

# Is it Really *BRCA1* or *BRCA2*? The Importance of Confirming the Familial Mutation in a “BRCA”-focused World

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## Background

Genetic testing for hereditary cancer predisposition syndromes has gained popularity in recent years due to increased access and affordability of genetic testing, as well as the development of next-generation sequencing. In addition, hereditary cancer predisposition syndromes have received increased exposure and attention from the general public, including hereditary breast and ovarian cancer (HBOC) syndrome, caused by pathogenic genetic variants (mutations) in the *BRCA1* and *BRCA2* genes. Popularity of the *BRCA1/2* genes is likely due to several factors, including the overall prevalence of *BRCA1/2* mutations in the general population and actor Angelina Jolie’s public decision to undergo testing and treatment related to her family’s *BRCA1* mutation. However, there are several other established causes of hereditary cancer that have not had the same level of exposure in the popular media. Lynch syndrome, caused by mutations in the *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes, increases the risk for several types of hereditary gastrointestinal and other cancers. Mutations in several additional genes have been associated with a moderate but clinically significant increase in breast cancer risk, including *ATM* and *CHEK2*.

The ideal strategy for ordering hereditary cancer predisposition testing generally starts with the family member who has a personal cancer history that is most suspicious for a hereditary cause. Once a causative gene variant is identified, other family members, with or without cancer, can be tested for this mutation to determine if they also have a predisposition to developing cancer. Rather than testing other family members via comprehensive gene testing, relatives can be tested via targeted testing that examines only the specific site in the genome where the familial mutation is located. This targeted testing is usually less expensive and often faster than comprehensive testing.

At ARUP Laboratories, complex genetic test orders undergo pre-test review by ARUP’s genetic counselors to ensure the most appropriate test is ordered based on the provided clinical information. **This pre-test review identified a recurring scenario in which testing is ordered for a family history of “BRCA mutation” but the familial variant is actually not in the *BRCA1* or *BRCA2* genes; familial variants were instead found in *ATM*, *CHEK2*, *MUTYH*, *NBN*, *PALB2*, *PMS2*, and other cancer risk genes.** Here we present three of these cases encountered by ARUP that demonstrate the importance of confirming familial variants prior to ordering testing on family members.

## Case 1

In this case, a pediatrician ordered full gene analysis for the *BRCA1* and *BRCA2* genes at ARUP Laboratories. Information provided to ARUP with the specimen indicated that the patient had a family history of a “BRCA mutation”. As part of the pre-test review process, the ARUP genetic counselor contacted the ordering healthcare provider to obtain additional information about the family history. The pediatrician contacted the patient’s family and obtained a copy of the mother’s test report which showed that **the familial mutation was not in *BRCA1/2* but instead was in the *CHEK2* gene.** Thus, the *BRCA1/2* gene test would not have given the pediatrician or the patient the information they were looking for. In addition, the patient was a minor and because screening for *CHEK2* mutation carriers is not recommended until adulthood, the pediatrician decided to cancel testing entirely after discussing the risks and benefits with the ARUP genetic counselor. Thus, the unnecessary cost of performing *BRCA1/2* analysis was saved and the family was counseled appropriately.

## Case 2

In this case, a surgeon ordered full gene analysis for the *BRCA1* and *BRCA2* genes at ARUP Laboratories prior to gynecologic surgery for a patient with no cancer. The patient had reported a family history of hereditary breast and ovarian cancer (HBOC) syndrome. When an ARUP genetic counselor requested further information prior to running the test, the surgeon provided a genetic test report from the relative reported to be affected with HBOC, **but this relative was negative for variants in *BRCA1/2*. Instead, the relative had a variant of uncertain significance in the *ATM* gene.** *BRCA1/2* testing was canceled and the surgeon decided not to test the patient for the familial *ATM* variant until more information becomes available about the clinical significance of the variant.

## Case 3

In this case, a physician’s assistant ordered full gene analysis for the *BRCA1* and *BRCA2* genes at ARUP Laboratories because the patient’s sibling had tested positive on a breast/ovarian cancer panel performed at a different laboratory. The ARUP genetic counselor called the physician’s assistant to request information about the sibling’s mutation. Upon review of the test result, it was determined that **the sibling was negative for *BRCA1/2* variants but positive for a pathogenic variant in the *PMS2* gene,** causative for Lynch syndrome. The *BRCA1/2* testing was canceled, and targeted testing for the familial *PMS2* mutation was ordered on the patient instead. The patient tested positive for the *PMS2* mutation and was thus diagnosed with Lynch syndrome, for which she then received the appropriate genetic counseling and medical management.

## Discussion

These three cases illustrate the importance of confirming the familial pathogenic variant prior to ordering genetic testing. Obtaining documentation of the familial variants allowed for the inappropriate *BRCA1/2* tests to be canceled, and targeted testing for the appropriate gene was offered instead, when clinically indicated. Without this correction in test orders, the *BRCA1/2* test results would, at minimum, have likely been clinically irrelevant because the familial variant for which testing was requested would not have been tested. The patient would have needed additional testing for the familial variant, adding to the cost of testing as well as delaying clinically relevant results. In addition, negative *BRCA1/2* results in these cases could have been falsely reassuring if the testing order error wasn’t identified. **These cases demonstrate the need for clinicians to confirm reported family history whenever possible by obtaining documentation of familial genetic variants, thereby ensuring a clinically relevant result is issued for the patient.** In addition, these cases also illustrate why laboratories should investigate orders for which family history information is incomplete, to ensure the correct test is performed.

As genetic testing for hereditary cancer predisposition and *BRCA1/2* continues to receive attention from the media, **it is crucial to raise awareness of the growing list of clinically actionable hereditary cancer genes.** Education of healthcare providers should include instruction about the many important cancer genes in today’s genetic testing landscape. Advocacy and support for patients with all hereditary cancer predisposition syndromes should be encouraged so that patients, healthcare providers, and laboratories understand that a family history of a “breast cancer mutation” doesn’t always mean *BRCA1/2*.

## References

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