Session 3: Interpreting Genetic Testing Results

American College of Medical Genetics guidelines for standards and interpretation of sequence variants
https://www.nature.com/articles/gim201530/figures/1
**JAX Labs Interpretation Tool**


**NOTE:**
- Positive = pathogenic or likely pathogenic
- Negative = benign or likely benign
- You will need to talk to the specific genetic testing company you are working with to determine the threshold they use for calling something pathogenic/benign or likely pathogenic/benign (example: some use a 99% threshold for pathogenic/benign and 95% for likely pathogenic/benign).
<table>
<thead>
<tr>
<th>Clinical Presentation of Person to be Tested</th>
<th>Genetic Testing Result</th>
<th>Interpretation</th>
<th>Recommendations for Family Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected</td>
<td>Positive</td>
<td>True positive. Disease-causing variant identified. Test confirms clinical diagnosis or clinical suspicion.</td>
<td>Targeted testing of first-degree family members is strongly recommended. Those with positive results are at risk for developing cancer. Those with negative results are not at increased risk.</td>
</tr>
<tr>
<td>Affected</td>
<td>Negative</td>
<td>The result does not rule out the diagnosis or a genetic cause of the cancer.</td>
<td>Testing of family members not indicated.</td>
</tr>
<tr>
<td>Affected</td>
<td>Variant of uncertain clinical significance (VUS)</td>
<td>The result, at this time, is uninformative.</td>
<td>Testing of family members not typically indicated.</td>
</tr>
<tr>
<td>Unaffected</td>
<td>Positive</td>
<td>Patient is at risk for developing cancer.</td>
<td>Targeted testing of first-degree family members is strongly recommended. Those with positive results are at risk for developing cancer. Those with negative results are not at an increased risk.</td>
</tr>
<tr>
<td>Unaffected</td>
<td>Negative</td>
<td>Patient is likely not at increased risk of cancer, but a genetic cause cannot be ruled out unless familial variant is known.</td>
<td>Testing of family members may be indicated, depending on the family history.</td>
</tr>
<tr>
<td>Unaffected</td>
<td>Variant of uncertain clinical significance (VUS)</td>
<td>The result, at this time, is uninformative.</td>
<td>Testing of family members not typically indicated.</td>
</tr>
</tbody>
</table>

**Options for Variant Interpretation**
(remember, all differences in DNA are called variants, we frequently use the term “mutation” to mean pathogenic variant).
- Contact testing lab directly to get more information
- Contact other labs to get their interpretation
- Refer patient to a genetic specialist
Considerations when selecting a genetic testing laboratory:

1 Quality

What is the analytical sensitivity and specificity of the test? How was this validated?

What processes are in place to reduce potential sample handling errors?

What are the review and confirmation procedures before a result is reported (+, -, or VUS)?

What certifications and accreditations do your lab and tests have (CLIA, CAP, NY State, California, Florida)? What is your proficiency testing status?

What technology is used for sequencing and Large Rearrangement testing?

What is the coverage area for BRCA 1 and 2 genes during analysis, How far into the introns does the lab sequence?

For NGS panels, what is the average depth of coverage? What is the minimum depth of coverage that is required by the lab to report results?

How does the lab perform the validation of its tests (how many samples, what kinds of samples, quality controls, is inter- laboratory correlation done to prove findings)?

What is your company’s process for investigating and classifying variants (what methods or techniques are used to classify variant)?

Does your company investigate variants at the molecular level, functional and clinical levels?

What is the VUS rate on naively tested patients for each test? How many naïve patients have been tested and make up the VUS rate?

Does the lab have a program to reclassify variants? What types of evidence are used to reclassify variants? What is the confidence threshold to reclassify a variant (95%, 99%, >
99%) Does the lab automatically send amended reports when a variant is reclassified? When assessing variants, how does the lab report the information to clinicians? Are there scientific references?

What quality control measures do you have in place to ensure appropriate testing?

2 Customer service

What level of customer service & clinical support that is available for providers and patients?

What is your turnaround time?

What sample types are accepted (blood, buccal)?

What is your QNS/redraw rate?

How does the lab contact clinicians about abnormal results?

Who pays for shipping and/or transportation of the specimens and how do you ship?

Does your company have Genetic Counselors and laboratory staff to discuss complex results via telephone at no charge?

Does the lab offer FREE posttest Genetic counseling tele-health services

Will our organization have convenient access to knowledgeable clinical and lab experts when needed?

How do you handle specimen problems?

3 Costs
What is the price of the test(s)?

Has your organization completed any costs effectiveness studies for your tests? If yes, please describe which test(s) and the results.

What major payers do you have contracts with and for what tests?

Does your lab perform insurance pre-authorizations?

Does your lab offer a financial assistance program for patients, payment plans?

4 Other

Do you currently have the infrastructure to handle additional capacity obtained from this contract?

What supplier performance metrics does your lab commit to?