

# CDC/ClinGen collaboration results in a significant new genetic variant resource

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The Centers for Disease Control and Prevention's (CDC) Genetic Testing Reference Material Program (GeT-RM) has partnered with the Clinical Genome Resource (ClinGen) to develop a publicly available list of 546 expert curated pathogenic variants in 84 genes for use in next-generation sequencing (NGS) genetic testing. This list serves as a knowledge resource for designing comprehensive analytical validation

studies and creating computer-modulated or simulated reference materials for clinical genomic test development by defining variants that are either major contributors to disease or difficult to detect. Their work is presented in the *Journal of Molecular Diagnostics*.

Genetic testing has evolved from interrogating small sets of known pathogenetic variants in one or a few genes to examining hundreds or thousands of genes simultaneously using NGS. For these large assays, it is logistically difficult (and often impossible) to obtain genomic DNA reference materials containing the full scope of variants and variant types needed to perform a comprehensive validation study.

It can be challenging for laboratories to maintain the expert knowledge to identify representative variants appropriate for inclusion in validation studies to assure analytic and clinical validity. In addition, a comprehensive validation study using traditional reference materials can be costly. The new expert curated variant list will help address these complexities. This is important because well designed and validated clinical assays can provide accurate and reliable results to patients, enabling accurate diagnoses and appropriate treatment decisions.

"I am very excited that we are able to catalyze this important novel approach. It will remove a critical bottleneck for test developers and may help harmonize test development and validation across laboratories," said co-lead investigator Birgit Funke, Ph.D., Division of Genomic Health, Sema4, Stamford, CT, U.S..

ClinGen Variant Expert panels were asked to nominate clinically important variants in the genes they cover. Each expert panel was asked to nominate roughly 10 variants per disease area, including pathogenic variants that are the largest contributors to the disease as well as variants that may represent potential analytic challenges to laboratories. Overall, 546 unique variants were identified in 84 genes. The nominated variants

cause a wide range of diseases, many of which are commonly tested by NGS, including heritable cancers, inborn metabolic errors, cardiomyopathy, diabetes, and immune disorders.

The ClinGen Allele Registry was used to standardize nomenclature for all nominated variants, and ClinVar Variation IDs and associated disorders were added where available. The Food and Drug Administration (FDA) has recognized ClinGen's curation process and its resulting classifications as a regulatory-grade variant database. The curated variants are available via the National Center for Biotechnology's (NCBI) ClinVar database and ClinGen's Evidence Repository.

"ClinGen is excited to have formed this partnership with the CDC to expand the GeT-RM project with expert-curated content," said Heidi Rehm, Ph.D., Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge; and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, U.S..

The FDA and professional societies including the Association for Molecular Pathology and the College of American Pathologists have begun to acknowledge the challenges of large assays and have responded with guidance that permits the use of in silico (computer modeled or simulated) reference materials to supplement clinical test validation and operation. These in silico resources are truly scalable and can be tailored to meet the needs for any gene panel size including whole exome/whole genome approaches, which are increasingly implemented in the clinic.

"The [genetic testing](#) community has been very supportive of this effort, and we have started a pilot project to demonstrate how the curated variants identified as part of this project could be used to create reference materials by in silico mutagenesis of NGS sequencing files," noted co-lead investigator Lisa Kalman, Ph.D., Informatics and Data Science Branch, Division of Laboratory Systems, CDC, Atlanta, GA,

U.S.. "The pilot will examine whether the added variants can be detected by the clinical laboratories that generated the NGS files and demonstrate a general process that labs can use to develop electronic [reference materials](#) to fit their own needs."

GeT-RM and ClinGen will continue to collaborate to add to the current [variant](#) list and invite input from the genetics community about the list and the processes used to generate it. Visit the Expert Curated Variant List for Clinical Genomic Test Development and Validation: A ClinGen and GeT-RM Collaborative Project at <https://www.clinicalgenome.org/tools/get-rm-collaborative>.

**More information:** Emma Wilcox et al, Creation of an Expert Curated Variant List for Clinical Genomic Test Development and Validation, *The Journal of Molecular Diagnostics* (2021). [DOI: 10.1016/j.jmoldx.2021.07.018](https://doi.org/10.1016/j.jmoldx.2021.07.018)

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