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Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with Brian L. Shaffer, MD and Society for Gynecologic Oncology liaison Lee-may Chen, MD.

Consumer Testing for Disease Risk

ABSTRACT: With the increased emphasis on patient-driven health care and readily available access to patients as consumers through the internet and media, many genetic testing companies are marketing directly to consumers. Direct-to-consumer genetic testing may result in unique concerns and considerations, because of limited knowledge about available genetic tests among patients and health care professionals, challenges in interpretation of genetic test results, and lack of oversight of some companies, as well as issues of privacy and confidentiality. It is important to note that tests from different companies that evaluate the same condition or genes can vary greatly in scope and technical quality. When undergoing direct-to-consumer genetic testing, the consumer should be apprised of risk from screening or susceptibility test results that can neither prove nor eliminate disease potential but may be distressing for consumers. Because of these considerations and the fact that the interpretation of test results often requires specific training and medical knowledge, direct-to-consumer genetic testing ideally should be performed after counseling to review the test's potential benefits, risks, and limitations. Confirmatory genetic testing should be performed under the supervision of an appropriate obstetrician–gynecologist or other health care professional who is skilled in interpretation of genetic testing and risk assessment for the diseases of interest. This Committee Opinion has been updated to include information on counseling for patients who present with direct-to-consumer genetic test results, clinical vignettes, and an overview of currently available testing options as well as those potentially available in the near future.

Recommendations

The American College of Obstetricians and Gynecologists (ACOG) makes the following recommendations:

- The American College of Obstetricians and Gynecologists discourages direct-to-consumer genetic testing without appropriate counseling.
- Pretest counseling for direct-to-consumer genetic testing should include a discussion of privacy concerns, including who may have access to the results; what systems are in place to provide protection of confidential health information; how the sample will be handled after testing is complete; whether the test results will have an effect on issues related to life, long-term care, or disability insurability; and how genetic information will be handled if the company closes or is purchased.
- Direct-to-consumer genetic testing may suggest an increased or decreased risk for a disorder but can neither prove nor eliminate disease potential. Direct-to-consumer testing also may identify unanticipated information or results that may have implications for other family members.
- Patients may present after direct-to-consumer testing already has been performed, and clinicians should be prepared to review these results or refer to a health care professional with the appropriate knowledge, training, and experience in interpreting test results.
- In most circumstances, when a patient presents with a direct-to-consumer test result that putatively assesses the risk of specific diseases, the patient should be referred to an obstetrician–gynecologist or other health care professional who is skilled in risk assessment for the diseases or conditions of interest

and who can interpret genetic testing results in the context of the individual's relevant medical and family history.

- When a patient presents with a direct-to-consumer test result, medical intervention typically should wait for confirmatory testing in a clinical laboratory.
- Given the insufficient data to support the use of single nucleotide polymorphisms (SNP) testing for medical purposes, SNP testing to provide individual risk assessment for a variety of diseases or to tailor drug therapy outside of an institutional review board-approved research protocol is not recommended. The American College of Obstetricians and Gynecologists recommends that the use of these technologies be viewed as investigational at this time.

Direct-to-Consumer Testing and Precision Medicine

Direct marketing of genetic tests (direct-to-consumer genetic testing) has grown in response to a concomitant demand for precision medicine: the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better treatment. The concept of *precision medicine* has been defined as the tailoring of medical treatment to the individual characteristics of each patient, which incorporates not only genetics, but also other aspects of biology and prognosis (1). The National Academy of Sciences uses the term "precision medicine" rather than "personalized medicine" to clarify that it "does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment" (1). Precision medicine also is at times referred to as "precision health."

Predictive testing (which determines whether an individual carries a genetic variation associated with later development of a genetic condition) and pharmacogenetics (which attempts to identify DNA or RNA variations and their relationship to drug response) are examples of precision medicine that are prevalent in direct-to-consumer genetic testing. Variations in genes related to drug metabolism and other human diseases increasingly have been identified through advancing genetic technologies, including the completion of the sequencing of the human genome in 2001. In addition, predictive testing and pharmacogenetics recently have been marketed directly to consumers, and whereas some results may be reliable and accurate, the validity of others is less certain.

Direct-to-Consumer Genetic Testing

With the increased emphasis on patient-driven health care and readily available access to patients as consumers through the internet and media, many genetic testing companies are marketing directly to consumers. Companies offer genetic testing for nonmedical information, including ethnicity, athletic performance, behavior, aging, metabolism, or other traits. Also included may be testing for medically significant conditions, including carrier status for genetic diseases such as cystic fibrosis, hemochromatosis, and variations that increase the risk of breast, ovarian, and other cancers. The American College of Obstetricians and Gynecologists recognizes that tests are widely available and used by numerous patients.

The American College of Obstetricians and Gynecologists discourages direct-to-consumer genetic testing without appropriate counseling. Direct-to-consumer genetic testing may result in unique concerns and considerations, because of limited knowledge about available genetic tests among patients and health care professionals, challenges in interpretation of genetic test results, and lack of oversight of some companies, as well as issues of privacy and confidentiality. It is important to note that tests from different companies that evaluate the same condition or genes can vary greatly in scope and technical quality. Recognizing the concerns associated with direct-to-consumer genetic testing, the U.S. Federal Trade Commission, U.S. Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention advise consumers to be skeptical of claims about tests and encourage consumers to seek guidance from a knowledgeable health care professional before pursuing this type of genetic testing (2).

Direct-to-consumer genetic testing only should occur after adequate pretest counseling about the potential benefits, harms, and limitations of the testing (Table 1). Pretest counseling for direct-to-consumer

Vignette #1

A 30-year-old patient, gravida 1, presents for a routine prenatal visit. She reports that she recently received results from a direct-to-consumer genetic testing laboratory and the results indicated that she was at increased risk for bleeding due to Factor XI deficiency. She is concerned about bleeding during her upcoming labor and delivery. She has no history of heavy menstrual bleeding or excessive bleeding during a prior childhood surgery. She relates that her sister had a postpartum hemorrhage requiring a transfusion after delivery of twins. As a result of the direct-to-consumer genetic testing result, you order a plasma Factor XI activity to assess her bleeding risk, and her Factor XI activity is within the normal range, indicating that she is not at increased risk for bleeding due to a Factor XI deficiency. You explain that identification of a variant can be correct with high analytical validity (eg, genotype change), but how that change affects an individual in a clinical context (phenotype) can be unclear and may not actually impart an increased risk for a negative health outcome–in this case, hemorrhage associated with surgery or with childbirth.

Table 1: Direct-to-Consumer Testing Counseling–Benefits, Risks, and Limitations

Potential Benefits	Potential Risks and Limitations
Expanded access to genetic testing	Abnormal results may not accurately predict disease potential.
Promotion of healthy behaviors	Tests may reveal unexpected results about health risks.
Lower cost	Results may have a bearing on other family members.
Results may be reassuring	Some results are difficult to interpret.
Patients can access effective risk reducing medical strategies (eg, increased cancer surveillance)	Privacy may be compromised.
	Results may affect access to life or disability insurance.
	Results may be upsetting.

genetic testing should include a discussion of privacy concerns, including who may have access to the results; what systems are in place to provide protection of confidential health information; how the sample will be handled after testing is complete; whether the test results will have an effect on issues related to life, long-term care, or disability insurability; and how genetic information will be handled if the company closes or is purchased. Potential benefits of direct-to-consumer testing include an expansion of access to testing and awareness of genetic diseases, and the affordability of these tests may encourage individuals to be proactive about their health. Other potential benefits include reassurance from a (risk reducing) result as well as identification of a variant that is known to be linked to a disease (pathogenic variant), affording an opportunity to develop a strategy to maximize the chance for disease prevention or to facilitate an early diagnosis with improvement of health outcomes.

There also are potential risks and limitations to consider for those undergoing direct-to-consumer testing. Potential harms of direct-to-consumer testing include false-positive and false-negative results as well as a misinterpreted result. Limitations of direct-to-consumer testing include negative results, which demonstrate reduced risk but are not comprehensive, such as a test that does not include all known pathogenic variants or testing techniques. In other words, direct-to-consumer testing may suggest an increased or decreased risk for a disorder but can neither prove nor eliminate disease potential. Direct-to-consumer testing also may identify unanticipated information or results that may have implications for other family members. Patients may present after direct-to-consumer testing already has been performed, and clinicians should be prepared to review these results or refer to a health care professional with appropriate knowledge, training, and experience in interpreting test results. In most circumstances, when a patient presents with a direct-to-consumer test result that putatively assesses the risk of specific diseases, the patient should be referred to an obstetrician–gynecologist or other health care professional who is skilled in risk assessment for the diseases or conditions of interest and who can interpret genetic testing results in the context of the individual's relevant medical and family history. When a patient presents with a direct-to-consumer test result, medical intervention typically should wait for confirmatory testing in a clinical laboratory. Occasionally, if pregnancy is being considered or the patient is pregnant, the potential effects on the fetus are important to discuss.

When undergoing direct-to-consumer genetic testing, the consumer should be apprised of risk from screening or susceptibility test results that can neither prove nor eliminate disease potential but may be distressing for consumers.

Many direct-to-consumer testing panels offer testing for variants that can alter the risk of certain types of

Vignette #2

A 31-year-old patient, gravida 1, and her partner present at 9 weeks of gestation with direct-to-consumer testing carrier screening results indicating she is a carrier of cystic fibrosis (*CFTR*). No pathogenic changes were identified in her partner. They should be informed about the possible outcomes associated with cystic fibrosis and that if both partners carry a pathogenic variant, the risk for an affected fetus is 1 in 4; however, they also should be aware that false-positive and false-negative results can occur in direct-to-consumer genetic testing. You offer to confirm a pathogenic ΔF508 variant in your patient with a clinical diagnostic test. Review of the partner testing indicates that only some common pathogenic variants were assessed by the consumer test. Since all pathogenic variants may not be assessed in direct-to-consumer genetic tests, you explain that partner testing (even though the direct-to-consumer genetic test result was negative) with a standard panel, an expanded panel, or gene sequencing (with or without deletion/duplication analysis) may provide more comprehensive screening. If no pathogenic variant is found in the partner, a residual risk should be provided based on the best available information. In some circumstances, parallel testing, in which both partners undergo simultaneous testing, may be warranted to ensure timely availability of results. After this explanation, the partner opts for gene sequencing, which indicates that the partner also is a carrier of a pathogenic gene change. You then inform the couple that any pregnancy (including the couple's current pregnancy) will have a 1 in 4 risk for cystic fibrosis. Diagnostic testing can be discussed as well as the option of in vitro fertilization (IVF) with preimplantation genetic testing in future pregnancies.

cancer, such as breast and ovarian cancer. In 2018, the FDA authorized the first direct-to-consumer test to report on three specific *BRCA1* and *BRCA2* cancer gene mutations that are most common in people of Ashkenazi Jewish descent (3). As there are more than 1,000 known mutations in *BRCA1* and *BRCA2* genes, a negative result from these commercial tests reduces but does not eliminate the possibility that an individual carries pathogenic variants in these genes that increase cancer risk. Other variants in *BRCA1* and *BRCA2* genes, or other genes implicated in highly penetrant genetic disorders, may be identified in the raw data obtainable through direct-to-consumer testing, but this data can be inaccurate and misinterpreted without confirmation through a diagnostic laboratory or review with a qualified health professional (4). A negative test for three specific mutations may falsely reassure women leading to them decline cancer screenings they may need.

The interpretation of positive or abnormal test results similarly is problematic. The interpretation of a positive test requires the context of family history and an assessment of other risk factors to quantify personal risk accurately. There is limited data to support population-based genetic testing for hereditary breast and ovarian cancer in the absence of risk factors. The risk of breast and ovarian cancer is unclear for a woman who has a positive test result from these three mutations within the *BRCA* genes when performed outside of clinical recommendations and in the absence of a personal or family history (5). Therefore, clinicians are limited in their ability to accurately counsel a patient with a positive result. It is not clear which risk reduction strategies or subsequent screening would be appropriate. Nor is it clear whether this group of patients will benefit or be harmed by potential interventions, such as risk-reducing medications or surgeries.

Vignette #3

A couple contemplating pregnancy opt for a direct-to-consumer panel with carrier screening before consulting with you. They also included tests for ancestry, fitness, and health. The results indicate that your patient carries 2 alleles (4/4 APOE) that increase the risk of Alzheimer disease. Even in the context of a negative family history, the lifetime risk in this individual for Alzheimer disease is approximately 50%, and your patient is understandably distressed. This information can be particularly troubling because no specific interventions have been shown to reduce that risk. You discuss that although these alleles increase her risk, they are not causative of Alzheimer disease. Further, you review possible lifestyle behaviors to minimize her individual risk. You make her aware of clinicians more expert in caring for Alzheimer disease whom she may choose to consult and note the findings in her medical record.

Vignette #4

A healthy 42-year-old woman with two first-degree relatives with breast cancer was concerned about her individual risk for breast and ovarian cancer. She underwent direct-to-consumer genetic testing for *BRCA1/2*, and no pathogenic changes that would increase her risk of breast and ovarian cancer were found. She presented these results to her obstetrician–gynecologist who reviewed the results and recommended additional testing (gene sequencing), which revealed a pathogenic variant in *BRCA2*. Appropriate medical care and identification of additional family members with the same change led to risk reducing interventions including surgery.

There are also direct-to-consumer diagnostic genetic tests available that test for a panel of cancer predisposition genes, but the panels may only include a subset of genes that have a role in certain cancer (eg, breast and ovarian cancer). Women who test negative through one test may be candidates for a more expanded panel based on other risks, including personal and family history. False reassurance that an individual is at lower risk for cancer could lead that individual to avoid care and risk-reducing, potentially life-saving interventions.

The assessment of cancer risk includes the evaluation of a number of potential risk factors, including family history and personal medical history, and the assessment of indications for genetic testing (6). Because ordering an appropriate genetic test and interpretation of genetic test results are complex, an obstetrician–gynecologist or other health care professional with knowledge of genetics should be involved in ordering and interpreting the results of any genetic test with medical implications. It must be recognized that direct-to-consumer genetic testing will create downstream necessity for counseling, support, and care for those identified as carriers of genes associated with deleterious medical conditions. Counseling also should address cascade testing options for blood relatives of individuals who have been identified with specific genetic mutations (7).

Pharmacogenetic Testing

Pharmacogenetics refers to the interactions of multiple genetic factors and the environmental influence on drug response. Currently, the FDA includes pharmacogenetic testing in the labeling of a select few drugs (8). In specific situations, pharmacogenetic testing is performed to determine if an individual is likely to benefit from a specific therapeutic agent. For example, certain cancer treatments such as poly (ADP-ribose) polymerase inhibitors may be more effective in women with *BRCA* variants. Prospective clinical trials are needed to develop the appropriate algorithms to introduce

pharmacogenetic testing into routine clinical practice to improve health outcomes. There currently are no standard clinical indications for the use of pharmacogenetic testing in the routine practice of obstetrics and gynecology. However, given the potential applications to women's health care, obstetrician–gynecologists and other health care professionals should be aware of this rapidly evolving field.

Predictive Testing

A single nucleotide polymorphism, frequently called SNP (pronounced "snip"), is a variation at a single position in the DNA sequence. Single nucleotide polymorphisms occur throughout the human genome, on average once in every 300 nucleotides. Most SNPs are not causative of disease or impaired development but may be used to predict risk of a variety of complex diseases (such as heart disease or diabetes mellitus) which may have numerous genetic, environmental, and behavioral influences. Single nucleotide polymorphisms also may predict an individual's response to certain drugs or estimate susceptibility to environmental toxins. Predictive testing in precision medicine involves SNP testing to provide individual risk assessment for a variety of diseases or to tailor medication therapy. Ideally, such testing should be done under the care of a health care professional in the context of an individual's health status and family history and may be best accomplished in a traditional clinician–patient encounter, although patients may present with information after direct-to-consumer testing has occurred. Interpretation of this information may be beyond the scope of the specialist in general obstetrics and gynecology and may require additional counseling from a genetics professional before medical action is recommended.

Despite laboratories offering genetic testing for disease-associated SNPs, there remains a paucity of evidence in most clinical scenarios to support SNP testing as a method to provide medically actionable results. Few SNP testing protocols have been clinically validated (9, 10). Given the insufficient data to support the use of SNP testing for medical purposes, SNP testing to provide individual risk assessment for a variety of diseases or to tailor drug therapy outside of an institutional review board-approved research protocol is not recommended. Further investigation is necessary to prospectively assess the validity and use of incorporating disease-associated SNPs into management recommendations. Therefore, the American College of Obstetricians and Gynecologists recommends that the use of these technologies be viewed as investigational at this time.

Conclusion

Direct-to-consumer testing provides access to information for individuals interested in testing, usually at a lower cost than traditional clinical testing. All genetic testing, including pharmacogenetics and direct-to-consumer testing, should be considered medical testing because results may affect future medical care and clinical decision making. Because of these considerations and the fact that the interpretation of the results often requires specific training and medical knowledge, direct-to-consumer genetic testing ideally should be performed after counseling to review potential benefits, risks, and limitations. Obstetrician–gynecologists and other health care professionals should be prepared to provide pretest and posttest counseling for individuals interested in such testing. Confirmatory genetic testing should be performed under the supervision of an appropriate obstetrician–gynecologist or other health care professional who is skilled in interpretation of genetic testing and risk assessment for the diseases of interest. This Committee Opinion has been updated to include information on counseling for patients who present with direct-to-consumer genetic test results, clinical vignettes, and an overview of currently available testing options as well as those potentially available in the near future.

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