rapid and sensitive method, the PTT, which is based on a combination of RT-PCR, transcription and translation, and selectively detects translations-terminating mutations); Alex M. Garvin et al., *Informed Consent and BRCA1 Mutation Detection in Archived Breast Tumour Specimens*, 347 LANCET 1189, 1189 (1996) (stating that 52% of all BRCA1 mutations are detectable by the protein truncation test of exon eleven).