Sources of agreement and disagreement among variant classifications in ClinVar: Critical factors for clinicians

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Background and methods

Controversy has existed regarding the consistency of variant classifications both within and outside of ClinVar. Recently published studies have come to very different conclusions on this topic. For example:

- Vail *et al*. [1] reported high **discordance** among *BRCA1* and *BRCA2* variant classifications in various public databases, suggesting that these resources should be "precluded from clinical use." Similarly Gradishar *et al*. [2] compared public data against one lab's proprietary classifications and came to a similar conclusion.
- However, our recent systematic analysis of ClinVar [3] showed high **concordance** among *BRCA1* and *BRCA2* classifications, as did a prospective clinical study [4].
- Balmaña *et al*. [5] found high **discordance** in non-*BRCA1/2* cancer genes, whereas…
- Maxwell *et al*. [6] found high **concordance** in these genes. Re-analysis of the ClinVar data for Balmaña's variants [7] also shows high **concordance.**
- Van Driest *et al*. [8] found high **discordance** in arrhythmia genes, although the specific data they used may have been over-classified, inconsistent with the **ACMG guidelines.** [9]
- Finally, although Amendola *et al.* [10], Garber *et al.* [11], and Harrison *et al.* [12] found classification **discordances** in various genes, they also found that the sharing of information among laboratories, facilitated by ClinVar, led to far greater **concordance** even in difficult classification situations.

We performed a systematic analysis of data in ClinVar both to better understand the nature of agreement and disagreement among submitters, and to understand factors that could lead to the differing conclusions in these various studies.

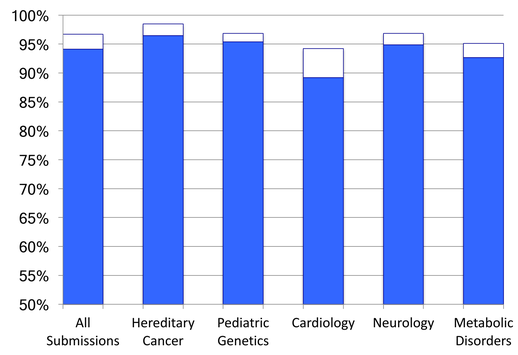
Methods: We compared ClinVar classifications on a **clinical actionability** basis, i.e. whether the variant would (if pathogenic or likely pathogenic) or would not (VUS, likely benign or benign) suggest a change in care for a patient. We further examined variants for which there was **majority consensus** (at least 2/3 submitters in agreement) but not complete agreement, and we cataloged properties of the **outlier** interpretations.

We repeated these analyses on a **pathogenicity** basis, where VUS was considered distinct from likely benign or benign in the comparison (see [13] for these results).

Concordance by clinical area

Variant classifications in ClinVar are highly concordant: 96.7% of variants reach consensus and 94.1% have complete agreement when considering all genes and submitters together. Concordance varies significantly by clinical area, with hereditary cancer and pediatric genes the most concordant, cardiology the least, and neurology and metabolic disease in between. Considering only the subset of hereditary cancer genes listed in the NCCN guidelines, 98.8% of variants achieved consensus (see [13]).

Figure 1
Fraction of variants that reach **complete agreement** (filled bars) or **majority consensus** (2/3 agreement, white bars) on a clinical actionability basis. Note that the Y-axis starts at 50% concordance.



Sources of discordance in ClinVar

Classifications from **non-clinical lab sources** are **6-fold** more likely to be outliers compared to **clinical lab submissions**. In hereditary cancer genes listed in the NCCN guidelines, non-clinical classifications are **16-fold more likely** to be outliers.

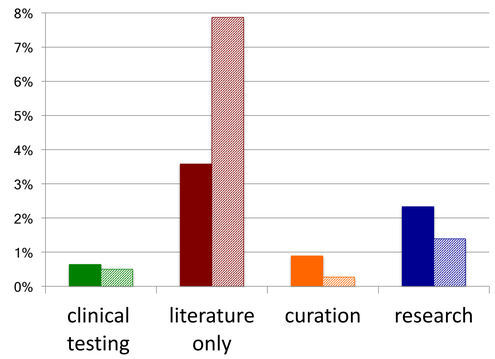
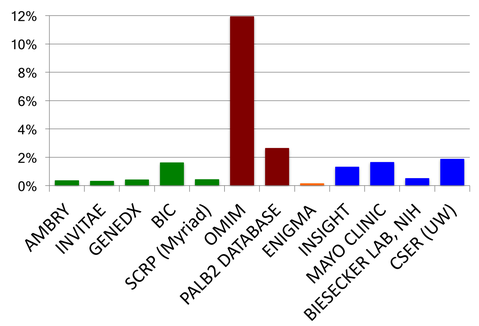


Figure 2a
Chance of a variant classification being an **outlier**, i.e. disagreeing with the consensus. Solid bars include all genes in ClinVar, hatched bars include only 23 hereditary cancer genes listed in the NCCN guidelines. The submission types (X-axis) are provided to ClinVar by each submitter.

Figure 2b
Chance of a variant classification being an outlier for the largest submitters in each category shown in Figure 2a. Color coding by submission type is the same as in Figure 2a. Only the left five bars are tagged as "clinical testing".



Old classifications are up to 5-fold more likely to be outliers compared to recent ones.

Also **Low penetrance** variants are often discordant: only 78.2% reach consensus and 49.2% complete agreement (see [13] for these results).

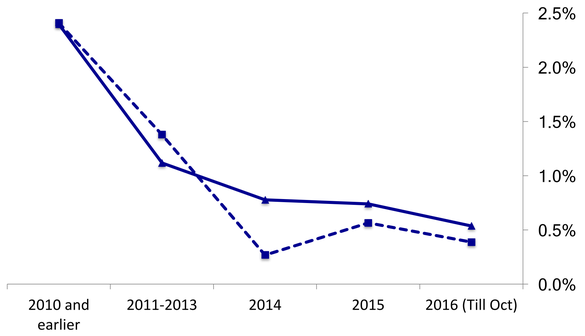


Figure 3
Chance of a variant classification being an outlier as a function of interpretation age. Solid line includes all of ClinVar, dotted line only the 23 hereditary cancer genes listed in the NCCN guidelines.

References: [1] Vail *et al., J Community Genet* 2015; [2] Gradishar *et al., The Oncologist* 2017; [3] Lincoln *et al., JCO Precision Oncology* 2017; [4] Lincoln *et al., J Mol Diag* 2015; [5] Balmaña *et al., J Clin Oncol* 2016; [6] Maxwell *et al., AJHG* 2016; [7] Nussbaum *et al., J Clin Oncol* 2017; [8] Van Driest *et al., JAMA* 2016; [9] Biesecker *et al., JAMA* 2016; [10] Amendola *et al., AJHG* 2016; [11] Garber *et al., AJHG* 2016; [12] Harrison *et al., Genet Med* in press. Data shown here are from [3] and from [13] Yang *et al. Genet Med* 2017.

BRCA1/2

In this data set, the only clinically actionability differences among established clinical laboratories are in rare variants carried by very few patients. P**er-patient concordance** (**99.8%**) and **per-variant concordance** (**98.5%**) thus differ by more than an order or magnitude [3].

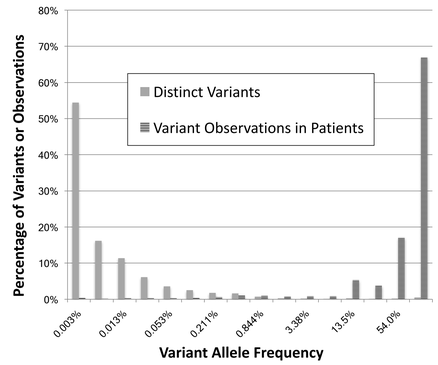
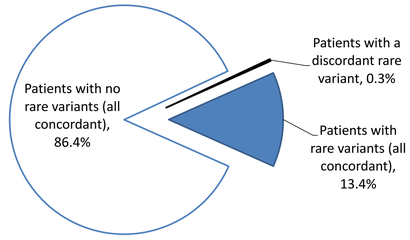


Figure 4
Percentage of ClinVar variants by population allele frequency in ExAC (grey bars) and prevalence in our clinical database (hatched bars). By either measure, most variants in ClinVar are rare, although the vast majority of variants observed in patients are repeated occurrences of a small number of relatively prevalent variants.

Figure 5
Summary of per-patient concordance. The only classification discordances were in the very rare variants, which (by definition) few patients carry. Nevertheless, most rare variants were completely concordant when observed by multiple laboratories.



Concordance on a per-patient basis is 99.7%. This increases to 99.8% when a small number of clear submission errors are fixed [3].

Best practices for ClinVar users

ClinVar is a valuable resource but users should consider all entries carefully:

- Classifications submitted by **non-clinical** sources are numerous and often disagree with the consensus classification from clinical laboratories. The largest sources of non-clinical classifications in ClinVar include OMIM and other databases (see Figure 2b).
- Similarly **old classifications** are likely to disagree with newer ones. Sources such as BIC provide many old classifications to ClinVar.
- **Low penetrance variants** are far more likely to have classification differences compared to high penetrance variants. One reason for this is the differing terminology used for such variants which is not always accommodated by ClinVar.
- Most variants in ClinVar are **very rare** and are observed in very few patients, despite their large numbers. Variants that are clinically prevalent are almost always concordant, compared to the rarest variants (when they are seen in more than one patient). Thus **per-variant** and **per-patient concordance rates** are very different.
- Published studies that show high discordance [1,2,5,8] ignore some or all of these factors and thus greatly overstate actual discordance among patients tested by clinical laboratories.