MAYO CLINIC

# CENTER FOR INDIVIDUALIZED MEDICINE

## Clinical Variant Interpretation Lab
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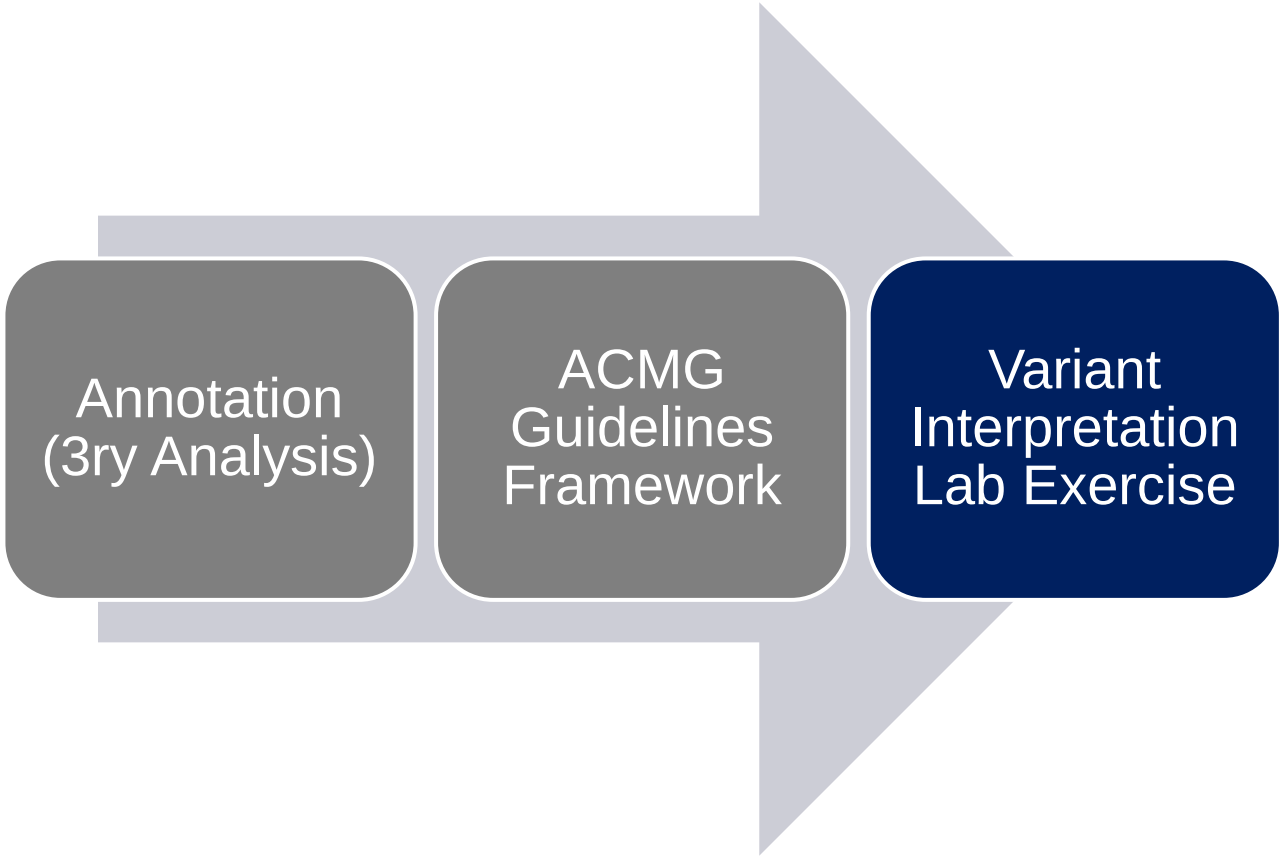
Annotation (3ry Analysis)
ACMG Guidelines Framework
Variant Interpretation Lab Exercise

# Objectives:

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


 

# Variant Interpretation Framework Summary

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


 

# FRANKLIN OVERVIEW



 

# 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.Trp993*
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


 