BRCA Testing
Frequently Asked Questions (FAQ)

Where is MLabs BRCA testing performed?
The Michigan Medical Genetics Laboratories (MMGL) is a comprehensive clinical genetics testing laboratory based in the University of Michigan's Department of Pediatrics whose goals are to provide state of the art testing and cutting edge Research and Development for genetic diseases. The MMGL Molecular Genetics Laboratory offers a full complement of BRCA testing.

What is the analytical sensitivity of BRCA testing at MMGL?
High quality and sensitivity are priorities at MMGL. We have several different testing options; please see below. Based on test design and sequencing methods, our validated BRCA test's analytical sensitivity for coding or splice site mutations is very high (>99%). Ongoing validation with known BRCA mutation carriers has so far disclosed 100% sensitivity. Our experience with 40 other gene sequencing assays over the past 7 years indicates 100% sensitivity for such variants. BRCA analytical sensitivity is maximized by including results of individual exon dosage information derived by MLPA (see below) from every exon of both *BRCA1* and *BRCA2*.

Given that some individuals will have disease-causing variants in regions of these genes (introns) that are not tested, or have very rare chromosomal translocations, the overall detection rate is less than 100%, which is no different than testing outcomes in other genetics labs.

What are BRCA test limitations?
Although the protein-coding exons and 50 base pairs on either side of the exons are carefully interrogated by MMGL testing, it is conceivable that pathogenic variants in far distant or unknown regulatory elements or deep intronic regions of *BRCA1* or *BRCA2* could be missed. For these reasons testing cannot be 100% sensitive for any *BRCA* testing at this time. Such variants likely constitute a very small percentage of pathogenic variants that would be missed by all currently available tests. In addition, the classification [benign, variant of uncertain significance (VUS), or pathogenic] of such remote variants cannot be made with certainty due to the lack of experimental data to support functional impairment of gene activity.

Even though large intragenic deletions and duplications affecting coding exons will be identified in MMGL BRCA testing, the MMGL test may not detect very rare balanced chromosomal translocations that disrupt *BRCA1* or *BRCA2*. Of note, these limitations are not specific to MMGL BRCA testing only, but rather these are limitations of the currently available methods that are being used in clinical laboratories offering BRCA testing. In addition, not all cases of Hereditary Breast and Ovarian cancer are caused by mutations in either *BRCA1* or *BRCA2*. Other assays for additional genetic causes of Hereditary Breast and Ovarian Cancer are available in MMGL.

What is the MMGL BRCA variant call process?
MMGL adheres to high quality standards to perform molecular testing and to report accurate results. MMGL Medical Geneticists and the MMGL BRCA Test Committee interrogate all available relevant literature sources, variant databases, experimental functional data, computer-based conservation assays and posterior probability modeling methods, and incorporate provided clinical history to determine the clinical significance of each variant. MMGL follows the American College of Medical Genetics (ACMG) guidelines for variant classifications [Richards et al. Genet Med 10(4):294-300, 2008]. In addition, a quarterly review of all variants is performed and amended reports are provided to the ordering provider for any variant classification change. For variants of uncertain significance (VUS), interpretation can be difficult; however, VUS are a small percentage of the calls. Since all labs who initiated *BRCA* testing have begun to sequence more cases, the frequency of such calls for each lab will be forthcoming once adequate numbers of patients are tested. MMGL is committed to making high quality, judicious calls, and uses many sources of information. MMGL also participates in de-identified "Free the Data" initiatives to make public DNA sequence variant information for the benefit of patients.

Does MMGL provide detailed interpretations of test results?
Yes, MMGL provides a comprehensive interpretation of BRCA1 and BRCA2 variants using a thorough review of medical literature sources and currently available bioinformatics tools and databases. The following are examples of interpretation we use for the different types of variants. In some cases, MMGL will provide more background for interpretation in unique variant circumstances.

- Pathogenic variant: indicates a higher risk for BRCA1/BRCA2 related cancers. However, it is important to note that not all individuals with pathogenic BRCA1 or BRCA2 variants will have breast or ovarian cancer. Women with BRCA1 or BRCA2 pathogenic variants face an estimated 40-80% lifetime risk for breast cancer and 11-40% for ovarian cancer. In addition men with BRCA1 or BRCA2 pathogenic variants face an estimated 1-10% lifetime risk for breast cancer (Ford et al. Am J Hum Genet 62:676-689, 1998; Antoniou et al. J Med Genet 42:602-603, 2002; Antoniou et al. Am J Hum Genet 72:1117-1130, 2003; http://www.ncbi.nlm.nih.gov/books/NBK1247/). Other types of cancers have also been reported in individuals with pathogenic BRCA1 and BRCA2 variants (http://www.ncbi.nlm.nih.gov/books/NBK1247/).
- Variant of uncertain clinical significance (VUS): indicates that the risk for BRCA1/BRCA2 related cancers cannot be determined based on this result. The result should be evaluated in conjunction with other clinical information, diagnostic findings and family history. Clinical targeted testing (single site BRCA analysis) of the VUS in other affected and unaffected family members may help clarify the clinical significance of this variant. Medical Genetics evaluation and counseling is strongly recommended.
- No pathogenic variants: indicates that variants associated with a higher risk for BRCA1/BRCA2 related cancers were not observed. This result should be evaluated in conjunction with other clinical information, diagnostic findings and family history. For patients without a personal history of cancer who have a family history of breast and/or ovarian cancer, testing of an affected family member should be considered. Medical Genetics evaluation and counseling is strongly recommended.

Does MMGL have genetic counselors that can talk to clients or are available to consult with?
Yes. For technical questions, please call 734-615-2028 or 734-615-2429. For clinical questions we would be delighted to refer you to the clinical service most appropriate to your question or test.

Does MMGL perform large rearrangement analysis?
Yes. Large genomic rearrangements have been previously reported in *BRCA1*. Our laboratory offers both *BRCA1* and *BRCA2* MLPA analysis that will detect single and multiple exon (intragenic) deletion or duplication mutations within *BRCA1* and *BRCA2*, including the common large rearrangements. Every exon of *BRCA1* and *BRCA2* is targeted so that previously unreported exonic deletions or duplications will be identified.

Does MMGL perform Ashkenazi Jewish founder mutation testing?
Yes. MMGL provides a variety of *BRCA* testing options including a focused panel for the three Ashkenazi Jewish founder mutations in *BRCA1* and *BRCA2*.

Does MMGL perform single site "site-directed testing" or testing for known familial mutations?
Yes. MMGL provides a variety of BRCA testing options:

- BRCA Panel: *BRCA1* and *BRCA2* gene sequencing and deletion/duplication MLPA
- Gene sequencing of either *BRCA1* or *BRCA2* or both
- Deletion/duplication MLPA analysis of either *BRCA1* or *BRCA2* or both
- Ashkenazi Jewish mutation panel (three mutations)
- Targeted single site or familial mutation testing in either *BRCA1* or *BRCA2*

Does MMGL perform deletion/duplication analysis for *BRCA1* and *BRCA2*?
Yes, we use Multiplex Ligation-dependent Probe Amplification (MLPA). Each exon of both *BRCA1* and *BRCA2* is targeted. In BRCA mutation positive Hereditary Breast and Ovarian Cancer syndrome, approximately 6-12% of individuals carry whole or partial gene deletions or duplications in *BRCA1* or *BRCA2* [Judkins et al. Cancer 118(21):5210-5216, 2012].

What methods does MMGL use in BRCA testing?

- Sanger Sequencing: The entire coding sequences (exons plus 50 bp on either side of each exon in the introns) are amplified using specific primers, and bidirectionally sequenced using Sanger sequencing. High quality primers, free of any known sites of single nucleotide polymorphisms (SNPs) or in/dels, are used for each coding exon. Many regions are doubly amplified by separate primer sets vastly minimizing allele dropout. Together with MLPA results, our analytical sensitivity is >99%.
- Multiplex Ligation-dependent Probe Amplification (MLPA): Each exon of both *BRCA1* and *BRCA2* is targeted. In BRCA mutation positive Hereditary Breast and Ovarian Cancer syndrome, approximately 6-12% of individuals carry whole or partial gene deletions or duplications in *BRCA1* or *BRCA2* (Judkins et al. Cancer 118(21):5210-5216, 2012).

How fast can MMGL complete testing?
We report our BRCA testing results within 14 days. Of course, we need the approval of the payor before we can complete testing. Please let MLabs know if you would like our help to expedite this. Rarely, challenging cases may take longer. In all such cases, we will contact the physician to inform him/her of the delay.

Is MMGL CAP and CLIA certified?
Yes. Those certificate numbers and others are listed at the following website: http://mlabs.umich.edu/about-us/licensure-accreditation.

What is the charge for the BRCA panel?
For information about charges for testing, please contact MLabs at 800-862-7284.

Does MMGL accept insurance?
Yes. Please contact MLabs for questions regarding insurance coverage or payment methods for testing. Each insurance plan is different with respect to co-pays, deductibles and covered benefits.