**Introduction**

The timely diagnosis of disease is essential for increasing positive health outcomes for patients and their families. Advances in next-generation sequencing have made genomic testing more affordable and have facilitated increased discussion around improving population health through genomic approaches. The identification of individuals and families who are unaware of their increased risk and carry pathogenic variants in disease-associated genes could significantly reduce morbidity and mortality. The CDC’s Office of Public Health Genomics (OPHG) has noted that nearly 2 million people in the United States are at increased risk for adverse health outcomes due to genetic variants which predispose them to three disorders: hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome (LS), or familial hypercholesterolemia (FH). The OPHG has determined that early detection in these individuals would have a significant positive impact on public health based on available evidence-based guidelines and recommendations.

**Healthy Screening: the CDC Tier 1 Panel**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Genes Tested</th>
<th>Disease Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome (HBOC)</td>
<td>BRCA1, BRCA2</td>
<td>Increased risk for breast, ovarian cancer (including fallopian tube and primary peritoneal cancers), prostate cancer, pancreatic cancer, and melanoma</td>
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<tr>
<td>Lynch syndrome (LS)</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Increased risk for colorectal cancer, and cancers of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin (sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas), pancreas, and prostate</td>
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<tr>
<td>Familial hypercholesterolemia (FH)</td>
<td>APOB, LDLR, LDLRAP1, PCSK9</td>
<td>Increased risk of premature cardiovascular events such as angina, myocardial infarction, and stroke due to high cholesterol levels</td>
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</tbody>
</table>

For consideration

A Careful understanding of variant classification and the relationship of variants to mechanism of disease is essential in being able to return accurate and appropriate findings.

- For the APOB gene, only pathogenic autosomal dominant gain-of-function (GOF) variants are associated with FH.
- For the LDLRAP1 gene, pathogenic autosomal recessive loss-of-function (LOF) variants are associated with hypobetalipoproteinemia.
- For the PCSK9 gene, only pathogenic autosomal dominant gain-of-function (GOF) variants are associated with FH.
- The LDLRAP1 gene is associated with autosomal recessive FH.

Variant classification for population studies requires increased stringency to account for unclear penetrance and expressivity.

- FH has the advantage of routine chemistry which can aid in the classification of variants. A careful

**RESULTS**

![Graph showing results](image)

**Detailed Positive Findings**

![Detailed findings](image)