MYRIAD®

CLINICAL 360

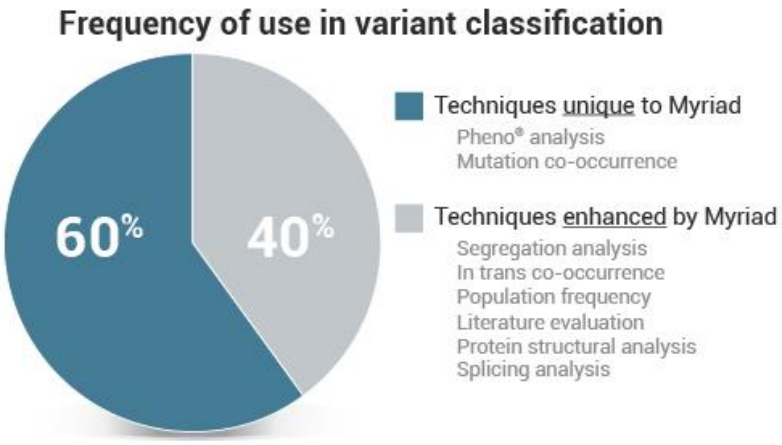
Variant Classification and Commitment to Patient Care

With twenty years' experience and over a million patients tested, Myriad Genetic Laboratories maintains the highest standards for accuracy in variant detection and variant classification. Myriad's commitment to accurate results has enabled healthcare providers to provide personalized medical management to their patients at risk for hereditary cancer.

Within the past year, other laboratories have entered the hereditary cancer testing space. You may be surprised to learn that currently there is limited regulatory oversight for laboratory developed test (LDT) accuracy. LDTs are not currently FDA-regulated, and CLIA does not evaluate the clinical validity or accuracy of these tests.[1] As such, it becomes the responsibility of the ordering healthcare provider to evaluate genetic testing laboratories using peer-reviewed and published validation studies to understand that laboratory's variant detection rate (the likelihood your patients' mutation would be identified.)[2]

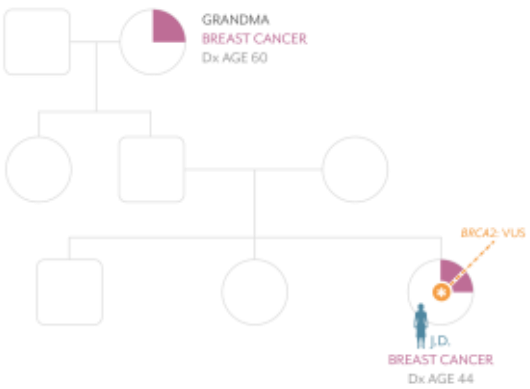
Variant detection, however, is only half of the equation. We all carry thousands of variants in our genomes, only a handful of which may affect our health. Variant classification, the process of determining whether a specific variant causes disease, is an equally important component of accuracy when evaluating laboratories. After all, the primary aim of clinical genetic testing is to provide results that inform medical management. A robust variant classification program that offers accurate, timely, and cost-effective interpretation of variants is a vital part of a diagnostic laboratory's services.[3]

Myriad's industry-leading variant classification program, myVision™, upholds the company's commitment to excellence, allowing Myriad's team of 30+ scientific experts from varying specialties to utilize and evaluate numerous methodologies for variant classification and reclassification. Myriad monitors variant data on a daily basis via automated and manual protocols, alerting scientists of sufficient statistical evidence to consider variant reclassification.[3] Myriad's unique quantitative methodologies, Pheno™ and Mutation Co-Occurrence, have been validated as >99% accurate.[6,7] The myVision™ literature management team continuously monitors the literature and other data that may influence variant classification. Additionally, this team critically evaluates family histories for opportunities for segregation analysis. Myriad has demonstrated that segregation analysis is a powerful method of determining truly deleterious mutations and complements the above-mentioned reclassification methods employed at Myriad.[8]



As a result of Myriad's investment into myVision™, Variant of Uncertain Significance (VUS) rates for *BRCA1* and *BRCA2* are <2%.[3] VUS rates for the Lynch syndrome genes are ~6%.[4] Additionally, each week the myVision™ team meets to reclassify VUSs, generally resulting in hundreds of amended reports to healthcare providers whose patients and relatives are impacted by this reclassification. Myriad's commitment to accurate variant classification and lifetime commitment to reclassification is unique among genetic testing laboratories.

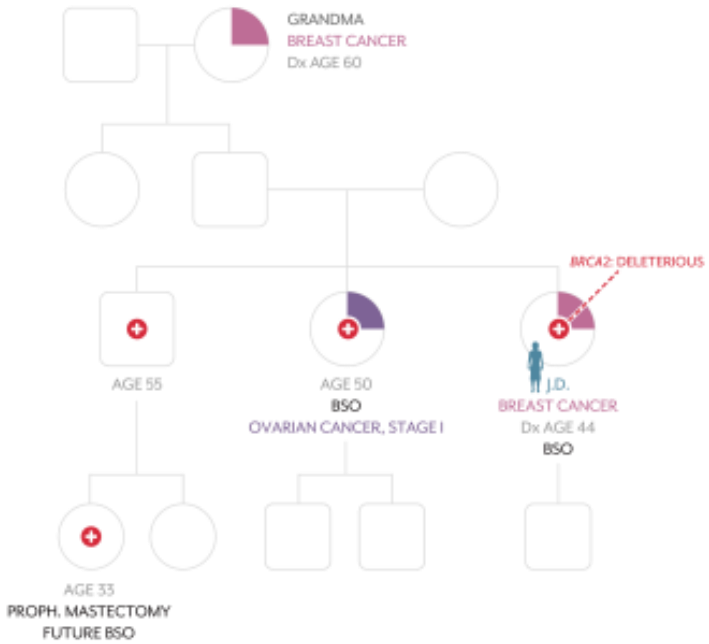
Case Study:



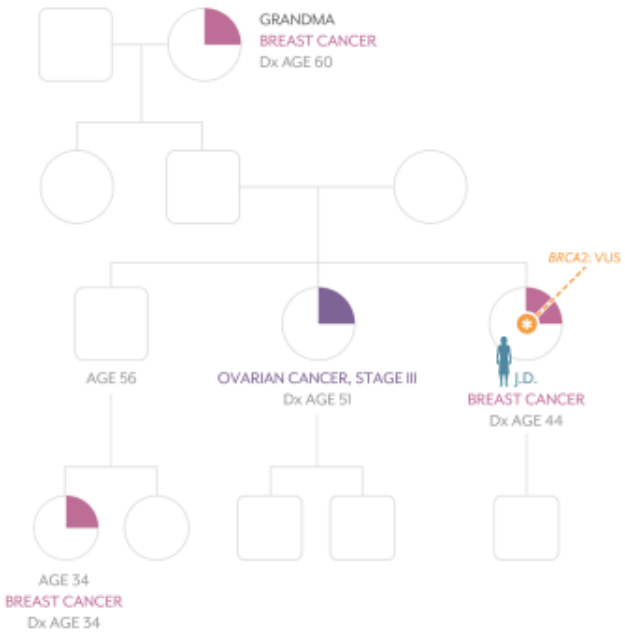
- Patient J.D. is a 44-year-old female
- Recently diagnosed with invasive ductal carcinoma, 44y
- Paternal grandmother, breast cancer in her 60s
- J.D.'s physician ordered *BRCA1/2* genetic testing in 2012 →*BRCA2* Variant of Uncertain Significance (VUS) was discovered
- Per medical management protocol for VUS's[5], she was managed based on her personal and family history. No relatives were tested for the VUS.

Due to Myriad's diligence and commitment to reclassification, Myriad's myVision™ team continued to study and evaluate her *BRCA2* VUS, resulting in a reclassification to DELETERIOUS in 2014. Myriad requires 2 independent lines of evidence (methods) with >99% certainty to reclassify a VUS to deleterious or benign.[3] In this case, Pheno™ and structural protein analysis were employed.

Myriad contacted J.D.'s provider with the reclassification to deleterious, and she promptly elected to pursue prophylactic bilateral salpingo-oophorectomy (BSO) to reduce her ovarian cancer risk. She informed her close relatives of her *BRCA2* mutation status and many pursued single site testing for the familial *BRCA2* mutation. Her sister tested positive and immediately elected to pursue prophylactic BSO; she was found to have a stage I epithelial ovarian carcinoma that she will very likely survive due to early diagnosis. Her brother and two nieces also pursued testing, and one niece tested positive for the *BRCA2* mutation. She elected to pursue prophylactic bilateral mastectomy now and prophylactic BSO after she completes childbearing.



If J.D.'s provider had ordered BRCA genetic testing through a different laboratory, it is possible that this *BRCA2* variant would not have been reclassified, as it has not been reported in the literature and other laboratories may not employ experienced structural biologists. Additionally, no other laboratories are utilizing Pheno™ for variant classification. For J.D.'s family, this could mean the difference between life and death. Her sister might only be diagnosed with ovarian cancer after symptoms had developed, resulting in a late stage diagnosis and slim survival rates. Her niece may not have discovered her significantly elevated breast cancer risk and therefore may not have been offered risk-reducing surgery and potentially could have developed early-onset breast cancer. Both of these potentially harmful outcomes may have been avoided had the patient been tested by a laboratory with a robust variant classification program such as Myriad's myVision™.



Bottom Line: Accurate variant detection as described in a published validation study, as well as a robust, industry-leading variant classification program should be the top priorities when selecting a genetic testing laboratory for your patients. Without these two qualities, you may receive inaccurate results that may negatively impact your patient care and outcomes. Myriad's myVision™ program continues to be committed to providing highly accurate test results and variant classification to you and your patients in order to help save lives.

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8. Eggington JM, et al. Segregation analysis offers a mechanism for variant reclassification in a small subset of cases but is especially powerful in classifying deleterious mutations. Presented at the 2013 American College of Medical Genetics and Genomics meeting.

If you have questions regarding this topic, please contact your local Regional Medical Specialist (RMS) or email medical services at helpmed@myriad.com. If you do not know how to reach your RMS, check with your Account Executive or call 800-4-MYRIAD (800-469-7423) and ask for contact information for your local RMS.