Objectives:

- Overview of challenges and examples of automated and manual variant interpretation.
- Varsome® does give a preliminary classification, however, students will review and verify each criteria/question discussed in class.

Variant Interpretation Framework Summary

<table>
<thead>
<tr>
<th>Concept</th>
<th>Questions</th>
<th>ACMG Criteria</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allele Frequency</td>
<td>(1) Common or rare?</td>
<td>BA1, BS1, PM2</td>
<td>gnomAD</td>
</tr>
<tr>
<td>Computational &amp; Predictive Data</td>
<td>(2) Variant Impact/Type</td>
<td>PVS1, PM4, BP3</td>
<td></td>
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<tr>
<td></td>
<td>Loss of function</td>
<td></td>
<td>VEP, UCSC web browser</td>
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<td></td>
<td>In-frame indel</td>
<td></td>
<td>vARSOME® summary</td>
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<tr>
<td></td>
<td>(3) In-silico predictions?</td>
<td>PP3, BP4, BP7</td>
<td>Special attention to:</td>
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<tr>
<td></td>
<td>Potential splicing impact?</td>
<td></td>
<td>SpliceAI, REVEL (&gt;0.7)</td>
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<tr>
<td></td>
<td>(4) Constraint metrics</td>
<td>PP2, BP1</td>
<td></td>
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<tr>
<td></td>
<td>Gene/regional level</td>
<td></td>
<td>gnomAD</td>
</tr>
<tr>
<td>Functional Knowledge</td>
<td>(5) Residue/Domain? Hotspot?</td>
<td>PM1</td>
<td>Uniprot, ClinVar, HGMD</td>
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<tr>
<td></td>
<td>(6) Variant effect functionally studied?</td>
<td>PS3, BS3</td>
<td>ClinVar, HGMD, Pubmed</td>
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<tr>
<td>Clinical Knowledge (published, or case/sample specific)</td>
<td>(7) Interpretation Databases - ClinVar</td>
<td>PP5, PM5, PS1</td>
<td>ClinVar, HGMD, Pubmed</td>
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<td></td>
<td>(8) Previously reported cases?</td>
<td>PS4, BS2, BP5</td>
<td></td>
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<td></td>
<td>(9) Phenotype specificity</td>
<td>PP4</td>
<td>Some of these criterias are also</td>
</tr>
<tr>
<td></td>
<td>(10) Segregation? De novo?</td>
<td>PP1, BS4, PS2, PM6</td>
<td>specific to the clinical details of</td>
</tr>
<tr>
<td></td>
<td>(11) Trans / cis observations</td>
<td>PM3, BP2</td>
<td>individual carrying the variant</td>
</tr>
</tbody>
</table>
Please review the classification for the following variant/case:

Case 1 Information:
- 22yo female underwent genetic testing for hereditary cancer predisposition.
- Patient was referred to clinical genomics because of strong family history of early onset breast and ovarian cancer (<45yo age of onset in mother, 2 maternal aunts and a cousin)

Variant Identified:

BRCA2
(NM_000059)
c.2979G>A
p.Trp993X
Heterozygous state

Genomic DNA (hg19):
Chr13(GRCh37):g.32911471G>A

Please review the classification for the following variant/case:

Case 2 Information:
- 30yo lawyer submitted his sample for state-funded project evaluating the effects
- Patient is alive and healthy. No self-reported history of hypercholesterolemia or any genetic disorder.

Variant Identified:

LDLR
(NM_000527.5)
c.1784G>A
p.Arg595Gln
Heterozygous state

Genomic DNA (hg19):
Chr19(GRCh37):g.11227613G>A
Please review the classification for the following variant/case:

**Case 3 Information:**
- 30yo patient with no family history underwent a predisposition screen assay with a clinical reference company.
- No other information available.

**Variant Identified:**

**PMS2**  
(NM_000535):  
c.989-1G>T  
p.?
Heterozygous state

**Genomic DNA (hg19):**  
Chr7(GRCh37):g.6029587C>A