Penetrance estimates for incidental genomic findings in ACMG-59

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Penetrance Estimates for Incidental Genomic Findings

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INTRODUCTION

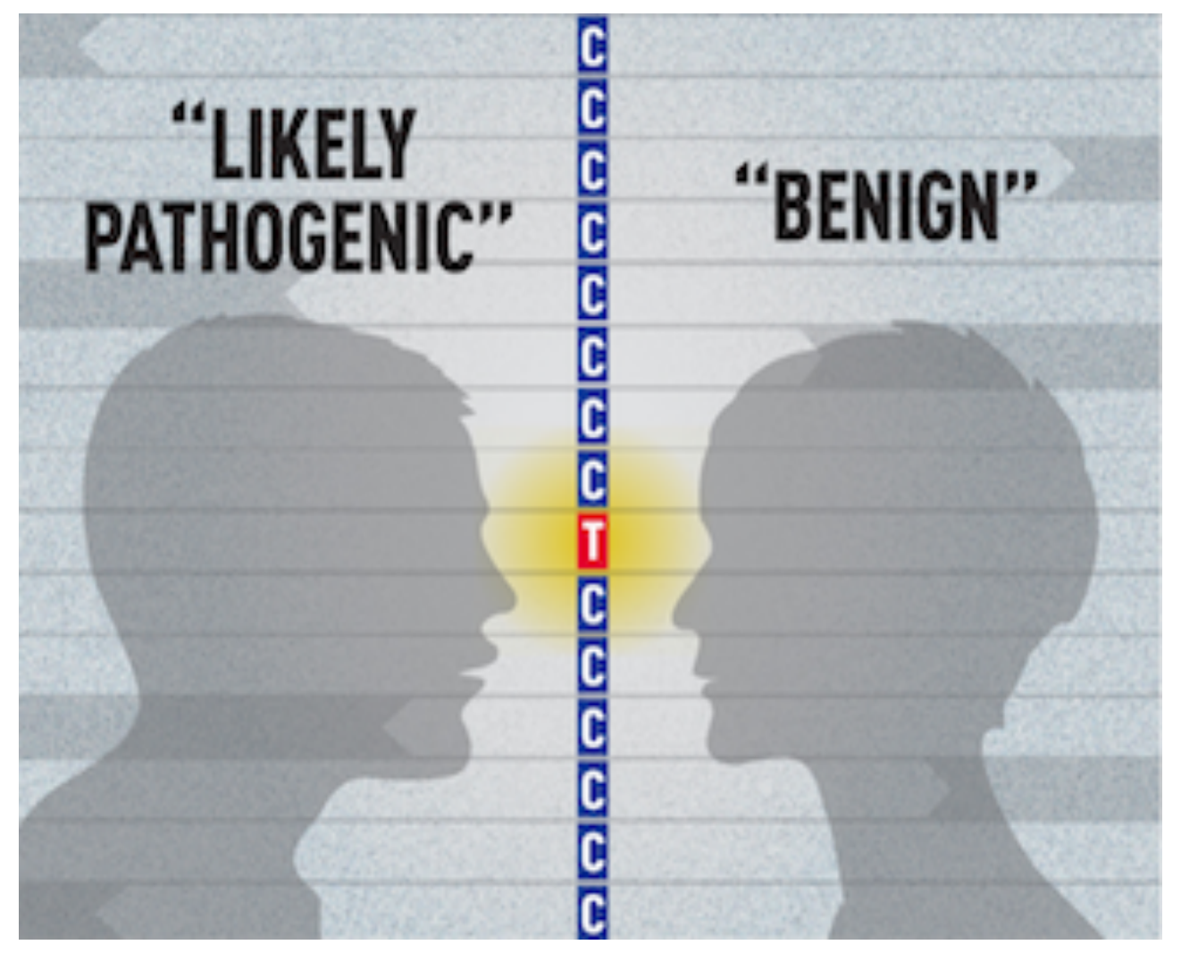
(Genetic Testing and Relevant Datasets)

Genetic testing: a difference from the reference genome (variant) may indicate disease.

Incidental finding: variant in gene unrelated to diagnostic indication that prompted sequencing.

-Due to multiple testing and low priors, these typically have high rates of false positives, so we normally don't report them.

ACMG (American College of Medical Genetics & Genomics): recommends an exception for 56 genes thought to be more indicative of disease.



1000 Genomes Project: contains whole-genome sequence data for 2,504 healthy adults from diverse ethnic populations.

ExAC: aggregates population-level data from 60,706 diverse human whole-genome sequences.

ClinVar: central repository of interpretations for genetic variants (benign vs. pathogenic).

OBJECTIVES

1. **Develop an ETL workflow** for extraction, transformation, and loading of genomic and interpretation data from relevant sources.
2. **Evaluate variant distribution** across a healthy, diverse cohort (1000 Genomes).
3. **Estimate plausible penetrance ranges** for the ACMG recommendations.

PENETRANCE MODEL

$$Penetrance = P(D|V) = \frac{P(D) * P(V|D)}{P(V)} = \frac{(prevalence)(allelic\ heterogeneity)}{(allele\ frequency)}$$

where D = disease, V = any variant

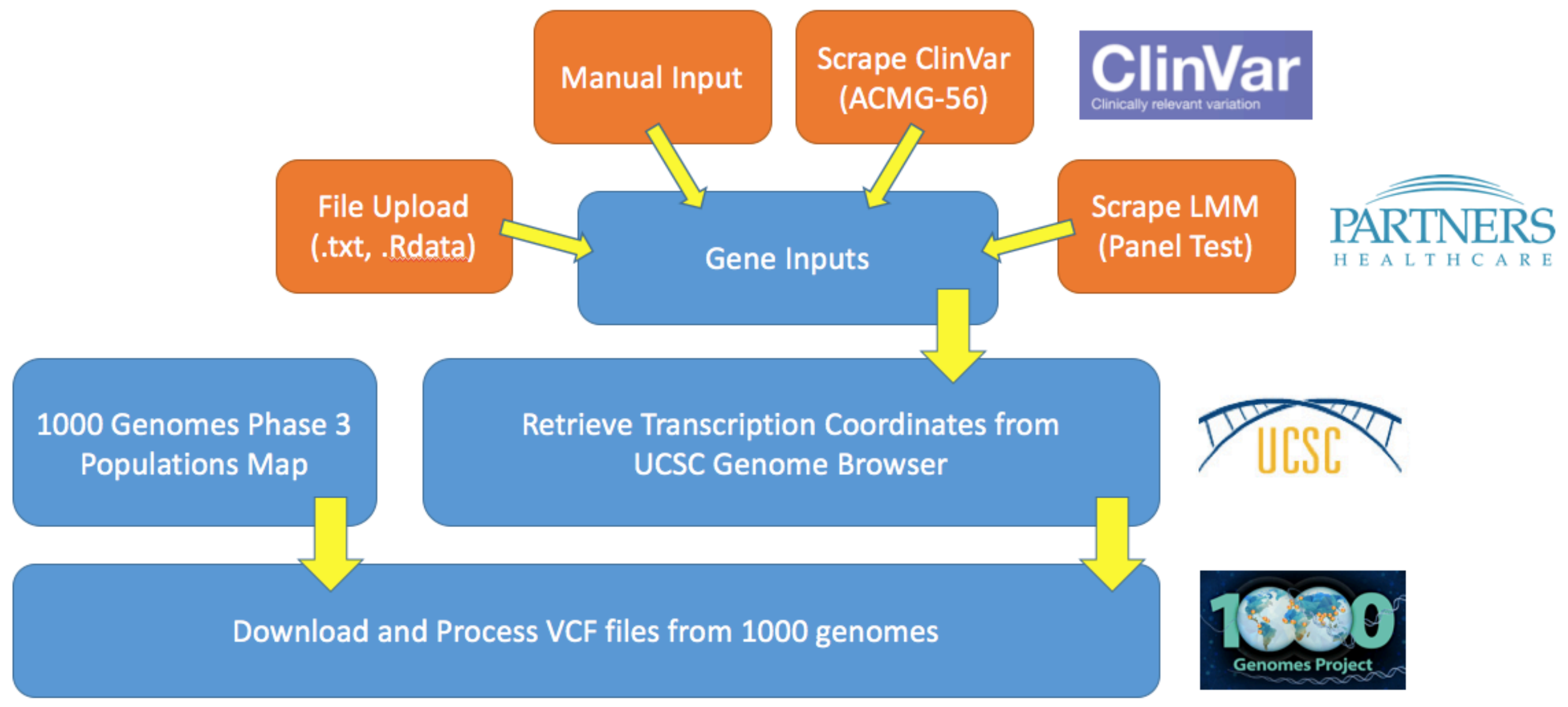
Penetrance:	Probability of developing disease, given a positive genetic test result.
Prevalence:	Proportion of general population with disease.
Allelic Heterogeneity:	Proportion of diseased population with a pathogenic variant.
Allele Frequency:	Proportion of general population with a pathogenic variant.

METHODS & WORKFLOW

ETL for Datasets

Pipeline + UI using R/Shiny/Markdown

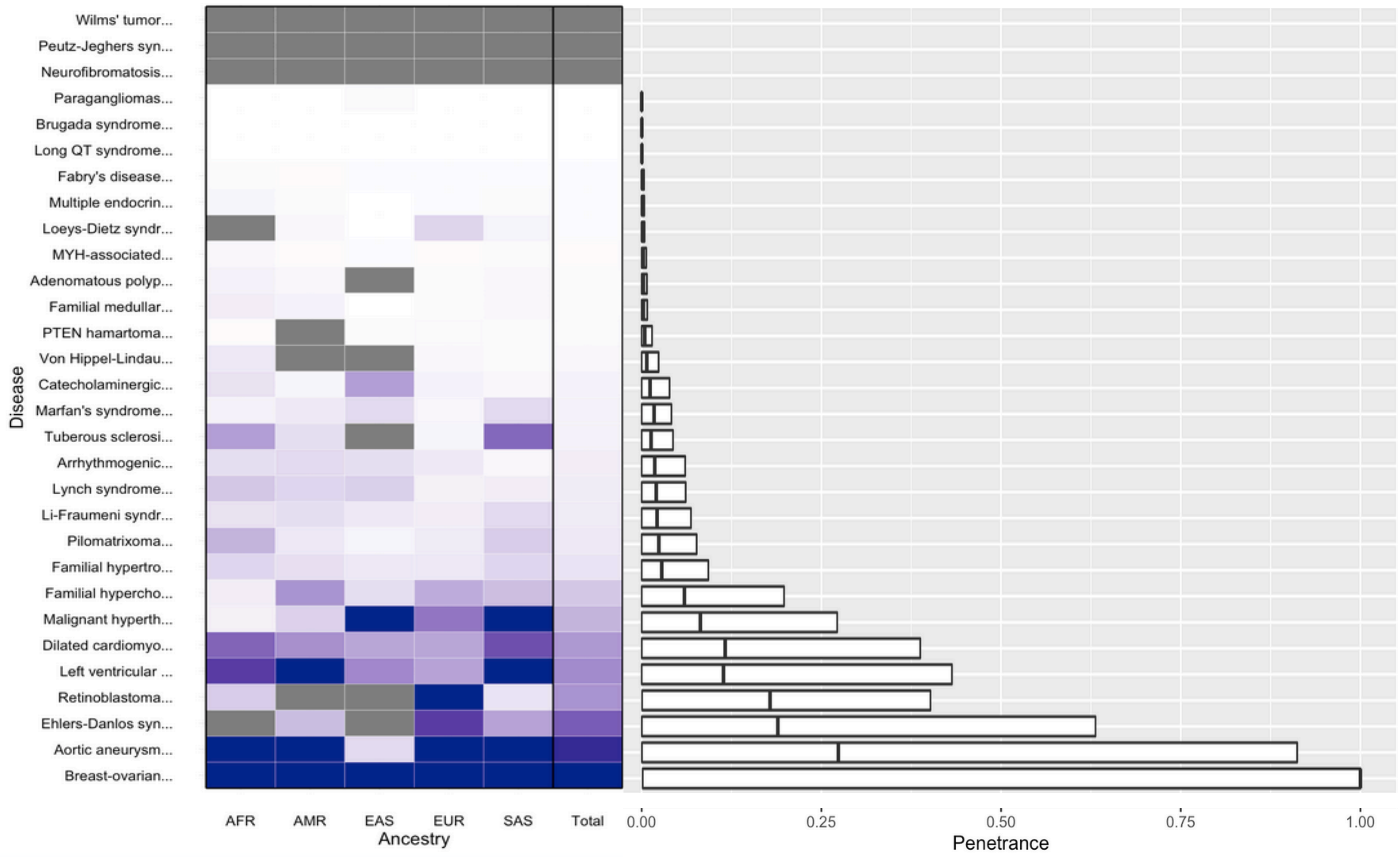
1. **Extract:** query UCSC Genome Browser for gene regions and retrieve corresponding VCF files from 1000 Genomes. Download ExAC manually from gene-level searches.
2. **Transform:** separate variants with multiple alternates; convert genotypes to allele counts, collect missense variants.
3. **Load:** Stage and merge final data objects.


Manual Input
Scrape ClinVar (ACMG-56)
File Upload (.txt, .Rdata)
Gene Inputs
Scrape LMM (Panel Test)
1000 Genomes Phase 3 Populations Map
Retrieve Transcription Coordinates from UCSC Genome Browser
Download and Process VCF files from 1000 genomes
ClinVar
Clinically relevant variation
PARTNERS HEALTHCARE
UCSC
1000 Genomes Project

https://github.com/jamesdiao/2016-paper-ACMG-penetrance

KEY FIGURES

Heatmap + Barplot: Penetrance Estimates are Low and Variable between Ancestral Groups



CONCLUSIONS

1. **High counts: 40-80%** of individuals have an incidental finding under ACMG guidelines, far higher than empirical disease prevalences.
2. **Clustered distribution:** by ethnicity – AFR (African) have the most findings, EAS (East Asian) have the fewest.
3. **High sensitivity:** findings dominated by a few high-frequency variants.
4. **Very low penetrance estimates:** Out of the 30 diseases (22 with data):
   (a) 20 have max theoretical penetrance **< 50%**
   (b) 12 have max theoretical penetrance **< 5%**
5. **High uncertainty around parameters:** translates into very large errors bars.

*-This is a preliminary "letter-of-the-law" evaluation and does **not** yet demonstrate real-world effects on patients.*

NEXT STEPS

1. **Identify questionable variants:**
   (a) high-frequency (common findings)
   (b) highly enriched in 1 ethnic population.
2. **Validation** with empirical penetrance values and other sequencing datasets (e.g. gnomAD).
3. **Model biases** in parameter estimates (prevalence, pathogenicity, etc.)
4. **Confer with clinical collaborators** to determine alternate protocols at Laboratory of Molecular Medicine and Partners HealthCare.

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