Errors in Genetic Testing

Common causes and strategies for prevention

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Genetic tests are continually increasing in scope and complexity, and genetic testing in oncology care is no longer as simple as ordering testing for one or two genes associated with a specific cancer syndrome. Now, genetics professionals acknowledge many diagnostic and technical laboratory considerations when selecting and interpreting genetic testing for hereditary cancer syndromes. Errors in genetic test ordering and interpretation are not only financially costly but also can lead to poor patient care outcomes.

The National Comprehensive Cancer Network (NCCN, 2017) recommends that genetic testing be ordered by a credentialed genetics professional, such as a medical geneticist, a board-certified genetics counselor, or credentialed advanced practice genetics nurse (advanced genetics nurse—board certified, or AGN-BC). The American College of Surgeons’ Commission on Cancer (2015) has established that facilities should provide cancer risk assessment, genetic counseling, and testing services to patients either on-site or by referral to a qualified genetics professional. Some insurance companies now require patients to be evaluated by a credentialed genetics professional for payment to be considered (Whitworth et al., 2017). Many of these recommendations have been implemented with the goal of decreasing genetic testing errors. This article will review potential causes of genetic testing errors and provide clinical examples and case analysis.

Inaccurate Assessment of Risk

Without accurate assessment of risk, making appropriate recommendations for cancer prevention, early detection, and genetic testing is impossible. Risk assessment includes the construction of a three-generation pedigree that comprises parents, siblings, aunts, uncles, and grandparents on the maternal and paternal sides. Prior to a counseling session, a family should gather the needed information to construct a pedigree, including the current age or age at death for family members, as well as the cause of death. For those family members diagnosed with cancer, having information about the site of the cancer, pathology characteristics (when available), and the presence of second primary cancers is important. Pedigree construction takes about 15–20 minutes and must be completed prior to making risk calculations. The latter is often difficult to accomplish in a busy practice setting.

Case Study 1: Incomplete Pedigree

A 42-year-old woman was referred for assessment. Her mother had been diagnosed with breast cancer at age 58 years, and her maternal grandmother had been diagnosed with breast cancer at age 49 years. The woman’s primary care provider (PCP) said the Tyrer–Cuzick model, which predicts the lifetime risk of developing breast cancer based on personal risk factors and family history, put her risk for developing breast cancer at 59% and recommended bilateral risk-reducing mastectomies based on this calculation. However, the genetics professional

AT A GLANCE

- Accurate assessment of risk for developing malignancy and appropriate genetic testing can lead to improved outcomes for individuals diagnosed with cancer and their family members.
- Credentialed genetics professionals have extensive training and experience in risk assessment, genetic test selection and interpretation, and coordination of care for the entire family.
- Errors in genetic testing may be associated with significant financial costs and can be attributed to inadequate knowledge about the genetic testing process, as well as lack of time to complete a comprehensive assessment and coordinate care among all family members.

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genetic testing; errors; risk assessment; hereditary cancer syndromes

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calculated her risk for developing breast cancer to be just 23%. The difference in the calculations is attributable to the PCP’s performing this calculation using only the two relatives with breast cancer. However, the patient had four maternal aunts and four sisters who were not diagnosed with cancer. Taking the time to create a complete pedigree enabled a more accurate risk assessment. The PCP was correct in that the patient needed further evaluation, but recommending risk-reducing mastectomies for a 23% risk for developing breast cancer is inappropriate.

**Case Study 2: Incomplete Assessment of Maternal and Paternal Family History**
A 63-year-old woman who had been diagnosed with breast cancer at age 48 years was referred to a genetics professional with a referral that stated, “Please order BRCA1/2 testing; insurance requires it come from a genetics person.” Her mother was diagnosed with breast cancer at age 60 years, and her maternal grandmother was diagnosed with breast cancer at age 58 years. Testing for a panel of breast cancer genes (not just BRCA1/2 testing) was deemed appropriate (NCCN, 2017). The genetics professional also noted that the patient’s paternal history included a sister, cousin, and niece with a diagnosis of pheochromocytoma. A breast cancer panel with additional genes associated with paraganglioma and pheochromocytoma syndromes were ordered to cover the risk on the paternal side. The patient tested negative for mutations associated with an increased risk for developing breast cancer. However, she was found to have an SDHB mutation, which is associated with increased risk for developing paragangliomas and pheochromocytomas. Follow-up imaging determined that the patient had a small paraganglioma, which was removed. Without complete pedigree construction, the SDHB mutation would have been missed, and the patient would not have had the screening, which led to the early detection and successful management of the paraganglioma.

**Wrong Test Ordered**
Genetic testing is expensive. When ordering testing, the goal is to order the correct test or panel of tests while avoiding redundancy (Suarez, Yu, Downs, Costa, & Stevenson, 2017). Sometimes, only a single test is appropriate and can result in a significant cost savings. In addition, in the primary care setting, patients often inquire about genetic testing. In most cases, initiating testing in a person who has a diagnosis of malignancy is best, because the chance of detecting a pathogenic mutation is higher. It is often easiest for the PCP to order the testing while the patient is in the office, instead of referring him or her to a genetics professional for a more extensive evaluation and coordination of testing in the person most likely to have informative test results.

**Case Study 3: Overtesting**
A 38-year-old woman was referred for counseling after her gynecologist ordered comprehensive BRCA1/2 testing and she tested positive for a known family mutation. A pedigree was constructed to identify other at-risk relatives. Multiple cases of breast cancer existed on the woman’s maternal side; in fact, her mother had the known mutation. No history of malignancy existed on the woman’s paternal side. Single-site testing for the known mutation would have been adequate and could have been ordered at a significantly lower price. This redundant testing results in unnecessary spending of healthcare dollars at the expense of insurance companies and/or the patient (Ronadies et al., 2014).

**Case Study 4: Testing Ordered on the Wrong Person**
A 39-year-old woman had testing done with her PCP during a routine wellness visit. The testing involved a panel of genes associated with increased risk for developing ovarian cancer, and she tested negative for known mutations. Possible interpretations are that the woman did not inherit a familial mutation, the family does not have a genetic predisposition for ovarian cancer, or the family has a genetic mutation for which testing is not available. However, if her 36-year-old sister with ovarian cancer (who was subsequently found to have a RAD51C mutation) had been tested first, the woman could have undergone single-site testing for the known RAD51C mutation and avoided the interpretation problems and saved considerable testing costs (single-site testing is much less expensive). In this family, two individuals underwent comprehensive cancer testing. Genetics professionals will often recommend that testing be initiated in the person who is more likely to provide informative information. If the first individual tested has a diagnosis of malignancy, there is a greater chance a mutation will be detected, making it easier to subsequently test individuals who do not have a diagnosis of malignancy and determine if they have increased risk. Once a mutation is identified, the interpretation is much clearer.

**Incorrect Test Interpretation**
Errors in test interpretation and recommended follow-up may occur with variants of unknown significance (VUSs). Many healthcare providers incorrectly interpret a VUS as a positive finding (Brierley et al.,

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2012). Individuals with a VUS should be managed based on their personal and family history. A VUS means that not enough data are available to determine if the change in the genetic material is harmful or harmless. In addition, understanding the meaning of a negative result is not always black and white.

**Case Study 5: Variants of Unknown Significance**
A 47-year-old woman without any family history of malignancy who was diagnosed with breast cancer was found to have a VUS in the TP53 gene. Her oncologist referred her for bilateral mastectomies based on the TP53 finding, but surgical decisions should be based on the patient’s history and preferences. Clinical management based on a VUS finding may be inappropriate or unnecessary, particularly if the VUS is eventually reclassified as benign (Korngiebel, Fullerton, & Burke, 2016).

**Case Study 6: Accurately Interpreting Negative Results**
A woman who tested negative for BRCA1/2 was told by her PCP that because she did not have the mutation, she did not have an increased risk for developing breast and ovarian cancer. Her daughter was not at an increased risk for developing cancer. When the daughter developed early-onset colon cancer, she also underwent testing for Lynch syndrome, which was negative. Despite having Ashkenazi Jewish ancestry on her maternal and paternal sides, the daughter’s PCP did not include BRCA1/2 testing for the three common founder mutations associated with Ashkenazi Jewish ancestry. When the daughter developed ovarian cancer, additional testing ordered by a genetics professional elucidated that she had inherited a BRCA founder mutation from her father. Because the woman’s PCP had not accurately assessed the daughter’s paternal history, the original interpretation was incorrect. In addition, the error was further compounded when the daughter’s PCP did not assess for and consider risks associated with Ashkenazi Jewish ancestry.

**Case Study 7: Provider Ordering Errors**
A genetics professional received a referral to see a man who had genetic testing that detected an NBN mutation. The PCP stated he had no knowledge of the NBN gene and wanted to know how to best manage the patient. Of concern is that the PCP ordered a test for a syndrome for which he was not familiar or aware of the clinical management. The management of genetic syndromes is continually evolving. Genetics professionals focus on this changing science and appropriate management recommendations. Proper management results in better clinical outcomes and best fiscal responsibility.

**Laboratory Limitations**
Interpreting genetic test results often requires consultation with the laboratory. Selecting a laboratory with this support is important.

**Case Study 8: Lack of Laboratory Support**
A 26-year-old woman was referred to a genetics professional for recommendations for care after she tested positive for a BRCA1 mutation. This testing was ordered by the woman’s PCP from a small laboratory that placed brochures in the office. The nomenclature on the report was unusual, and no interpretation data were available. A 1999 reference was cited at the bottom of the report, and the laboratory did not provide professional interpretation support. The genetics professional looked up the variant in multiple databases and determined that it was considered to be a benign polymorphism (a harmless change in the genetic material). The woman’s mother was alive and had been diagnosed with breast cancer at age 38 years; she was the ideal candidate to test in this situation and tested negative for known mutations associated with increased risk. The patient was placed in increased surveillance for breast cancer. Risk-reducing mastectomies based on a benign change would have been an inappropriate recommendation for care.

**Coordination of Care for the Rest of the Family**
Results of genetic testing have implications for many other family members. Genetics professionals routinely coordinate care for the entire family in the geographic area they serve and identify resources for families who live in other areas.

**Case Study 9: Lack of Care Coordination**
A 24-year-old woman presented with metastatic breast cancer after several PCPs told her to not be concerned about a breast lump because she was too young to be diagnosed with breast cancer. Genetic testing revealed a CHEK2 mutation. Her mother tested negative for the known mutation, and her father, who was estranged from the family, tested positive for the mutation. Pretest counseling included an extensive discussion regarding the fact that, assuming he was the father, he was likely to test positive for the mutation; if he tested positive, he was strongly encouraged to contact other family members and alert them of the potential risk. After testing positive, he called his sister, who told him she had tested positive for the same CHEK2 mutation several years earlier when she had been diagnosed with breast cancer. Her oncologist had correctly managed her based on the mutation but had not communicated the significance of the mutation to other family members or made arrangements for the coordination of their care. The father was devastated to learn that his daughter could have been screened and evaluated earlier, preventing her late diagnosis of breast cancer and premature death.

**Conclusion**
Errors in genetic testing have expensive financial ramifications. About 30%–50%
of healthcare dollars spent on genetic testing are wasted on inappropriate genetic tests, and most physicians, including PCPs, gynecologists, and even oncologists, order either too much or incorrect testing, even in straightforward situations (Bonadies et al., 2014). A study by Miller et al. (2014) found that genetic counselors at a diagnostic laboratory modified or canceled an average of 107 genetic test orders per month after reviewing the appropriateness of the order, resulting in a monthly savings of $48,000. Most of the errors described in this article would not be detected through quality assurance monitoring by the laboratory, so the costs are likely much higher.

Any of these errors may adversely affect a patient’s diagnosis, medical management, health status, and psychosocial functioning. Time pressures and lack of knowledge are underlying causes of errors in cancer genetic counseling and testing performed by PCPs who lack extensive training in genetics and the rationale for genetic testing strategies (Brierley et al., 2012). Genetic testing has enormous potential for improvements in patient care and negative outcomes, including correctly identifying individuals at increased risk and implementing appropriate recommendations for cancer prevention and detection. Safe clinical practice involves referral to a credentialed genetics professional who has expertise in pedigree and risk assessment, the ordering of genetic tests, interpretation of results, and coordination of care for the entire family, whenever possible.

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REFERENCES


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