Curation and Classification of Inherited Disease Variants in a High-throughput Clinical-Grade Genetic Screening Laboratory Environment

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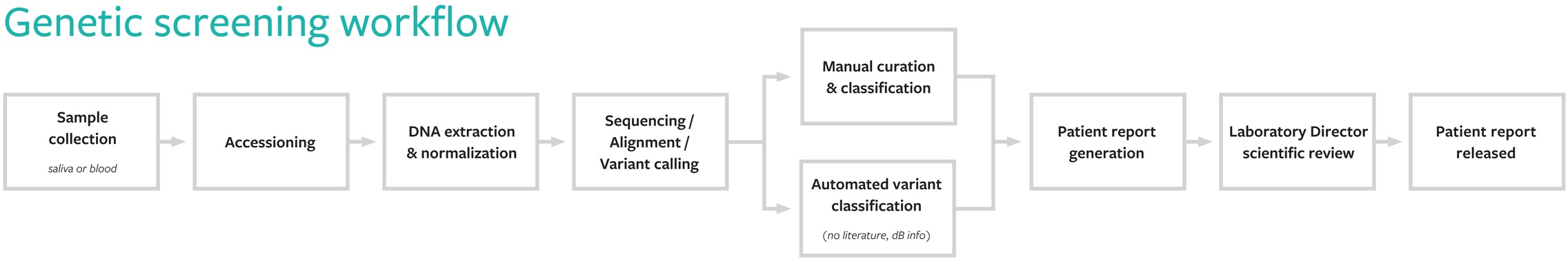
Abstract

Counsyl is a technology-driven clinical laboratory that offers clinically comprehensive, affordable, and high quality genetic screening and genetic counseling services. Our physician-prescribed genetic screens provide vital information on a panel of >100 rare autosomal recessive diseases, as well as determining risk for inherited breast, ovarian and prostate cancer. Counsyl has a robust system of variant interpretation and classification utilizing customized software analysis that gathers information from multiple sources including: patient data (case reports, and patient databases), population data, molecular functional data, mutational co-occurrence, protein structural analysis, conservation, in-silico predictors, and internal data. All variants are reviewed by a team of genetic counselors and PhD-level scientists, as well as our laboratory directors before the patient report is released. Manual curation of case reports and molecular functional data plays an important role in variant classification at Counsyl. To enable correlations between variants and disease phenotype, the following details are curated from case reports for each variant: Patient inclusion/exclusion criteria, variant allele frequency among unrelated patients and controls, patient zygosity/genotype, patient diagnosis/phenotype, ethnicity, gender, age of disease onset, and disease severity. Similarly, the following parameters are recorded from molecular functional studies for each variant: Experimental system, effect of variant on protein/mRNA expression, splicing, protein activity, intracellular localization, folding/processing and post-translational modifications.

Additional details

- Approximately 6% of variants require manual curation for classification.
- Variants are recurated (and reclassified as needed) on an periodic basis to ensure that the latest published evidence is included.
- Over 6000 variants have been expert curated/classified according to ACMG guidelines.
- Variant classifications (and supporting evidence) are submitted to the ClinVar public database as part of the "Free the Data" initiative to enable sharing of clinically relevant data and to allow for peer review of classifications.

Genetic screening workflow



Curation workflow