Genetic Variants of Uncertain Significance

In this month's posting, we present answers to commonly asked questions regarding variants of uncertain significance (VUS). Most genetic test results are either 'positive for a deleterious mutation,' or 'no mutation detected.' However, as in many areas of medicine, results are occasionally inconclusive; consequently, medical management decisions are based on other contributing factors.

What is a VUS? A variant of uncertain significance (VUS) is a genetic sequence change whose association with disease risk is currently unknown. As with other result types, Myriad sends the ordering provider a patient booklet explaining the meaning of a VUS result.

Are VUSs unique to Myriad's genetic tests? No. Essentially all genes have sequence variations, some of them easily recognized as benign (reported as 'no mutation detected' or 'variant, favor polymorphism') or deleterious (reported as 'deleterious' or 'suspected deleterious'). However, when it is uncertain whether a sequence change impacts gene function and subsequent clinical outcome, the variant is reported as a VUS.

How common are VUS results? At Myriad, the current rate of VUS results is about 2.9% for BRCA1/2 and about 6.6% for Lynch syndrome genes. These numbers have decreased significantly from around 40% in the early days of hereditary cancer genetic testing, owing to Myriad's Variant Classification Program (VCP).

How do I manage a patient with a VUS? Since it is not possible to classify the genetic change as deleterious or benign, the patient should be managed based on personal and family history. Individualized management may include increased surveillance and possibly other interventions, such as surgery or chemoprevention. Consider reviewing the case with your Regional Medical Specialist to discuss appropriate management in the context of the specific patient and family history, and to explore whether additional work-up is indicated for the patient or family.

What information is used for classifying variants? Myriad's laboratory is able to leverage its extensive database to utilize multiple, independent lines of evidence to classify variants, including co-occurrence with deleterious mutations, literature evaluation, evolutionary conservation, phenotype analysis, and segregation with cancer in families.

What happens once a variant is reclassified? Over time, a variant will often get reclassified as either a benign polymorphism or a deleterious mutation. When this occurs, an amended report is sent to the original ordering provider. While Myriad proactively reclassifies variants and communicates new findings to the original ordering providers, it is important to urge your patients with VUSs to keep in contact with your office or to notify the laboratory of an alternative provider if they move, so that they and their family can benefit from new information as it becomes available.

What is the purpose of the family history paperwork accompanying the VUS report? Patients found to have a VUS are invited to participate in Myriad's Variant Classification Program (VCP) by completing a detailed questionnaire about their family history. The laboratory may then offer free testing to selected relatives to determine if the variant tracks with any observed cancers in the family. Ultimately, this should speed up the reclassification process for that variant, thus providing a meaningful result for the patient and family. If your patient was tested in the past and found to carry a VUS, contact Myriad Medical Services (1-800-469-7423, extension 3850 or helpmed@myriad.com) to confirm the current classification and to request participation in the VCP if the patient is interested.
<table>
<thead>
<tr>
<th>Result</th>
<th>No mutation detected (about 90% of results)</th>
<th>Variant, favor polymorphism (rare)</th>
<th>Genetic Variant of Uncertain Significance (rare)</th>
<th>Variant, suspected deleterious (rare)</th>
<th>Positive for Deleterious Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Negative</td>
<td>Almost certainly negative</td>
<td>Inconclusive</td>
<td>Almost certainly positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Interpretation</td>
<td>Cause of cancer in family has not been determined; patient may have increased cancer risk, but hereditary cancer less likely</td>
<td>Cause of cancer in family not likely due to this variant; patient may have increased cancer risk, but hereditary cancer less likely</td>
<td>May turn out to be positive or negative; physician will be notified once reclassified</td>
<td>Patient likely has the syndrome with cancer risks defined by the syndrome</td>
<td>Patient is confirmed to have the syndrome; cancer risks defined by the syndrome</td>
</tr>
<tr>
<td>Management</td>
<td>Manage based on personal and family history</td>
<td>Manage based on personal and family history</td>
<td>Manage based on personal and family history; provider should receive invitation for patient to participate in Variant Classification Program</td>
<td>Manage according to guidelines for syndrome; suggest single site testing for family members</td>
<td>Manage according to guidelines for syndrome; suggest single site testing for family members</td>
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REFERENCES:


Do not reply to this message. If you have questions regarding information in this posting, 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.