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ARTICLE

BRCA1: TO TEST OR NOT TO TEST, THAT IS THE QUESTION

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YOU ARE A PHYSICIAN. This morning, you received a call from one of your regular patients who sounded very distressed. Mrs. X, a thirty-five year old Ashkenazi-Jewish woman, tells you she wants to be tested for the BRCA1 gene mutation that she understands can predict the eventual development of breast cancer. She heard from friends that Ashkenazi-Jewish women are at especially great risk. She also says that she wants testing immediately because she does not want to wait until it is "too late." Besides, she wants to put her fears of breast cancer to rest. What do you tell her? How can you help her to make an informed decision about having the test performed?

Because of the great media attention surrounding recent findings about the prevalence of the BRCA1 gene mutation in the Ashkenazi-Jewish community, different forms of this scenario has been repeating itself around the country. In the above vignette, there are numerous questions that must be addressed

before an informed decision can be made.

Some of these questions have their foundations in clinical medicine and its basic sciences. Others relate to the interest of other persons and forces in Mrs. X's environment. And still others are of a very personal nature to Mrs. X, including her attitudes towards risk and uncertainty, as well as her personal views of her health and bodily and psychological well-being.

Fundamental to asking these questions is the understanding that Mrs. X must make a decision. At its most superficial level, the decision involves a choice to undergo BRCA1 testing or not. At a slightly deeper level, the decision implies an acceptance of the consequences of her choice. This may include facing *other* decisions about further testing and/or preventive treatment. For example, for women believed to be at an exceptionally high risk of breast cancer, the term "preventive treatment" typically involves the surgical removal of both breasts (prophylactic mastectomy) while they remain disease-free. Other approaches include using experimental medications (such as a drug called tamoxifen). The nature of Mrs. X's decision, relatively simple at first blush, quickly becomes complicated. Some questions that you and she must consider include the following:

1. If she has a positive (abnormal) test, would she consider prophylactic mastectomy and/or tamoxifen?

2. How effective is prophylactic mastectomy (or tamoxifen) in preventing breast cancer? Would she need to undergo treatment now, or could she wait? Would her insurance pay for it? If not, how much is treatment and follow-up likely to cost?

3. What are the chances that she will have a positive test? What would a positive test mean in terms of the chances that she will develop breast cancer, and when?

4. Would a positive test carry a stigma? Would it hinder her employment opportunities? Would it affect her ability to obtain life, health care or disability insurance? How would it affect her marriage?

5. Are there any reasonable alternatives to obtaining the BRCA1 test now?

6. Does she have a religious perspective that might be a factor in deciding whether or not to have the test?

I. DECISION ANALYSIS

One approach to examining choices such as those faced by Mrs. X is to use decision analysis. Decision analysis is a structured approach to examining decisions which have inherent uncertainty or competing risks. Decision analysis has been used increasingly in the medical and health care policy community over the past two decades. This methodology has a number of advantages. For example, decision analysis does the following: 1) it helps make sure that all relevant components of the decision are included; 2) it helps make sense of all the pieces of information and how they interrelate; 3) it allows for and estimates the impact of uncertainty in the data; and 4) it is easily updated and re-analyzed as more information becomes available.

Before applying this approach to the decision of whether to be tested for the BRCA1 mutation, it might be best to briefly discuss what decision analysis is.[1] A decision analysis has three main parts: a graphical component, a decision tree, and an analytic component. The process begins with a graphical model of the relevant decisions and outcomes. The flow of decisions and outcomes is represented by lines, called branches. The point where a decision is made is called a decision node or a choice node, and is represented by a box. Outcomes emanate from chance nodes, shown as circles. They are called chance nodes because the different outcomes, or events, have an associated probability of the event occurring. Endpoints are called terminal nodes and are depicted as a left-pointing triangle. Following a path from left to right you can trace a series of decisions and events, culminating in some endpoint. As an example, Figure 1 is a simple decision tree for treating some hypothetical ailment. The original decision is whether to treat with drugs, surgery, or not to treat at all. Surgery may or may not succeed, and may result in operative death. The endpoint is life status at some time in the future, for example, one year.

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1. *See generally* MILTON C. WEINSTEIN & HARVEY V. FINEBERG, CLINICAL DECISION ANALYSIS (1980) (providing an in-depth treatment of decision making analysis).
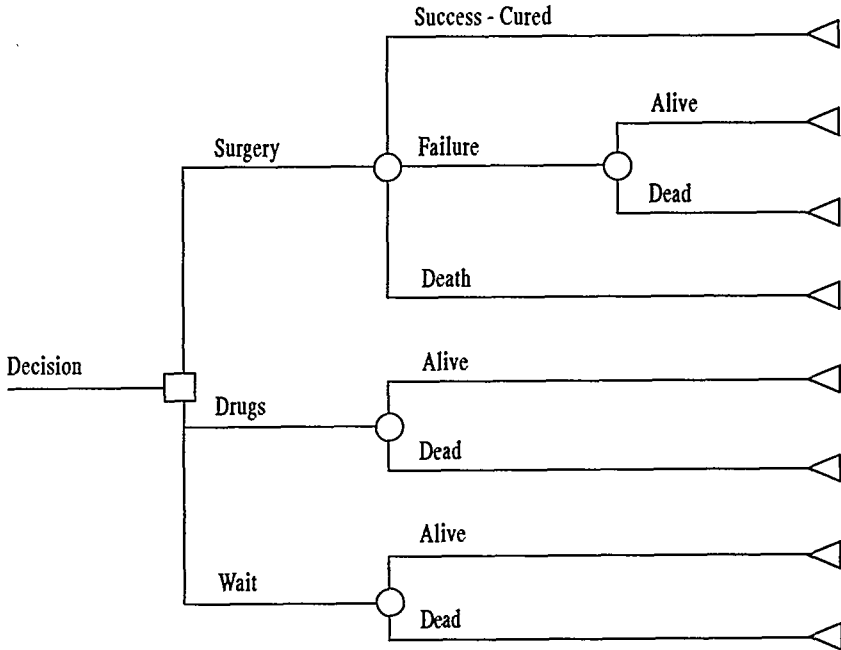
The graphical representation helps to ensure an accurate model that correctly captures the interrelationship of the otherwise disjointed components of the decision process. It also forces the decision maker to consider the possibility of adverse outcomes, as well as successful outcomes, for all choices.

The analytic component comes into play when probabilities are assigned to the chance events. In the hypothetical example, surgery leads to a chance node with three possible outcomes. An analysis will require the assignment of probabilities to each of the three outcomes. Probabilities for a decision tree might be based on clinical trials, analysis of hospital records, analysis of claims data, or expert opinion. After assigning all of the required probabilities, probability theory can be invoked to calculate the decision that maximizes the probability of survival at the specified time horizon; in this case, one year.

Of course, we do not live in a world of unlimited financial resources, and so the decision must, to some degree, be made in the context of cost. Comparing the relative cost and effectiveness is called cost-effectiveness analysis, and requires an appropriate measure of effectiveness.

Often, mortality is not the relevant endpoint. For example, whether to prescribe antibiotics before the result of a throat culture for streptococcal infection is known would not be based primarily on reducing mortality. Sometimes, the endpoint can be captured in some other objective form of effectiveness, such as the number of bedridden days, or the number of additional cancers detected. When we divide cost by effectiveness we obtain a cost-effectiveness ratio. Although it is common for the cost-effectiveness ratio to be used as the yardstick to measure different interventions, there is an important adjustment that should be made.

Medical interventions strive either to prolong life or to improve the quality of life. What is needed for more complete evaluation is a measure that incorporates length of life and any factors a patient may deem important in evaluating the quality of life in a given health state. The approach that has been most prevalent, and the approach that is recommended by the United States Public Health Service's Panel on Cost-Effectiveness in Health and Medicine[2] is to use a quantity known as Quality Adjusted Life Years (QALYs). This approach requires the valuation of the possible health states on a scale from zero to one, with one being perfect health and zero being death. This value is called a utility (a term borrowed from consumer economics) and represents a patient's preferences. This allows incorporation of not only the patient's health state, but also his/her overall quality of life. The utility score serves as a "weight" for the health state. The time spent in a health state is multiplied by the utility to produce a value that is expressed in terms of an equivalent amount of time in perfect health. For example, if life with mild arthritis is valued at 0.9, then one year with mild arthritis is considered to be equivalent to nine-tenths of a year of perfect health. In the case of breast cancer, for example, we will need to value life after mastectomy including all of the associated physical and emotional aspects. Through the use of utilities, tradeoffs of length of life for quality of life can be evaluated. Competing medical interventions are then compared on the basis of the additional cost incurred

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2. *See* MARTHA R. GOLD ET AL., COST-EFFECTIVENESS IN HEALTH AND MEDICINE 308 (1996).

to purchase an additional year of perfect health.[3]

Sensitivity analysis consists of asking "what if" questions. A one-way sensitivity analysis involves changing the value of a single parameter, such as the cost of an operation, while holding all other values in the model constant. The results are compared to those obtained with the original, baseline values to establish how sensitive the decision is to changes in the parameters. This is particularly critical in problems where some of the information is not known with great certainty. A wide range of values can be tested (covering reasonable lower and upper bounds) and if the decision is not sensitive to these changes, then a more precise estimate may not be required to make a confident decision. If small changes to the input value result in a different recommendation, then precise estimates of this value are required before a conclusion can be drawn. Sensitivity analysis can be used to identify those areas of uncertainty that are likely to have an impact on the decision. This can be used to set research priorities.

II. A DECISION TREE FOR BRCA1 TESTING

To develop a decision model for BRCA1 testing, the choices and possible outcomes must be outlined. The initial decision is whether to be tested for a BRCA1 mutation. This might be a relatively simple test for the 185delAG deletion for which Ashkenazi Jews are at particular risk,[4] or it might be a more complex test for any clinically important mutation of the BRCA1 gene. After this decision is made, and the test results, if taken, are known, there is a choice of what to do in the

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3. *See generally* George W. Torrance, *Measurement of Health State Utilities for Economic Appraisal: A Review*, 5 J. HEALTH ECON., Fall 1986, at 1 (detailing methodologies for health state economic appraisals); George W. Torrance & David Feeny, *Utilities and Quality-Adjusted Life Years*, 5 INT'L J. TECH. ASSESSMENT HEALTH CARE 559 (1989) (providing an in-depth discussion of utilities and QALYs); George W. Torrance, *Utility Approach to Measuring Health-Related Quality of Life*, 40 J. CHRONIC DISEASE 593 (1987) (providing an in-depth discussion of measuring utilities). For a general methodology of cost effectiveness analysis, refer to MICHAEL F. DRUMMOND ET AL., METHODS FOR THE ECONOMIC EVALUATION OF HEALTH CARE PROGRAMMES (1987); FRANK A. SLOAN, VALUING HEALTH CARE: COST, BENEFITS, AND EFFECTIVENESS OF PHARMACEUTICALS AND OTHER MEDICAL TECHNOLOGIES (1995).

4. *See* Jeffrey P. Struewing et al., *The Carrier Frequency of the BRCA1 185delAG Mutation is Approximately 1 Percent in Ashkenazi Jewish Individuals*, 11 NATURE GENETICS 198, 199 (1995).

follow-up of the test results. Currently, the options are very limited: Mrs. X may be offered a screening program which would consist of some frequency of mammography and clinical breast exam. She may have a prophylactic mastectomy or tamoxifen. Or she may "watchfully wait." Regardless of the patient's decision, she will be followed over time. She may remain without disease or develop breast cancer at some point in time. Breast cancer may progress through the four stages of the disease before a patient either discovers the disease or responds to treatment, if it is undertaken. The different health conditions are called states, and the method for capturing the movement between different health states over time is called a Markov model. Inputs to the Markov model include the proba-bilities for all possible transitions from one state to another, and the cost and utility associated with being in a particular health state for a given period of time. This is referred to as the cycle time. Figure 2 depicts the basic decision model for BRCA1 testing.
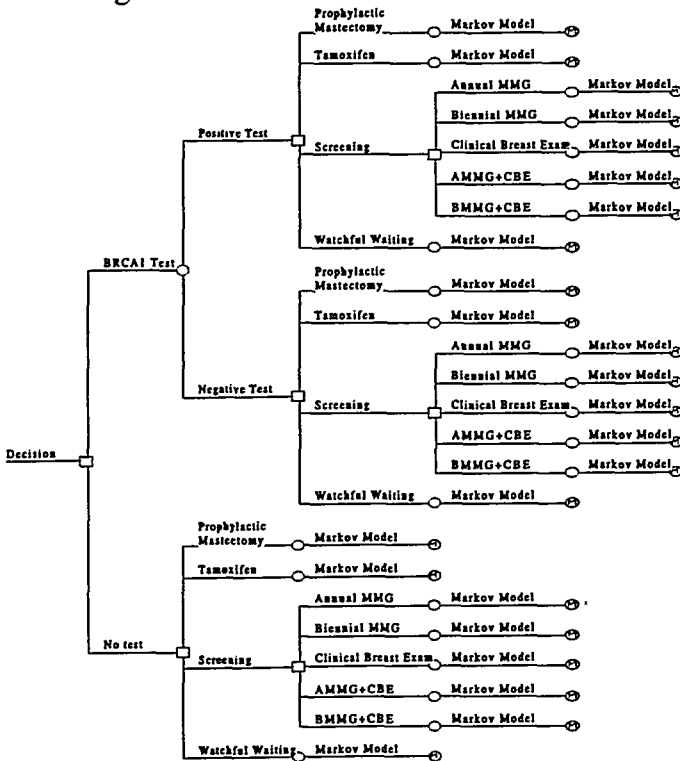

Figure 2. MMG = mammography, AMMG = annual mammography, BMMG=biennial mammography, CBE = clinical breast exam.

A schematic representing the Markov model is shown in Figure 3. It allows for health states corresponding to when a patient is well, when a patient has each of the four stages of breast cancer, and when a patient is dead. These are the choices regardless of the path traversed in the model prior to entering the Markov model. However, the path leading to the Markov model will affect the probabilities, costs, and utilities inside the Markov model.
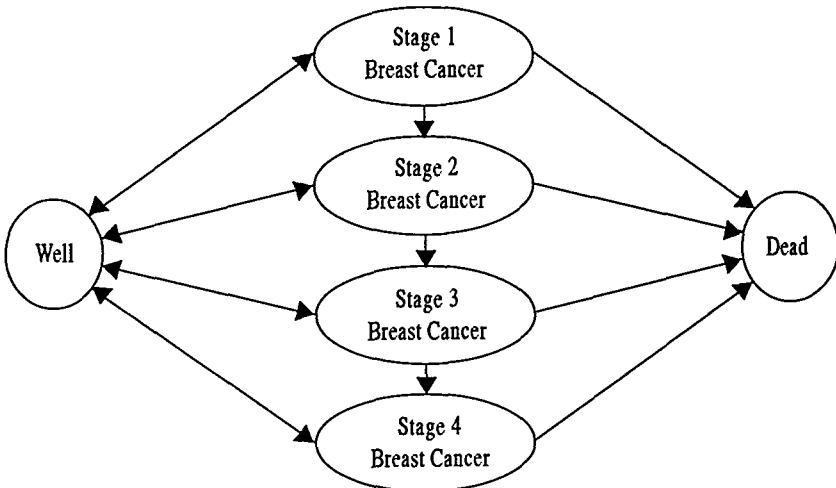
This is a basic model. The purpose of this Article is to demonstrate how decision analysis can be employed to deal with the complex issue of whether an individual should undergo BRCA1 testing. Accordingly, the model presented is simplified to allow for easier understanding and discussion of its components.

There are many alternative models that could be formulated. Screening programs for breast cancer come in many forms. For example, the frequency of clinical breast exam could be six months or one year. It may or may not be done in combination with annual or biannual mammography. Other technologies could be considered in place of mammography.

Following prophylactic mastectomy, there could be an allowance for various screening options. Additionally, there

was an attempt to include only commonly used interventions. A notable exception is tamoxifen, because there is some evidence to suggest that tamoxifen may have preventive value.[5]

In the interest of simplicity, prophylactic oophorectomy (removal of the ovaries) is not included in the model presented here. At this time, it is not known how much prophylactic oophorectomy reduces the chance of breast cancer among women with family history of breast cancer.[6] Estrogen replacement often is prescribed to treat the significant side effects that often accompany the abrupt onset of menopause caused by prophylactic oophorectomy in premenopausal women. It is not known how much the effectiveness of prophylactic oophorectomy is reduced by estrogen replacement therapy.[7]

Another issue that is not dealt with explicitly in this model is the issue of timing. An individual will make a decision appropriate for her current age and situation, but will need to reevaluate this decision periodically. As is discussed later, when a person passes menopause, her chance of breast cancer increases, but the probability of a genetic-based breast cancer decreases. Thus, the value of preventive measures or heightened screening increases, but the value of a BRCA1 test decreases. The model discussed here will deal with an individual person, with her own unique risk profile for a given point in time.

In order to perform the decision analysis, the associated probabilities, costs, and utilities must be estimated. The complexity involved is masked by the relative simplicity of the decision tree. In particular, there are numerous factors that must be accounted for in determining the probabilities and utilities. The following sections will discuss the different components of the decision tree and the current state of knowledge about the probabilities, costs, and utilities, and what is involved in obtaining these numbers.

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5. *See* Susan G. Nayfield et al., *Potential Role of Tamoxifen in Prevention of Breast Cancer*, 83 J. NAT'L. CANCER INST. 1450, 1452 (1991) (citing the length of time tamoxifen has been used as a treatment for breast cancer).

6. *See* Mary-Claire King et al., *Inherited Breast and Ovarian Cancer: What are the Risks? What are the Choices?* 269 JAMA 1975, 1979 (1993) (discussing the complexity of prophylactic mastectomy).

7. *Id.*

A. Risk of Breast Cancer

The results of this decision analysis are likely to depend upon the probability of developing breast cancer. When considering the overall population, it is a simple matter to use existing epidemiologic data to estimate this. Current estimates of the chance of breast cancer by age eighty-five are approximately one in nine, with a lifetime risk of one in eight.[8] These estimates can be used for the general population in the absence of knowledge specific to the individual. However, in a decision model for BRCA1 testing, estimates of the risk of breast cancer will be needed based on: 1) BRCA1 status: positive, negative, or untested; and 2) the presence of other risk factors, especially family history. Carrier status will only be known according to the degree of accuracy of the gene test, which will be discussed later. Models have been developed by Elizabeth B. Claus, et al.[9] and Mitchell H. Gail, et al.[10] that estimate the probability of breast cancer based on family history alone. According to the Claus model,[11] a patient with one first degree relative who had breast cancer diagnosed between forty and forty-nine years of age, would have a thirteen percent chance of breast cancer by age eighty, contrasted with a probability of 10.4% in the general population.[12] Likewise, if the first degree relative's cancer was diagnosed between the ages of twenty and twenty-nine, the chance increases to twenty-one percent.[13] Finally, having two first degree relatives diagnosed between forty and forty-nine, raises the risk to thirty-five percent.[14]

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8. *See* Eric J. Feuer et al., *The Lifetime Risk of Developing Breast Cancer*, 85 J. NAT'L CANCER INST. 892, 892 (1993) (citing statistical references for calculating lifetime risk of breast cancer).

9. *See generally* Elizabeth B. Claus et al., *Autosomal Dominant Inheritance of Early-Onset Breast Cancer*, 73 CANCER 643, 643-50 (1994) (describing a population-based, case-controlled study to provide age-specific risk estimates of breast cancer for women with a family history of breast cancer).

10. *See generally* Mitchell H. Gail et al., *Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who are Being Examined Annually*, 24 J. NAT'L CANCER INST. 1879 (1989) (presenting a method to estimate the chance that a woman with a given age and risk factors will develop breast cancer over a specified interval).

11. *See* Claus et al., *supra* note 9, at 645.

12. *See* Feuer et al., *supra* note 8, at 894.

13. *See* Claus et al., *supra* note 9, at 645.

14. *See id.* at 646.

It is particularly difficult to estimate the probability of breast cancer when taking into account the results of a BRCA1 test. Using a model based on analysis of 214 families, D.F. Easton, et al.[15] estimated that BRCA1 carriers have a fifty-nine percent chance by age fifty and an eighty-two percent chance by age seventy of developing breast or ovarian cancer. However, these numbers were based on families with multiple affected individuals. In other words, these probabilities are for people considered to have an extremely high risk of breast cancer prior to any knowledge concerning BRCA1 status. It is not yet known what the risk of breast cancer is among BRCA1 carriers with limited or no family history of breast cancer.[16] The role of other genetic and environmental factors is easily overlooked when focusing on a single gene.[17] At this point in time, the excess risk due to carrier status remains unclear.

It also is unclear if the disease *progresses* differently in BRCA1 carriers. BRCA1 carriers are at increased risk of ovarian cancer, as well as breast cancer.[18] Recent evidence suggests that BRCA1 carriers who develop ovarian cancer may fare better than noncarriers of similar age and disease.[19] It is not known if this same benefit might extend to breast cancer.

It has been stated that noncarriers (those with a negative test for BRCA1) have a risk equivalent to the general population,[20] thus "canceling" the effect of family history. However,

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15. D. F. Easton et al., *Genetic Linkage Analysis in Familial Breast and Ovarian Cancer: Results from 214 Families*, 52 AM. J. HUM. GENETICS 678, 678 (1993) (relating findings of the study).

16. *See* 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, 148 (1996) (explaining that more studies will have to be performed to determine the exact penetration of the allele of the BRCA1 gene); Streuwing et al., *supra* note 4, at 199 (describing the Ashkenazic carrier rates for the BRCA1 185delAG mutation); Heather Bryant, *Genetic Screening for Breast Cancer in Ashkenazi Women*, 347 LANCET 1638, 1638 (1996) (commenting that the selected members of the Ashkenazi population studied may not reflect the Ashkenazi population as a whole).

17. *See* Stephen H. Friend, *Breast Cancer Susceptibility Testing: Realities in the Post-Genomic Era*, NATURE GENETICS, May 1996, at 16 (explaining that data suggests multiple factors affecting breast cancer susceptibility).

18. *See generally* D. Ford et al., *Risks of Cancer in BRCA1 Mutation Carriers*, 343 LANCET 692, 692-95 (1994).

19. *See* Stephen C. Rubin, *Clinical and Pathological Features of Ovarian Cancer in Women With Germ-line Mutations of BRCA1*, 333 NEW ENG. J. MED. 1413, 1413-16 (1996) (finding that cancers associated with BRCA1 mutations appear to have a significantly more favorable clinical course).

20. *See, e.g.*, Kent F. Hoskins et al., *Assessment and Counseling for Women with a Family*

their risk should actually be slightly lower than that of the general population because one risk factor, the BRCA1 mutation, has been eliminated. The reduced risk due to a negative test for BRCA1 is limited because the BRCA1 mutation is estimated to account for only about seven percent of all breast cancer cases.[21] Although the Ashkenazi-Jewish community is at higher risk for the 185delAG deletion, it is not yet known whether they have a higher prevalence of BRCA1 mutations overall. As pointed out by Lori S. Friedman, et al.,[22] such a finding would be consistent with results suggesting a higher proportion of inherited breast cancer in the Ashkenazi Jewish population.[23] If this is the case, the benefit of a negative test would be greater for Ashkenazi-Jews than for the general population.

B. Screening for Breast Cancer

There are numerous cost-effectiveness analyses in the literature which address breast cancer screening.[24] They are an

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History of Breast Cancer, 273 JAMA 577, 581 (1995) (calculating the risk of developing breast cancer with respect to BRCA1 and BRCA2 in mutation carriers, noncarriers, and the general population); Donna Shattuck-Eidens et al., *A Collaborative Survey of 80 Mutations in the BRCA1 Breast and Ovarian Cancer Susceptibility Gene*, 273 JAMA 535, 541 (1995) (stating that at-risk women who do not inherit the BRCA1 mutation have the same risk of breast and ovarian cancer as the general population); Mary-Claire King et al., *supra* note 6, at 1977 (stating that the lifetime risk of breast cancer for both noncarriers and women in the general population of the United States is approximately 10%).

21. *See* Elizabeth B. Claus et al., *The Genetic Attributable Risk of Breast and Ovarian Cancer*, 77(11) CANCER 2318, 2318 (1996).

22. Lori S. Friedman et al., *Novel Inherited and Variable Expressivity of BRCA1 Alleles, Including the Founder Mutation 185delAG in Ashkenazi-Jewish Families*, 57 AM. J. HUM. GENETICS 1284, 1294 (1995) (suggesting a higher proportion of inherited breast cancer in the Ashkenazi-Jewish population).

23. *See* Susan P. Helmrich et al., *Risk Factors for Breast Cancer*, 117 AM. J. EPIDEMI-OLOGY 35, 44 (1983) (finding that Jewish women are at a greater risk of getting breast cancer); Jennifer L. Kelsey et al., *Exogenous Estrogens and Other Factors in the Epidemiology of Breast Cancer*, 67 J. NAT'L CANCER INST. 327, 331 (1981); K. Egan et al., *Jewish Religion and Risk of Breast Cancer*, 347 LANCET 1645, 1645 (1996).

24. *See, e.g.*, Martin L. Brown & Lou Fintor, *Cost-Effectiveness of Breast Cancer Screening: Preliminary Results of a Systematic Review of the Literature*, 25 BREAST CANCER RES. & TREATMENT 113, 113-18 (1993); Jeanne S. Mandelblatt et al., *Breast Cancer Screening for Elderly Women With and Without Comorbid Conditions*, 116 ANNALS INTERNAL MED. 722, 724 (1992); David M. Eddy, *Screening for Breast Cancer*, III ANNALS INTERNAL MED. 389, 389-99 (1989); Alvin I. Mushlin & Lou Fintor, *Is Screening for Breast Cancer Cost-Effective?* 69 CANCER 1957, 1959-61 (Supplement 1992); Anthony B. Miller et al., *Canadian National Breast Screening Study: Breast Cancer Detection and Death Rates Among Women Aged 40 to 49 Years*, 147(10) CAN. MED. ASS'N J. 1459, 1459 (1992); Ichiro Okubo et al., *Cost-Effectiveness of Mass*

excellent source of data, although some of the models were not based on data from the United States, and some data are based on Medicare reimbursement rates which will not apply to younger women. The structure of these models can form the basis for the screening component of the model presented here. However, these models have all been developed for the general population. Thus, the probabilities will have to be modified to take into account information specific to Mrs. X, such as her risk profile.

C. BRCA1 Testing

There are many issues concerning BRCA1 testing that must be considered in the decision model. These may be categorized as follows:

1. Accuracy of the test
2. Probability of a positive test
3. Cost of testing (including education and counseling)
4. Emotional effect of a positive test on the patient
5. Emotional effect of a negative test on the patient
6. Effect of a positive test on compliance with screening
7. Effect of a negative test on compliance with screening

Accuracy of medical tests may be characterized by the rate of false negative and false positive test results, i.e., the frequency with which true carriers are missed or true noncarriers are falsely identified as carriers. Currently, there are no published data for accuracy of testing for the known mutations of BRCA1, let alone those that have yet to be discovered. Donna Shattuck-Eidens, et al.[25] comments that the variety of methods used and the heterogeneity of the patient samples with regard to family history make it virtually impossible to ascertain the accuracy of testing for BRCA1 mutation. Kent F. Hoskins, et al. notes that once a BRCA1 mutation has been identified in a

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Screening for Breast Cancer in Japan, 67 CANCER 2021, 2021-29 (1991); C. John Rosenquist & Karen K. Lindfors, *Screening Mammography in Women Ages 40-49 Years: Analysis of Cost Effectiveness,* 191 RADIOLOGY 647, 647-50 (1994); Martin L. Brown, *Sensitivity Analysis in the Cost-Effectiveness of Breast Cancer Screening,* 69 CANCER 1963, 1963-66 (1992).

    25. Shattuck-Eidens et al., *supra* note 20, at 541.

family, screening for the specific mutation in other family members is not complicated, but the complexity in identifying the mutation for the first time in a family cannot be underestimated.[26] Looking for the 185delAG mutation, however, should be more accurate because a specific mutation, especially a deletion, is easier to detect.[27] However, other mutations in BRCA1, that are not deletions, will be more difficult to detect. This could potentially result in more false negatives. Testing for other mutations will also result in more false positives, due to the difficulty of judging whether or not the mutation is clinically significant.

The probability of an individual inheriting the trait from a carrier parent is fifty percent.[28] Thus, given information about the probability of the parent having the trait, we can estimate the probability of a particular child being a carrier.

Jeffery P. Struewing[29] found a .9% prevalence of 185delAG deletion in the general Ashkenazi population. However, the results of Kenneth Offit, et al.[30] suggest a somewhat lower figure. Studies have shown that about twenty percent of early-onset breast cancer patients in the Ashkenazi population have this particular mutation,[31] as opposed to a rate of about eight percent in the non-Jewish population for any BRCA1 mutation.[32] These studies provide a reasonable basis for estimating the probability of a positive test for this particular BRCA1 mutation.

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26. Hoskins et al., *supra* note 20, at 581.

27. *See* Shattuck-Eidens et al., *supra* note 20, at 541.

28. *See* King, *supra* note 6, at 1976.

29. Struewing et al., *supra* note 4, at 148.

30. Kenneth Offit et al., *Germline BRCA1 185delAG Mutations in Jewish Women with Breast Cancer*, 347 LANCET 1643, 1644 (1996) (stating that Struewing et al.'s figures (for the citation *see* Struewing et al., *supra* note 4) may be higher because of the bias toward probands with family histories of cancer).

31. *See* Offit et al., *supra* note 30, at 1644 (explaining that the 185delAG gene has an estimated incidence of 22% and an actual incidence of 20%); FitzGerald et al., *supra* note 16, at 143 (explaining that the 185delAG gene is a detectable trait in 21% of Ashkenazi-Jewish women who were treated as early-onset breast cancer patients).

32. *See* FitzGerald et al., *supra* note 16, at 147-48 (stating that 2/26 of the non-Jewish population has this mutation).

D. Cost of Testing

The Genetics and I.V.F. Institute in Fairfax, Virginia, for a fee of $295, has been testing specifically for the 185delAG mutation.[33] Likewise, in October of 1996, Myriad Genetics, Inc., of Salt Lake City, Utah, announced the introduction of "BRCAnalysis (tm)."[34] The charge is $2400 for a comprehensive sequence analysis of BRCA1 and BRCA2.[35] Once a mutation has been identified in a family, additional family members can be tested for that particular mutation for $395.[36] In addition, the cost of pre-test education and counseling must be considered.

E. Emotional Impact of Testing

What emotional effect does the test result have on the patient? Caryn Lerman, et al.[37] found that noncarriers (those with a negative test) showed statistically significant reductions in depressive symptoms and functional impairment compared with carriers and nontested individuals. Thus, a negative test result may provide sufficient reassurance value to effect improvements in quality of life. Likewise, in this particular study, carriers did not show any adverse effects after a positive test.[38] However, this failure to detect a decrease in quality of life in people who tested positive may be misleading because the population sampled consisted of people from families with high family history of breast and ovarian cancer.[39] Since they knew they were at great risk for breast cancer, the positive test result did not significantly change their situation. It is noteworthy that only forty-three percent of the people tested were

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33. *See* Gina Kolata, *Breaking Ranks: Lab Offers Test to Assess Risk of Breast Cancer*, N.Y. TIMES, Apr. 1, 1996, at A1.

34. *Myriad Genetics Introduces the First Comprehensive Breast/Ovarian Cancer Susceptibility Test*, (visited Nov. 31 1996) <hhtp://www.myriad.com/Launch%20PR>.

35. *See id.*

36. *See id.*

37. Caryn Lerman et al., *BRCA1 Testing in Families With Hereditary Breast-Ovarian Cancer*, 275 JAMA 1885, 1885, 1887 (1996) (administering the Center for Epidemiologic Studies for Depression Scale during the baseline and follow-up interviews to assess depressive symptomatology).

38. *See id.*

39. *See id.* at 1886.

interested in knowing their result.[40] Thus, for those who did not want their test results, it may be that they did in fact associate a significant reduction in quality of life with a positive test result and that was the basis for their decision.

F. Impact of Test Results on Subsequent Compliance

Another important issue in relation to BRCA1 testing is the effect it might have on compliance with mammographic screenings and clinical breast exams. It has been well-established that compliance with screening is correlated with perceived risk.[41] This especially is true with younger women.[42] Although many women may be reluctant to participate due to cancer anxiety, compliance is generally improved when the patient is aware of the risk.[43] At this point, it is too soon to have any evidence of compliance after individuals learn the results of genetic testing. Will people with a positive test be more diligent in following through with an increased level of screening? Will people with a negative test have a tendency to think that they are "off the hook?" As the vast majority of breast cancers are not genetic in origin, noncarriers must be told that they still need to follow-through with regular screening at the appropriate ages. Since the effectiveness of mammography prior to age fifty is in question,[44] will a younger woman choose to postpone screening until then? Will the "relief" of the negative test wear off by then, thus having no effect on compliance? The issue of the effect of the test result on

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40. *See id.* at 1888 (indicating that 57% did not want to know the test results).

41. *See* Victoria Lee Champion, *The Relationship of Selected Variables to Breast Cancer Detection Behavior in Women 35 and Older,* 18 ONCOLOGY NURSING 733, 735-36 (1991) (describing the relationship between selected variables and the practice of breast self-examination); Stephen Taplin et al., *Breast Cancer Risk and Participation in Mammography Screening,* 79 AM. J. PUB. HEALTH 1494, 1494 (1989) (stating that women in a high-risk group for breast cancer are the most likely to participate in mammographic screening).

42. *See* Taplin et al., *supra* note 41, at 1496.

43. *See* Kathryn M. Kash et al., *Psychological Distress and Surveillance Behaviors of Women with a Family History of Breast Cancer,* 84 J. NAT'L CANCER INST. 24, 27 (1992) (finding a negative relationship between cancer anxiety and regular clinical breast examination).

44. *See* Anthony B. Miller et al., *supra* note 24, at 1460 (stating that yearly mammography and physical examination of breasts detected considerably more node-negative, small tumors than usual care, but had no impact on the rate of death from breast cancer); Rosenquist & Lindfors, *supra* note 24, at 649-50 (stating that reduction in mortality results from screening mammography in women between the ages of forty and forty-nine remains unknown).

compliance with screening is purely speculative at this time. In the context of a decision analysis, this could be handled in the sensitivity analysis. Likewise, if it turns out that the decision to be tested is insensitive to this parameter, then it would be unnecessary to obtain a precise estimate of the effect of test status on compliance with screening.

G. Prophylactic Mastectomy

The only established prophylactic option currently available is a mastectomy. Historically, the most common procedure is a subcutaneous mastectomy. Though this procedure leaves behind about five percent of the breast tissue, it yields a much better cosmetic result than total mastectomy. Subcutaneous mastectomy is not one-hundred percent successful as there have been cases of breast cancer reported in patients who have had subcutaneous mastectomy.[45] To date, there have been no epidemiologic studies of the effectiveness of prophylactic mastectomy. Animal studies have failed to find significant benefit, let alone a guarantee.[46] In all of these studies, complete mammectomy was not possible and the residual breast tissue was at

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45. *See* David G. Bowers Jr. & Charles B. Radlauer, *Breast Cancer After Prophylactic Subcutaneous Mastectomies and Reconstruction with Silastic Prostheses*, 44 PLASTIC & RECONSTRUCTIVE SURGERY 541, 541-42 (1969) (detailing two cases of breast cancer occurring after prophylactic subcutaneous mastectomies); Miguel A. Mendez-Fernandez et al., *Paget's Disease of the Breast After Subcutaneous Mastectomy and Reconstruction With a Silicone Prosthesis*, 65 PLASTIC & RECONSTRUCTIVE SURGERY 683, 683 (1980) (detailing a case where Paget's Disease occurred after subcutaneous mastectomy); Vincent R. Pennisi & Angelo Capozzi, *The Incidence of Obscure Carcinoma in Subcutaneous Mastectomy*, 56 PLASTIC & RECONSTRUCTIVE SURGERY 9, 10 (1975) (discussing the results of a national survey which led to the belief that subcutaneous mastectomy is the most effective procedure available for women with a high-risk of developing breast cancer); Walley J. Temple et al., *Technical Considerations for Prophylactic Mastectomy in Patients at High Risk for Breast Cancer*, 161 AM. J. SURGERY 413, 413 (1991) (documenting an incidence of breast cancer in follow-up reports of prophylactic mastectomy cases).

46. *See* Christopher F. Jackson et al., *The Effectiveness of Prophylactic Subcutaneous Mastectomy in Sprague-Dawley Rats Induced with 7, 12-Dimethylbenzanthracene*, 73 PLASTIC & RECONSTRUCTIVE SURGERY 249, 254 (1984) (detailing experiment showing no benefit from prophylactic subcutaneous mastectomy in Sprague-Dawley rats); Jan H. Wong et al., *Analysis of the Risk Reduction of Prophylactic Partial Mastectomy in Sprague-Dowley Rats with 7, 12-Dimethyl Benzanthracene-Induced Breast Cancer*, 99 SURGERY 67, 67 (1986) (detailing experiment showing no significant difference in number of tumors among groups given varying degrees of partial mastectomy); Heidi Nelson et al., *Effectiveness of Prophylactic Mastectomy in the Prevention of Breast Tumors in C3H Mice*, 83 PLASTIC & RECONSTRUCTIVE SURGERY 662, 662 (1989) (concluding that mammary tumor incidence was not decreased, even by 100% mammectomy).

increased risk of cancer.[47] However, it is well-accepted that not all of the breast tissue is removed by total mastectomy in humans,[48] and the remaining breast tissue may be at increased risk.

Florence Houn, et al. studied the recommendations and performance of prophylactic mastectomy in Maryland.[49] Practice patterns varied significantly across specialty, not only in terms of a risk threshold before performing prophylactic mastectomy, but also in terms of the type of mastectomy (subcutaneous or total).[50] Florence Houn, et al. conclude that there is a need for better evaluation of the efficacy and appropriateness of prophylactic mastectomy.[51] Certainly, in terms of doing a proper decision analysis a reasonable figure for recurrence of breast cancer after prophylactic mastectomy is needed. Rates of 0.5 percent[52] and one percent[53] in short term follow-up after subcutaneous mastectomy have been cited. However, these numbers cited must be taken in the context of the likelihood of breast cancer before the mastectomy. Thus, the rate of breast cancer after mastectomy is not known, and screening may still be needed.

Cost of prophylactic mastectomy varies greatly depending on the type of mastectomy performed and the amount of reconstruction. This amount can range from $5,000-$50,000.[54]

The issue of utility of prophylactic mastectomy is extremely complex. Utility measures must model not only the patient's perception of her medical well-being, but also her emotional well-being. In essence, it is a measure of quality of life. In this case, beyond the usual issues of health risk, functional status, and personal attitude, there are many "outside" factors that may play a very significant role. These include the

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47.   *See* Nelson, *supra* note 46, at 666.

48.   *See id.*; King, *supra* note 6, at 1979.

49.   Florence Houn et al., *The Practice of Prophylactic Mastectomy: A Survey of Maryland Surgeons*, 85 AM. J. PUB. HEALTH 801, 804-05 (1995).

50.   *See id.* at 801.

51.   *Id.*

52.   *See* Pennisi & Capozzi, *supra* note 45, at 9-10 (relying on a questionnaire with a 44% response rate that included a mix of risk factors (many low-risk patients)). Furthermore, this data may be out of date.

53.   *See* Temple et al., *supra* note 45, at 413 (relying on anecdotal reports).

54.   *See* Hoskins et al., *supra* note 20, at 583.

following: 1) cultural attitude; 2) religious beliefs; 3) spouse's attitude; 4) marriageability; 5) insurability; and 6) potential employment discrimination. Jane Hall, et al. summarizes several reports that deal with utility of mastectomy.[55] Of particular importance are the findings that psychological aspects outweigh the physical, and that women with breast cancer assigned higher utilities than potential patients.[56] In light of these findings, it is very unclear how to extend these results to the case of prophylactic mastectomy. The extreme complexity of the non-physical issues require investigation. It may be that the role of non-physical factors will be more extreme in prophylactic treatment. Cultural or spousal attitudes may be much less accepting of mastectomy as a response to risk of breast cancer as opposed to mastectomy as a treatment for the development of breast cancer. In the context of a decision analysis, this utility will be contrasted with the utility of living with the risk of breast cancer of the individual patient. However, the risk of breast cancer is itself an important factor in determining the utility. Thus, BRCA1 carrier status would be expected to be an important factor in the utility of prophylactic mastectomy. Religious beliefs may also be a factor. In the case of Ashkenazi women, following a rabbinic ruling may provide a sense of comfort. Likewise, not following it may cause feelings of "guilt." There is a great need to better understand the role of the many important non-physical factors in the utility of prophylactic mastectomy. For now, the limited utilities available can be used as baseline values, with sensitivity analysis to allow for a wide range of utilities. However, because a patient at risk for genetic breast cancer will be considering prophylactic mastectomy at an early age, thus spending many years in a post-mastectomy state, the model may be very sensitive to this utility.

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55. Jane Hall et al., *A Lost Utility Analysis of Mammography Screening in Australia*, 34 SOC. SCI. MED. 993, 1001-03 (1992) (summarizing cost utility reports related to mastectomy to determine the utility of mastectomy and other medical interventions that are implemented as a result of breast cancer).

56. *See id.*

H. Tamoxifen

Tamoxifen has been used as a treatment for breast cancer for over twenty years.[57] Used as an adjuvant therapy for early-stage breast cancer, it has been associated with a thirty-five percent decrease in developing a second primary tumor in the contralateral breast.[58] This suggests a preventive effect, and as a result, there are clinical trials in progress which are examining use of tamoxifen in a preventive setting. Although tamoxifen has been in use since the early 1970s, the benefits and risks associated with its long-term use by younger, high-risk women is unknown.[59] Likewise, use as a preventive drug outside of the trial might be considered inappropriate.[60] Insurance coverage would be unlikely, and the cost is significant.

Tamoxifen has a low incidence of side effects.[61] However, it has been associated with depression, thrombotic events, and several forms of cancer, including endometrial, hepatic, and possibly liver cancer.[62]

Given the success of tamoxifen in preventing second primary cancers, and its demonstrated chemopreventive and/or chemosuppressive activity in rodent models,[63] there is much hope for this drug. At this point, however, its efficacy in the preventive setting is not known. This is particularly true for premenopausal women who have been underrepresented in clinical trials that studied the prevention of contralateral breast cancer.[64] At this point, there does not seem to be a basis for

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57. *See* Nayfield et al., *supra* note 5, at 1450 (stating that benefits of tamoxifen include overall survival as well as disease-free survival for women over age fifty).

58. *See id.* at 1452 (citing statistics relating to the efficacy of tamoxifen in preventing second primary tumors in the contralateral breast).

59. *See* King, *supra* note 6, at 1979 (clarifying that as part of a randomized controlled study, questions of risk can be clarified and tamoxifen's role in prevention can be determined for women in general).

60. *See id.*

61. *See* Nayfield et al., *supra* note 5, at 1451 (indicating that tamoxifen may have a potential role in chemoprevention of breast cancer in healthy women with increased risk of disease).

62. *See id.* at 1455-56 (stating that the estrogenic effects of tamoxifen may be dose dependant and related to duration of therapy).

63. *See id.* at 1451 (stating that tamoxifen is associated with approximately a 35% decrease in contralateral breast tumors for women with early-stage breast cancer in the adjuvant setting).

64. *See id.* at 1452 (suggesting that because there is a strong inverse association between age and risk of contralateral breast cancer, premenopausal patients may experience greater risk reduction with adjuvant tamoxifen therapy than postmenopausal women).

estimating the effectiveness of tamoxifen in prevention. As results from the prevention trials become available, they can be incorporated into the decision model.

I. Genetic Discrimination

A person who tests positive for a BRCA1 mutation runs the risk of some form of genetic discrimination. This may be in the form of employment discrimination or impaired ability to obtain certain types of insurance, such as life, health care, or disability. The individual has some protection from the Rehabilitation Act of 1973[65] and the Americans with Disabilities Act of 1990 (ADA),[66] as well as varying degrees of protection from state laws.[67]

Genetic discrimination is still a new and relatively untested area of the law. A United States Supreme Court decision seems to have defined a carrier of a susceptibility gene as "disabled," thereby enabling that person to be covered by the ADA.[68] Of particular importance is the extent that state anti-discrimination laws cover insurance companies, an area largely ignored by the ADA.[69] Insurance companies routinely require full disclosure of relevant matters that only the applicant may know. Likewise, withholding this information could be fraudulent.[70] As genetic research continues to advance, opportunities for genetic discrimination will increase dramatically.

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65.   See generally The Rehabilitation Act of 1973 § 501, 29 U.S.C. 794 (Supp. V 1993).

66.   See generally The Americans with Disabilities Act § 102, 42 U.S.C. § 12101-213 (Supp. V. 1993).

67.   See Marvin R. Natowicz et al., Genetic Discrimination and the Law, 50 AM. J. HUM. GENETICS 465, 471-72 (1992) (stating that although all states prohibit unfair discrimination by life insurers and some states prohibit unfair discrimination by health insurers, in general, state law provides minimal protection against genetic discrimination in the insurance field).

68.   See Sch. Bd. of Nassau County v. Arline, 480 U.S. 273, 284 (1987).

69.   See Natowicz et al., supra note 67, at 471, 473 (stating that the greatest weakness of the ADA is the exception it provides for insurance companies).

70.   See Bernard M. Dickens et al., Legal and Ethical Issues in Genetic Testing and Counselling for Susceptibility to Breast, Ovarian and Colon Cancer, 154(6) CAN. MED. ASSOC. J. 813, 816 (1996) (stating that insurance companies expect that applicants who have genetic test results will disclose them and that nondisclosure could render the contract voidable even if death or disability is unrelated to the undisclosed risk); Maxwell J. Mehlman et al., The Need for Anonymous Genetic Counseling and Testing, 58 AM. J. HUM. GENETICS 393, 394 (1996) (stating that although probands should be cautioned that withholding information could be fraudulent, the law is evolving in terms of whether employers and insurers even have the right to ask for this information).

Thus, present and future laws that cover genetic discrimination will be tested. The potential for genetic discrimination, and the great uncertainty about its future effects, contribute significantly to a woman's assessment of the utility of a positive BRCA1 test.[71] Also, the possibility of restricted access to health care insurance could have adverse effects on decisions concerning therapeutic and prophylactic alternatives, as well as their costs.

III. OTHER ISSUES

The role of insurance may be extremely important. Prophylactic mastectomy (especially with reconstruction) and long-term use of tamoxifen are both expensive options. Given the limited knowledge of effectiveness, it is questionable how many insurers would pay for these treatments. As more data become available, and the marketing value of being perceived as sensitive to women's health needs is re-analyzed, many insurers may choose to reevaluate whether to cover such treatments.

An important component of any decision analysis is the perspective adopted. Although the model here has been discussed from the perspective of the patient, it also can be looked at from the perspective of a governmental or private insurer. This would involve looking at risks for groups, rather than individuals, and would also have a significant impact on the cost numbers used in the model. Likewise, different populations can be analyzed separately to effectively consider the different risk groups. However, many of the most complex issues, such as the role of culture and religion on the decision process, may be considered in modifying the utility scores. The

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71. For a more complete discussion of discrimination, refer to Jean E. McEwen & Philip R. Reilly, *State Legislative Efforts to Regulate Use and Potential Misuse of Genetic Information*, 51 AM. J. HUM. GENETICS 637, 637-47 (1992) (studying laws relating to confidentiality, informed consent, discrimination, and related issues); Mehlman et al., *supra* note 70, 393-97 (proposing a form of anonymous testing and counseling whereby personal information and test results would be stored and released solely on the basis of a code); Natowicz et al., *supra* note 67, at 465-74 (discussing the applicability of various relevant federal and state laws in the areas of employment and insurance discrimination); Dickens et al., *supra* note 70, at 813-18 (stating that traditional ethical orientations and principles may be applied to genetic testing and counseling for susceptibility to breast, ovarian, and colon cancer, but that female ethics will have particular importance).

prominent role of these factors, combined with the intensely personal nature of the disease, provides a setting where the parameters of the model may vary greatly among individuals.

IV. SUMMARY

The decision of whether an individual should be tested for BRCA1 carrier status is multifaceted. The complex medical, emotional, religious, social, and economic aspects make it extremely difficult to reach an informed choice. Decision analysis is a methodology that can consider all of these aspects and be customized to fit an individual's unique situation. Although there is much uncertainty, sensitivity analysis will overcome this limitation or identify those areas of uncertainty that require further study.

There are many women who will not have the luxury of waiting for more data before making a decision about BRCA1 testing. Decision analysis is a technique that physicians can use to help their patients come to an informed choice.