

Introduction

An increasing number of diagnostic laboratories have begun offering gene panels to assess hereditary cancer risk, yet the genes most frequently analyzed have varying degrees of evidence of disease causality. Even among genes associated with well described hereditary cancer syndromes, there remain large numbers of conflicting variant assertions and variants of uncertain significance deposited in ClinVar.

The Hereditary Cancer Clinical Domain Working Group, part of the Clinical Genome Resource (ClinGen), is focusing efforts on gene and variant curation to help patients and clinicians better understand genetic results. On a variant level, our goal is to create expert panels to perform high-level reviews of variants associated with disease, and decrease the number of variants of uncertain significance and conflicting variant assertions in ClinVar.

We performed a needs assessment analysis to prioritize genes to focus gene and variant curation efforts.

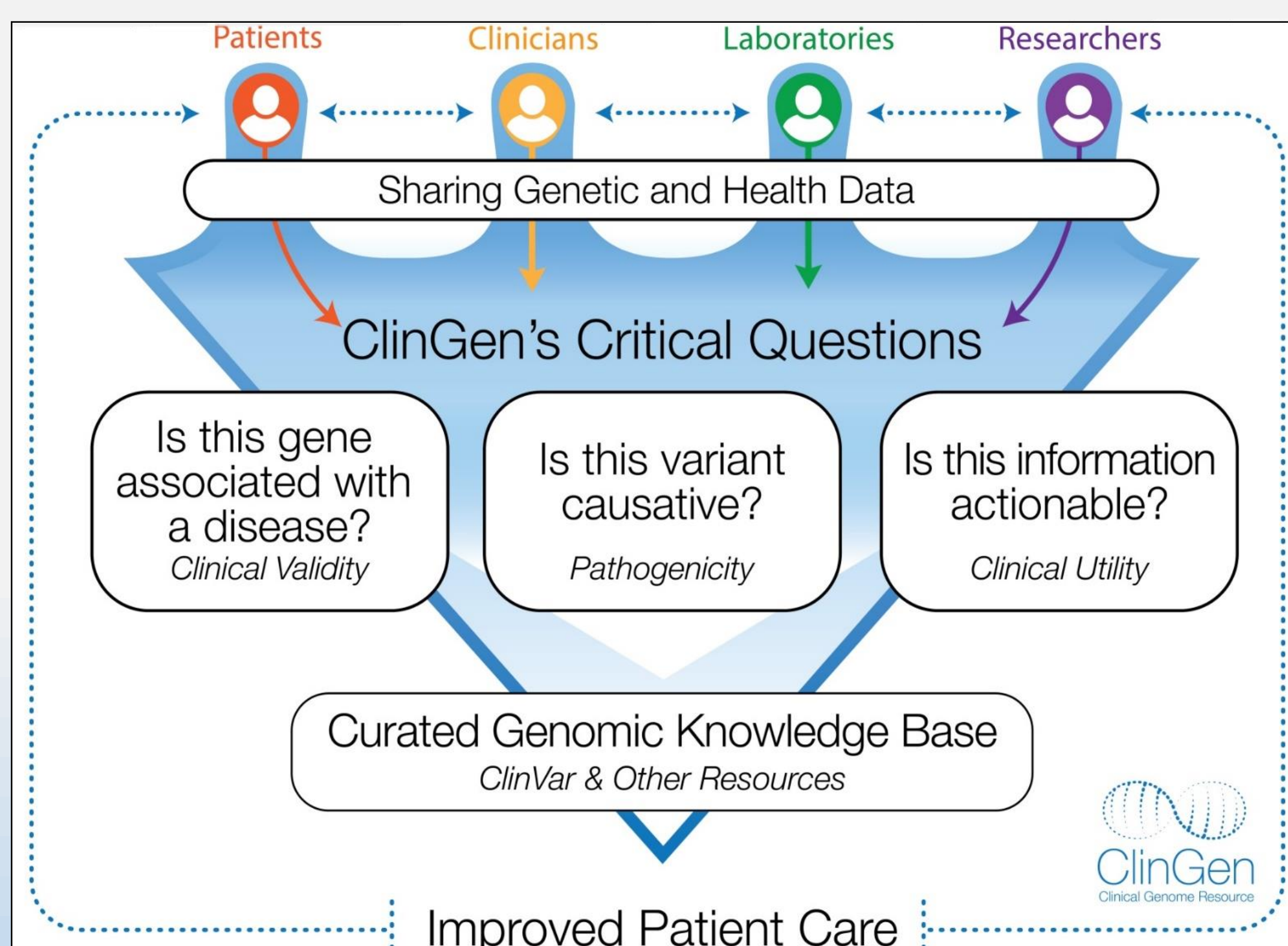


Figure 1- ClinGen seeks to build an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

Methods

Seven large diagnostic laboratories were surveyed to determine the most frequently tested genes on hereditary cancer panels.

We collected the following information for each gene:

- (1) Any known ongoing variant curation effort (i.e. – *BRCA1* & *BRCA2* and ENIGMA).
- (2) Highest estimated cancer risk in literature.
- (3) Number of conflicting variants in ClinVar.
- (4) Number of variants of uncertain significance (VUS) in ClinVar.
- (5) Whether the gene is included on the list of 56 genes recommended for incidental findings by the ACMG.

Figure 2- Genes Most Frequently Analyzed on Hereditary Cancer Panels

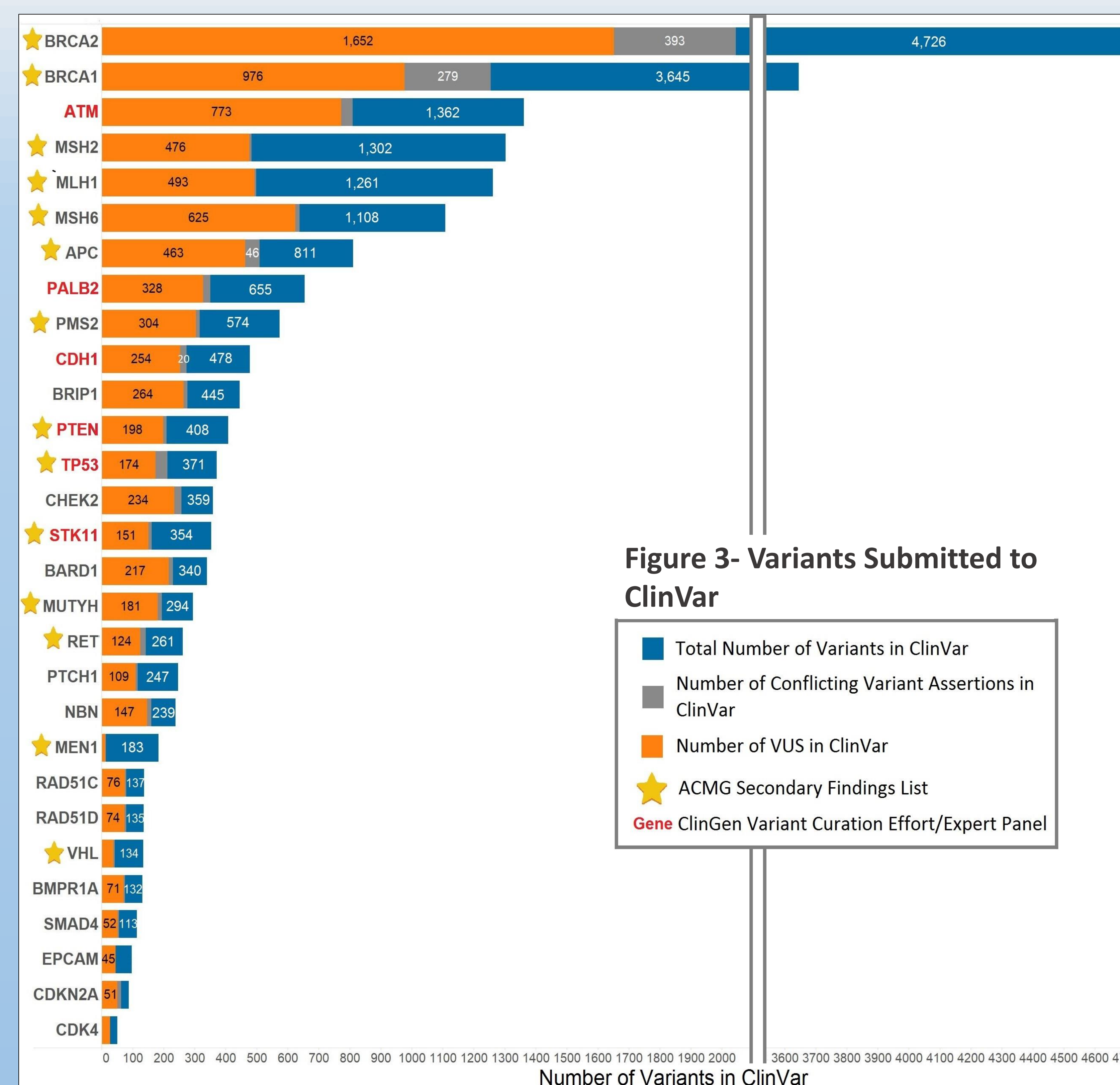
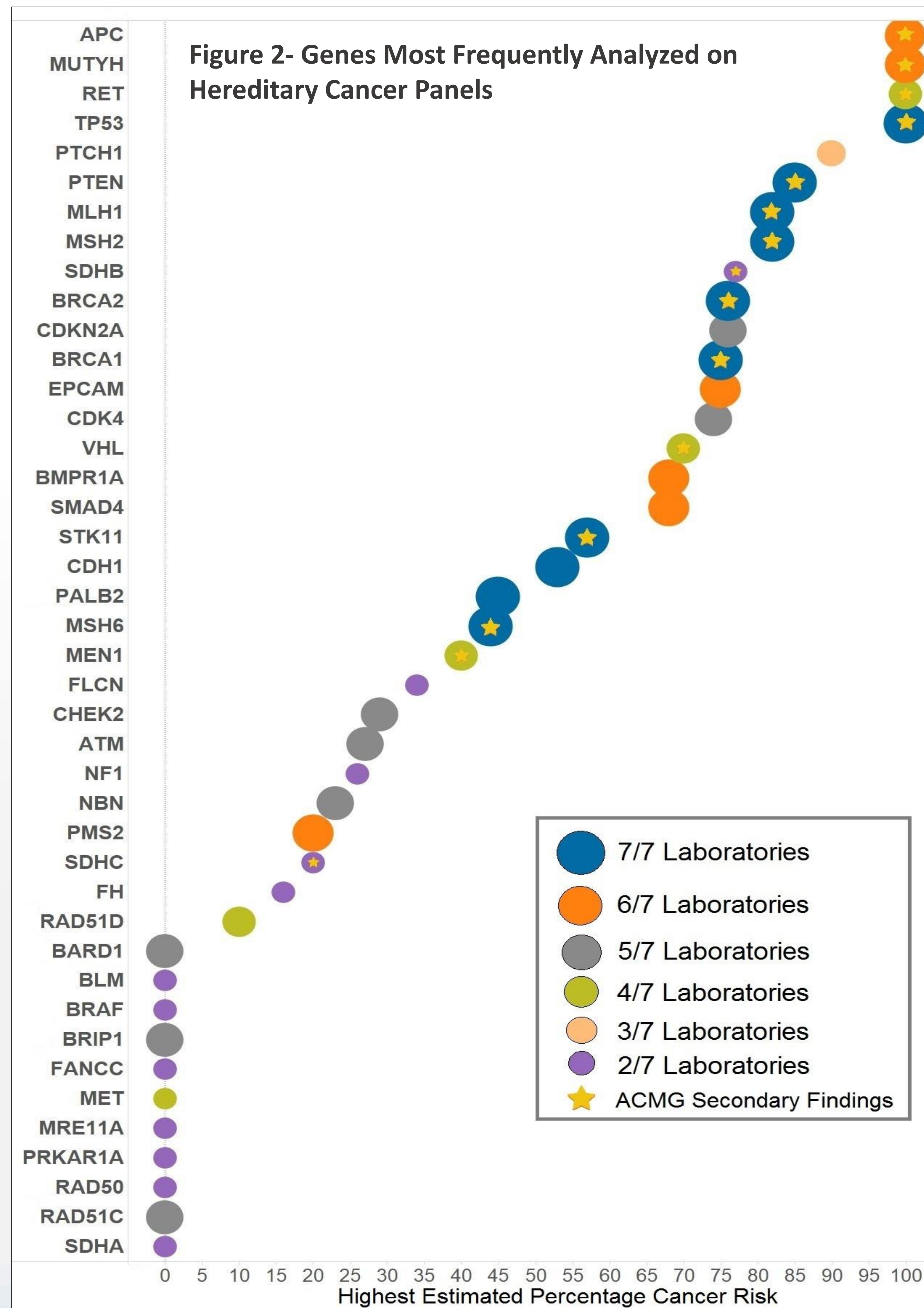


Figure 3- Variants Submitted to ClinVar

Results

Genes analyzed by most laboratories were associated with increased breast and/or ovarian cancer risk, Lynch syndrome and polyposis colon cancer; such as *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PTEN*, *STK11*, and *TP53*. Figure 2 illustrates the numbers of laboratories who offer testing for each gene, along with that genes' estimated cancer risk when an individual harbors a pathogenic variant.

Figure 2- Genes most frequently analyzed on hereditary cancer panels. Highlighted in blue are well known cancer-susceptibility genes. Marked with a star are the genes in the ACMG list of secondary findings.

Even among well-known genes with well-described hereditary cancer syndromes, there remain large numbers of VUS and conflicting assertions in ClinVar (Figure 3).

Discussion

Consistent with this prioritization, we have developed international panels of experts to begin variant curation for the *PTEN*, *TP53*, and *CDH1* genes using the ACMG/AMP variant classification guidelines as a framework. Additionally, we have established partnerships with the existing curation efforts of ENIGMA and InSiGHT working groups, who have now been approved as ClinVar Expert panels.

This assessment will allow us to focus on genes that are commonly offered on hereditary cancer panels and have large numbers of variants that are currently difficult to classify, making genetic testing less informative for patients and their providers. We have also initiated gene curation efforts for breast, ovarian and colorectal cancer to systematically define the level of evidence for disease association.

We plan to continue to develop additional expert panel working groups based on results from this needs assessment.

Figure 3- Total number of variants submitted to ClinVar (Blue) with conflicting assertions (Grey) and number of VUS (Orange) per gene. Genes highlighted in red have been prioritized to create Expert Panels tasked to start variant classification.

Acknowledgements

We would like to thank the ClinGen Hereditary Cancer Clinical Domain Working Group members. This work is supported by funding from the National Institutes of Health (5U01HG007537-01).