Research on testing phase:
what tests to recommend, how are they offered and what types of results are provided

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Types of tests in terms of intended use

- Test with a single specific purpose
  - Diagnostic ES/GS/Panels, Carrier screening, CDC Tier I, Single drug PGx, etc
- Opportunistic use of content from one test for a distinct purpose
  - Secondary findings return from exome/genome
- Broad tests intended for multiple uses (exome/genome)
  - Many virtual panels for distinct indications (symptom-based and screening)
  - May be used sequentially or in parallel

How do they differ in sensitivity and cost?

Under what context is each test type offered?

Uptake may relate to test complexity and length/complexity of consent process

- HBOC vs Cancer panel
- PGx panel vs Warfarin Test
- ES/GS with or without SF return – SF consent process has led to lack of testing

How can we reduce complexity of, and standardize, pre-test consent and ordering (CDS tools, etc)?

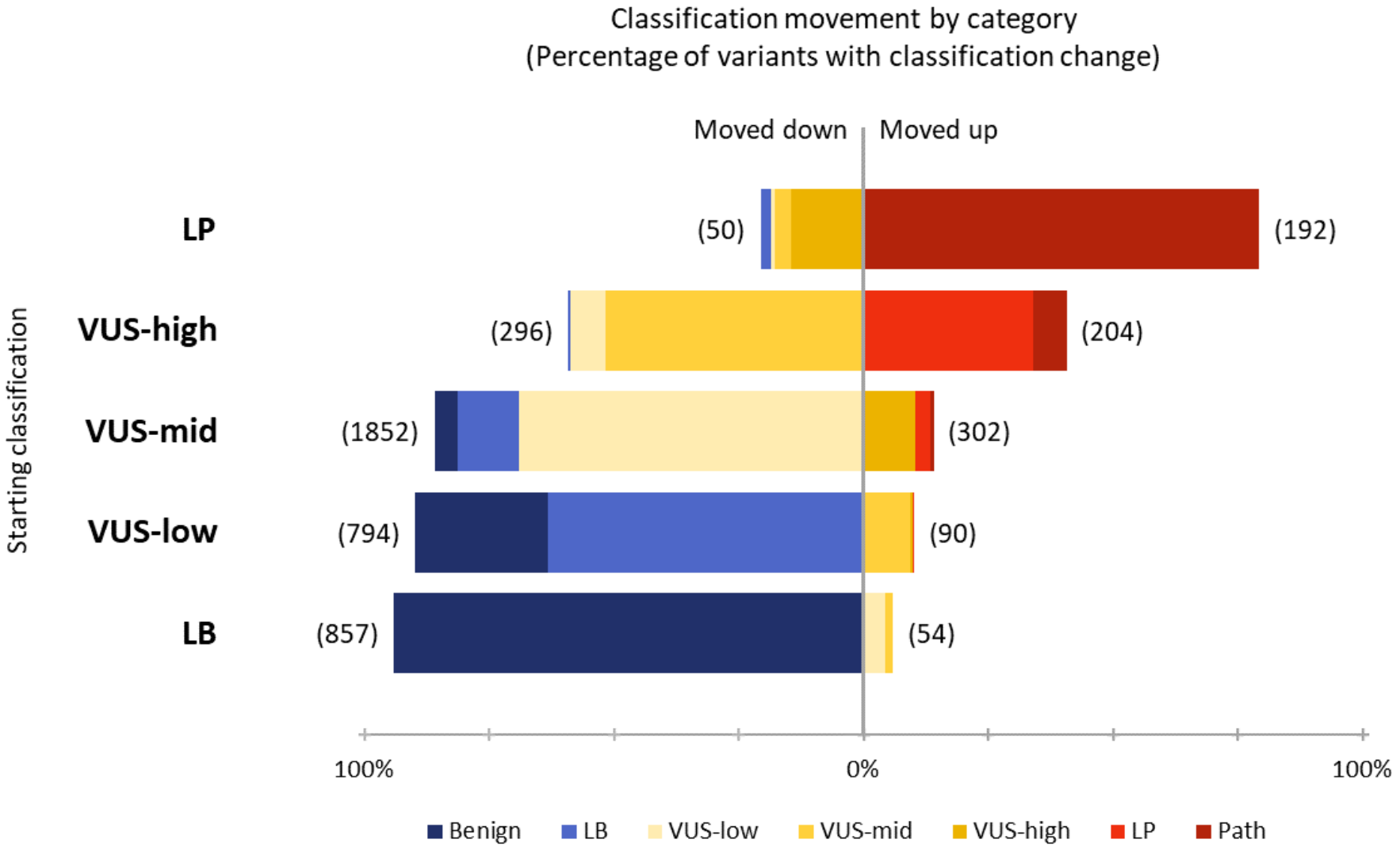
When is a genetic counselor or genetic counseling assistant needed? Can they be disconnected from clinic?

How can we most efficiently transmit phenotype and indications for testing?

What level of certainty is needed to return results?

- Today:
  - Symptomatic: VUS, LP, P variants returned
  - Screening/SF/IF: LP and P returned
- Most variation returned in germline clinical testing is rare or unique to a family
  - 75% of the >2 million variants in ClinVar have only a single lab submission
  - Returning only pathogenic has a negative impact on underrepresented populations
- Should we indicate the presence of a VUS on a screening report?
  - Reduce surprise to patients when VUS is reclassified as LP/P and updated report released
- In the next sequence variant classification guidelines, we will add VUS sub-tiers. How should these sub-tiers be used in reporting (include/not include VUS-low; push VUSs to supplements to reduce emphasis)?
- What is the best design of a genetic report to highlight what's important, suppress what's not and make it most usable?
- How do we support compound heterozygous cases in single variant centric systems?

VUS tiering correlates with reclassification



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Carrier screening complexity

- ACMG carrier screening standards indicate that only P/LP variants should be reported except that VUSs should be reported if in a gene for which the partner has a P/LP variant

- Most carrier screening happens during pregnancy with mother getting tested first – does not allow maternal VUSs to be reported if in genes with paternal P/LP result

- Need to develop approaches to support preconception “couple-based” carrier screening
  - Partners may change requiring the need to go back to primary data and change what is reported

How do we make test results most useful and understandable?

- Define the value of EHR integration for improving utility of genetic testing
- Labs cannot provide care recommendations specific to a patient yet physicians want explicit directions
- Are there models to pair lab reports with physician consultation?
- What clinical decision support tools could be developed to guide decision-making after a test result?
    - Different guidance by confidence in variant evidence (e.g. VUS vs LP vs P)
    - Different guidance by confidence in causality – correlation of gene with patient's phenotype
    - Different guidance based on patient choices (e.g. perceptions of risk, importance of outcomes)

Supporting a gLHS

- How should patients be consented for genetic testing to ensure the most robust learning from the data?
  - ClinVar submission – classifications – no consent required
  - Case level data sharing – genotype and phenotype – consent required
    - Phenotype sits in healthcare system
    - Genotype sits in external reference lab
  - Need flow of data into a G2P repository
    - Define phenotypes of rare diseases
      - Example: DECIPHER
    - Create a variant-level data source for query (e.g. federated variant level matching)
      - GA4GH Beacon v2, VLM Project
  - Consent to share data with family members
- How can physicians or patients provide data back to the lab when follow-up evidence is generated, without burdening the healthcare system?
  - Results of clinical tests (e.g. enzyme testing, imaging, metabolic, etc)
  - Results of segregation testing (need phenotype of family members)
- Need to study, develop and align genomic data and knowledge standards.

Genome Reanalysis and Reuse

- What type of infrastructure is needed to most effectively support reanalysis and reuse of existing data?
- What if data was generated from one lab but secondary use/reanalysis happened in another lab/clinic?
  - Need universal quality metrics to determine when data is analytically valid versus requires orthogonal confirmation
- What results can be used directly from a genome (e.g. PGx variants queried upon drug ordering) versus requires professional interpretation (e.g. new symptoms)
- How long is an exome or genome useful before technical advances indicate running a new test?
- How do we ensure ongoing contact/communication with patients when knowledge changes, given the changes in connection to healthcare systems?