Genetic Susceptibility Testing for Breast Cancer: Implications for Practitioners

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DR. LIANG: Introduction

Genetic susceptibility testing for breast cancer—as well as for other diseases—is a significant policy issue in health care today. With advances in molecular biology, an individual’s susceptibility to a wide range of diseases can be ascertained. However, the use of information obtained through genetic testing may affect patients adversely. As this case study indicates, physicians should not regard genetic testing lightly, especially when discussing with patients the potential benefits and risks of genetic testing. The implications of genetic testing are particularly significant for breast cancer, in which genetic disposition accounts for 10% to 15% of all breast cancer cases.1

Health policy issues involved with genetic testing should be noted by any physician considering recommending genetic testing for a patient. The patient’s employment status and access to insurance (either new or existing) may be directly affected by the results of genetic testing.2,3

Implications on employment. Employers who request or require employees to undergo testing may make decisions—for example, about hiring, promotions, or termination—based on genetic test results that are not considered acceptable by the employer.4 Employers may be concerned by positive genetic testing results of their employees or potential employees. For example, employers may perceive that the employee will cost the company more money if he or she has positive genetic testing results because of increased health insurance rates due to the potential for developing the disease. The employer may also mistakenly believe that testing positive for a gene means the employee will definitely develop the disease. If the employee tests positive for a gene, the employer may believe the employee will have a shorter employment period, or may anticipate that the employee will request additional vacation or time off via the Family and Medical Leave Act. Employer concerns may also extend to genetic susceptibility of family members.

Although the extent to which employers use genetic information in hiring and firing employees is unknown, the belief is common among employees that employers use genetic information against them. In a study published in 1996,20% to 25% of employees surveyed believed that they were denied employment or were fired because of their genetic family history; they reported that they do not reveal genetic information to employers for fear of reprisal, and that they do not undergo genetic testing because they fear discrimination.5

Implications on privacy and health insurance. Recognizing the implications of allowing unfettered use of genetic information by health insurers and employers, many states have enacted genetic information privacy laws. For example, Maryland prohibits health insurers from using genetic information “to reject, deny limit, cancel, refuse to renew, increase the rates of, affect the terms and conditions of, or otherwise affect a health insurance policy . . . request or require a genetic test for the purpose determining whether or not to issue or renew health benefits coverage; or . . . release the results

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(continued on page 41)
of a genetic test without prior written authorization of the individual . . . . 62 Other state statutes have similar provisions.7,8 States have also prohibited employer discrimination on the basis of genetic information.8,9

In addition, federal law has been used to protect inappropriate use of genetic information. Major federal statutes in this area include Title VII of the Civil Rights Act10,11 the Health Insurance Portability and Accountability Act;12 and the Americans with Disabilities Act.13,14 However, these statutes do not necessarily cover each and every use of genetic testing information by employers and health care insurers. In fact, several bills to regulate the use of genetic information have been introduced in Congress because of the limited protections of federal statutes.15–21 States are also continuing to consider and pass legislation due to similar concerns.22–24 The federal Employee Retirement Income Security Act may preempt these state efforts as it preempts other health care legislation,25 making it imperative that a federal regulatory scheme be established.

Other implications. In addition to the risks of inappropriate use of genetic information by employers and health insurers, there are additional risks in genetic testing. For example, a woman may incorrectly perceive that a positive breast cancer gene test indicates that she will inevitably develop breast cancer, or that a negative test indicates she will never develop breast cancer. Risks for misperceptions and data misinterpretation are exacerbated by the fact that most patients are not provided with thorough, careful counseling regarding the results and implications of genetic testing.26 Only 2700 health care professionals are certified by the American Board of Genetic Counseling or the American Board of Medical Genetics.27

Furthermore, commercial development of genetic testing capabilities allows patients to obtain genetic testing without a physician’s recommendation. Again, this scenario potentially provides patients with information they do not know how to correctly interpret.28

Finally, there is a lack of standardization in the medical school curricula for physicians in the areas of genetics, genetic testing, and genetic testing results and interpretation. In a 1996 study, 20% of primary care physicians were unaware that a predisposition to breast cancer could be determined through genetic testing; and for other disease states, primary care physicians misinterpreted the genetic test results almost 33% of the time.29

Summary. The risks in genetic susceptibility testing for breast cancer extend beyond the clinical sequelae of the disease itself. Issues in employment, health insurance, and data misinterpretation by the patient and the physician make it critical that the primary care physician is aware of how genetic testing can affect his or her patients. Through careful consideration of the benefits and costs of a particular test and its results, physicians can continue to advocate for their patients’ best interests as the knowledge gleaned from the human genome continues unabated.

CASE STUDY
Initial Presentation
A 41-year-old woman presents to her primary care physician for a checkup. She reports feeling well since her last appointment 1 year ago but mentions that her 64-year-old mother recently died of breast cancer. The patient says that she has read several articles about the availability of genetic testing for breast cancer and asks to be tested in order to learn “whether or not I’m going to get the disease.” She would also like to know if her 2 daughters, ages 21 and 16 years, are at increased risk.

History and Physical Examination
The patient denies any problems, reporting only occasional upper respiratory infections and mild menstrual cramps. She does not use drugs or alcohol, does not smoke, and walks on a treadmill for 30 minutes twice weekly. She is employed as a college development officer and lives with her husband and daughters in suburban Philadelphia.

Physical examination reveals a neatly dressed, mildly overweight female. Blood pressure is 110/68 mm Hg, pulse is 80 bpm, and respirations are normal. The patient is afebrile. Breast examination reveals symmetrical breasts without masses, palpable abnormalities, or breast discharge. No axillary or supraclavicular lymphadenopathy is appreciated. On pelvic examination, external genitalia are normal. There is no vaginal discharge and the uterus is anteverted, nontender, and normal in size. No adnexal masses are appreciated. The remainder of the physical examination is within normal limits.

Pertinent laboratory results include a mammogram that is unchanged from a baseline examination performed 2 years ago.

QUESTIONS
• What are risk factors for breast cancer?
• How do gene alterations affect risk?

DISCUSSION
Breast cancer is a commonly diagnosed cancer and the second leading cause of cancer death in women in
the United States. In 1999, an estimated 176,000 cases of breast cancer will be newly diagnosed, and 43,700 women will die of the disease.

It is now known that inherited gene alterations affect the risk of breast and ovarian cancers. In 1990, a susceptibility gene for breast cancer was mapped by genetic linkage to the long arm of chromosome 17. This gene, BRCA1 (Breast Cancer 1), was subsequently isolated and sequenced in 1994. A second BRCA gene, BRCA2, was localized to chromosome 13 and sequenced in 1996.

Risk factors and probable risk factors for breast cancer include advanced age, family history of breast cancer, early menarche, late menopause, nulliparity or late age at first pregnancy, history of atypical hyperplasia, lobular carcinoma in situ, radiation exposure, and history of multiple breast biopsies. Other possible risk factors may include exogenous hormone use, obesity, alcohol consumption, high-fat diet, and environmental factors. It should be noted that three quarters of all breast cancers are sporadic and occur in women with no major risk factors. Approximately 15% to 20% of breast cancer cases occur in families with a history of breast cancer. In familial breast cancer, there is currently no gene mutation to explain how the disease is transmitted. Only 5% to 10% of all breast cancers are hereditary, that is, associated with a known gene mutation.

Women carrying germline mutations in BRCA1 or BRCA2 have an extremely high lifetime risk for developing breast and/or ovarian cancer. In women carrying germline mutations in BRCA1 or BRCA2, the cumulative lifetime risk of breast cancer is 50% to 85%, compared with 12% for women in the general population; risk of ovarian cancer is 5% to 40%, compared with 1.5% in the general population. Although their exact function is not known, BRCA1 and BRCA2 are believed to be genes that code for suppression of tumor growth. These mutations are thought to produce a truncated protein product, increasing susceptibility to breast cancer. The inheritance pattern for both genes is autosomal dominant. Penetrance is variable, probably on the basis of other genes that also have a modifying effect on tumorigenesis. In patients with an inherited mutation, breast cancer develops at a younger age, and tumors tend to be high-grade and estrogen receptor-negative.

**QUESTION**

- Who should be screened for BRCA1 and BRCA2 mutations?

**DISCUSSION**

Since the vast majority of breast cancer cases are not due to inherited alterations in BRCA1/2, most women would not benefit from genetic testing. Two major genetics professional societies and the National Human Genome Research Institute (NHGRI) have asserted that it is premature to engage in genetic testing outside of a research setting. In a recent editorial, the director of NHGRI stated, "The technical ability to perform tests for mutations should not be confused with a mandate to offer them."

The American Society of Human Genetics issued a statement recommending that testing be initially offered only on an investigational basis. However, this may pose a barrier for patients who lack access to major medical centers.

The American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be offered only in the case of a "strong family history of cancer or very early age of onset of disease," correlating with a greater than 10% probability of having a BRCA mutation and resultant clinical value. Ideally, the affected family member should be tested first to identify the mutation that exists in that family. This maximizes the chance that the testing in subsequent family members will yield a meaningful result. If a mutation is present, interested family members can be tested for that specific mutation.

**Methods for Estimating Risk**

A detailed family cancer history can help determine if a patient is from a family at high risk for hereditary breast cancer, in which case genetic testing might be indicated. The history should go back several generations, if possible, and include all cases of breast and ovarian cancer in the family. The history should also include age at diagnosis, tumor histology, the occurrence of bilateral primary tumors, tumor sites, and history of metastatic disease. The age and relationship of unaffected relatives should also be obtained. BRCA1/2 mutations are more likely to be present in families with a history of breast and/or ovarian cancer in multiple relatives across several generations, multiple cases of premenopausal breast cancer, bilateral breast cancer, male breast cancer, and in Ashkenazi Jewish families. Patients without these hallmarks are unlikely to have a hereditary syndrome.

Statistical models have been developed that estimate the probability of inheriting a mutation in BRCA1 or BRCA2. Figure 1 shows a model developed by Shattuck-Eidens and colleagues that estimates risk for women with breast or ovarian cancer. **Table 1**
**Figure 1.** Estimated probability of carrying a deleterious BRCA1 mutation. Adapted with permission from Shattuck-Eidens D, Oliphant A, McClure M: BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. JAMA 1997;278:1242–1250.
presents probability tables developed by Couch et al\textsuperscript{48} that can be used to inform a woman with a family history of breast cancer of the odds that she carries a BRCA1 mutation.

Two models for predicting individualized breast cancer risk are widely used in research studies and clinical counseling: the Gail model\textsuperscript{49} and the Claus model.\textsuperscript{50} The Gail model projects the probability of developing breast cancer based on predictors of risk identified in the Breast Cancer Detection Demonstration Project study and has been validated in women who adhere to regular mammography screening. A computer program based on the Gail model is available from the National Cancer Institute (800-4-CANCER). The Claus model estimates risk based solely on family history using data from the Cancer and Steroid Hormone Study. Both models have limitations and may overestimate risk in patients from low-risk families. However, they may be useful in the process of deciding who would benefit from further testing.\textsuperscript{51} Neither model was designed to be used for prediction of likelihood of carrying a BRCA1 or BRCA2 mutation.

**QUESTION**

- What are the implications of a positive test? A negative test?

**DISCUSSION**

A positive test in a patient who is a member of a family with a known mutation indicates that the patient has inherited the mutation and is at increased risk for breast and ovarian cancer. In cases where a known mutation exists in the family and the patient tests negative for that mutation, the patient is presumed to have the same lifetime cancer risk as persons in the general population. She cannot pass the family risk on to her children. Women who have a negative test may feel a tremendous sense of relief, but they should be reminded that their risk is not zero and that they need to continue to employ effective preventive strategies such as mammography. Further, they need to know that approximately 15\% of negative tests are falsely negative. A true-negative test result may be associated with survivor’s guilt if another family member tests positive.

In the absence of information from another relative, a negative result is not very informative and can yield a false sense of security, as it overlooks the hundreds of other possible mutations in BRCA1/2 or in as-yet-undiscovered genes that may be the source of the family’s predisposition to the disease.

**QUESTION**

- What are management options in the setting of a positive test result?

**DISCUSSION**

Options for managing cancer risk in patients found to have a mutation in a BRCA1 or BRCA2 gene include surveillance, prophylactic surgery, and chemoprevention.

**Surveillance**

The goal of surveillance is to detect cancer early, when it is most treatable. Recommendations by Burke et al\textsuperscript{36} for cancer surveillance among women with BRCA1/2 mutations include monthly breast self-examination, clinical breast examination every 6 to 12 months, and annual mammography beginning at age 25 years. However, it has not been established that high-risk women who follow these guidelines have a greater disease-free or overall rate of survival or that women who develop cancer while following these guidelines are diagnosed at an earlier stage.\textsuperscript{52}

**Prophylactic Surgery**

Prophylactic mastectomy is a surgical option for the prevention of breast cancer. The procedure greatly reduces (but does not eliminate) the risk of developing breast cancer in high-risk patients. In 1 large-scale retrospective cohort study conducted at the Mayo Clinic,\textsuperscript{53} only 7 out of 575 at-risk women who underwent prophylactic mastectomy developed breast cancer, correlating with a 89\% reduction in risk for women at moderate risk and a 90\% to 94\% reduction for women at high risk. In this study, the genetic status of patients was unknown. Estimates of the failure rate of prophylactic mastectomy with respect to preventing breast cancer range from 1\% to 19\% as studies have been complicated by the heterogeneity of women enrolled.\textsuperscript{54}

Decision analyses of prophylactic surgery in BRCA1- or 2-positive patients indicate that prophylactic surgery at a young age substantially improves survival. Schrag et al\textsuperscript{55} compared prophylactic surgery with no prophylactic surgery in women carrying BRCA1/2 mutations and found that in a 30-year-old woman with an inherited mutation, prophylactic mastectomy conferred a 2.9- to 5.3-year gain in life expectancy and prophylactic oophorectomy conferred a 0.3- to 1.7-year gain, depending on the cumulative risk of cancer. Gains declined with age and were minimal for a 60-year-old woman. Grann et al\textsuperscript{56} found that prophylactic surgeries were cost-effective compared with surveillance for years of life saved.
Table 1. Probability of Detecting a BRCA1 Mutation in Families*

<table>
<thead>
<tr>
<th>Average Age at Diagnosis of Breast Cancer (years)</th>
<th>Predicted Percent Probability (95% CI)†</th>
<th>Average Age at Diagnosis of Breast Cancer (years)</th>
<th>Predicted Percent Probability (95% CI)†</th>
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<tbody>
<tr>
<td>Families with breast cancer only</td>
<td></td>
<td>Ashkenazi Jewish families with breast cancer only</td>
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<tr>
<td>&lt; 35</td>
<td>17.4 (6.5–38.8)</td>
<td>&lt; 35</td>
<td>47.9</td>
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<tr>
<td>35-39</td>
<td>11.7 (5.1–24.6)</td>
<td>35-39</td>
<td>36.7 (12.8–69.6)</td>
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<td>40-44</td>
<td>7.7 (3.6–15.6)</td>
<td>40-44</td>
<td>26.8 (9.7–55.3)</td>
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<tr>
<td>45-49</td>
<td>5.0 (2.3–10.8)</td>
<td>45-49</td>
<td>18.7 (6.8–42.0)</td>
</tr>
<tr>
<td>50-54</td>
<td>3.2 (1.2–8.1)</td>
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<td>12.7 (4.3–31.8)</td>
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<tr>
<td>55-59</td>
<td>2.1 (0.6–6.5)</td>
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<td>8.4 (2.5–24.8)</td>
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<tr>
<td>&gt; 59</td>
<td>1.3 (0.3–5.5)</td>
<td>&gt; 59</td>
<td>5.5 (1.3–20.0)</td>
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<td>Families with breast and ovarian cancer</td>
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<td>Ashkenazi Jewish families with breast and ovarian cancer</td>
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<td>&lt; 35</td>
<td>55.0 (27.2–80.0)</td>
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<td>84.2</td>
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<td>57.2 (24.9–84.3)</td>
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<td>45.7</td>
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<tr>
<td>55-59</td>
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<td>34.7 (10.8–70.0)</td>
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<td>&gt; 59</td>
<td>7.1 (1.7–24.8)</td>
<td>&gt; 59</td>
<td>25.1</td>
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<tr>
<td>Families with breast and ovarian cancer in a single member</td>
<td></td>
<td>Ashkenazi Jewish families with breast and ovarian cancer in a single member</td>
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<tr>
<td>&lt; 35</td>
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<td>&lt; 35</td>
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<td>85.3</td>
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<td>54.5</td>
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<td>17.3</td>
<td>&gt; 59</td>
<td>47.8</td>
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<tr>
<td>Families with breast and ovarian cancer and 1 member with both breast and ovarian cancer</td>
<td></td>
<td>Ashkenazi Jewish families with breast and ovarian cancer and 1 member with both breast and ovarian cancer</td>
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<tr>
<td>&lt; 35</td>
<td>96.6</td>
<td>&lt; 35</td>
<td>98.8</td>
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<td>95.5</td>
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<td>54.9</td>
<td>&gt; 59</td>
<td>81.3</td>
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*The optimal use of this table requires a detailed family history and knowledge of all cases of breast and ovarian cancer in the family. The predicted probabilities are for families as a whole. The predicted probability of a BRCA1 mutation in a woman with breast or ovarian cancer is equal to the probability for the family. For example, a woman with breast cancer who is from a family in which the average age at diagnosis of breast cancer was 40 to 44 years has a predicted probability of 7.7% (95% CI, 3.6 to 15.6) of having a detectable BRCA1 mutation. For an unaffected family member, the predicted probability is determined by the relationship to the affected family member. In the case of an unaffected sibling or child of a woman with breast or ovarian cancer, the predicted probability of a BRCA1 mutation is half the probability for the family. For an unaffected grandchild, the predicted probability is 25% of the probability for the family.

†Confidence intervals (CIs) could not be calculated for some entries because of the absence of a data point matching the criteria in the original data set.
Chemoprevention

The agent tamoxifen is approved by the U.S. Food and Drug Administration for reducing the incidence of breast cancer among women at increased risk. It is an anti-estrogen that induces a conformational change to the estrogen receptor, thus restricting the ability of the breast tissue to respond to the hormone. Tamoxifen has a mild estrogenic effect on the endometrium that can promote the development of endometrial cancer, limiting its use in premenopausal women. Most of the data supporting tamoxifen's role as a primary prevention agent were collected on high-risk women age 35 years or older whose BRCA status was unknown. The most comprehensive study evaluating the effect of tamoxifen on incidence of breast cancer and breast cancer mortality to date is the Breast Cancer Prevention Trial (known as the P-1), a national study of 13,000 at-risk women. After a mean follow-up period of 3.5 years, cancer rates were 45% lower in women taking tamoxifen compared to controls.

QUESTION

- What issues should be discussed with the patient prior to testing?

DISCUSSION

Genetic testing should be made available only in conjunction with appropriate patient education and counseling. Topics addressed should include the purpose of testing; the technical accuracy of the test and associated costs; and the benefits, risks, and clinical implications of testing, including the possible prevention strategies available. The elements of informed consent identified by ASCO (Table 2) provide a comprehensive list of what should be reviewed in the discussion.

All patients considering genetic testing should receive counseling from a trained genetic counselor or a physician or health care professional knowledgeable in the implications of the test results. Deficiencies in genetics knowledge among physicians suggest that patients may benefit from referral to a genetic counselor or geneticist. In a 1991 survey to assess physicians' knowledge of genetics, primary care physicians and psychiatrists had a 74% accuracy rate compared to a 95% accuracy rate for genetics professionals. Genetic counselors are trained to consider the ethical issues of patient autonomy and nonmaleficence and to recognize the elements of consent necessary to ensure informed consent or informed refusal of testing. They can tailor information to the individual and provide patients with an opportunity to examine their preferences and values in order to make an educated decision. Unfortunately, there are only an estimated 1000 to 2000 licensed counselors in the United States, raising issues of access for many patients and physicians.

Family Cancer History

The physician acknowledges the patient's fear of developing cancer and her desire to know her risk. He explains that testing is not helpful in the vast majority of patients, being likely to yield useful information only in certain high-risk families. The physician asks about additional cases of breast and ovarian cancer in the family. The patient reports no cases of ovarian cancer and no other cases of breast cancer besides her mother, who developed cancer later in life. In light of the fact that there are no cases of ovarian cancer, no other cases of breast cancer besides her mother, who developed cancer later in life. In light of the fact that there are no cases of ovarian cancer, no bilateral disease, and no premenopausal breast cancer, the likelihood of the patient harboring a BRCA1/2 mutation is very low. The patient is reassured by the information.
but the physician reminds her that she does have a positive family history and should be aware of her cancer risk. He uses her age at menarche (12 years), age at first live birth (20 years), number of first-degree relatives with breast cancer (1), and number of previous breast biopsies (0) to calculate her lifetime risk using the Gail model. He encourages her to take active steps to promote breast health through lifestyle changes and regular mammography.

**REFERENCES**

7. Colo RevStat § 10-3-1104.7.
8. Geotnick S: Courts are jumping into the gene pool. Dallas Morning News September 6, 1998;7B.
12. 26 USC §§ 9801-9806.
13. 42 USC §§ 12101-12213.

**DISCUSSION**

Genetic testing is not indicated in the daughters. In the case of the older daughter, however, it is generally agreed that women at age 20 years should be asked about family history and undergo further risk assessment if family history is positive.

Had a BRCA mutation been discovered in their family, what then? In such a case, it would be appropriate to provide education and counseling to the older daughter, who at age 21 years is presumably mature enough to make her own informed decision regarding testing. However, given the complexity of the information, the cognitive maturity level of the individual patient should be taken into account. The American Society of Human Genetics and the American College of Molecular Genetics hold that genetic testing is justifiable in children only if it confers an immediate medical benefit to the child, and the United Kingdom Cancer Family Study Group advises against testing individuals under 18 years of age. Testing should probably be deferred in a 16-year-old girl, with the physician encouraging the family to wait until the child is older. HP

**QUESTION**

- What should this patient’s daughters be told about their risk?

**REFERENCES**

7. Colo RevStat § 10-3-1104.7.
8. Geotnick S: Courts are jumping into the gene pool. Dallas Morning News September 6, 1998;7B.
12. 26 USC §§ 9801-9806.
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