EVALUATION OF INTER-LABORATORY CONCORDANCE

Study	Description	Observed Concordance	Reasons for Inconsistency	Remarks
Amendola et al. Am J Hum Genet 2016	Comparison of concordance of 9 CSER-labs classifying 99 variants	**34% before** and **71% after** consensus discussion / only 5% of differences are clinically relevant	Correct use of several ACMG rules was not clear / challenging variants	training is necessary for consistent classification / underscores importance of not only having a standardized approach to variant assessment but also sharing variant interpretations for identifying and resolving discordance
Harrison et al. Genet Med 2017	ClinVar Laboratory comparison and consistency assessment	**83% initially concordant** **87% of discordant** variants **could be resolved**	ACMG rules not applied to ClinVar variants (53%) Internal data not published (33%) Differences in use/ weighting of data (14%)	Participating laboratories increased their overall concordance from 88.3 to 91.7%, sharing variant interpretations in ClinVar is critical to moving toward more consistent variant interpretations
Pepin et al. Genet Med 2016	Comparison and evaluation of consistent variant classifications (outside labs vs in house) in a distinct disease field (COLx)	**29% complete**, **29% „moderate“** **58% not actionable**	Lack of reference of the biology (48%) Lack of access to unpublished data (33%)	In diseases with a „special biology“ expert knowledge is important for accurate classification / unpublished data are a major source of inconsistent classification
Balmana et al. J Clin Oncol 2016	ClinVar study comparing variant classifications of 603 variants in non-BRCA cancer genes	**74% concordance** **11% clinically relevant**	many observed differences were because of variants in low-penetrance genes (RR<2)	Conflicting interpretation of genetic findings is frequent and may have implications for medical management decision
Yang et al. Genet Med 2017	ClinVar search of discordant actionable classifications, evaluation of reasons for inconsistencies	**96% major consensus** **94% complete consensus**	Non-clinical lab subm. Clinical areas differ Old data points Literature citations	Recent variant classifications from clinical testing laboratories have high overall concordance.

Are there really large inconsistencies in ClinVar ?

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Sources of discordance among germ-line variant classifications in ClinVar

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Purpose: ClinVar is increasingly used as a resource for both genetic variant interpretation and clinical practice. However, controversies exist regarding the consistency of classifications in ClinVar, and questions remain about how best to use these data. Our study systematically examined ClinVar to identify common sources of discordance and thus inform ongoing practices.

Methods: We analyzed variants that had multiple classifications in ClinVar, excluding benign polymorphisms. Classifications were categorized by potential actionability and pathogenicity. Consensus interpretations were calculated for each variant, and the properties of the discordant outlier classifications were summarized.

Results: Our study included 74,065 classifications of 27,224 unique variants in 1,713 genes. We found that (i) concordance rates differed among clinical areas and variant types; (ii) clinical testing methods had much higher concordance than basic literature curation and research efforts; (iii) older classifications had greater discordance than newer ones; and (iv) low-penetrance variants had particularly high discordance.

Conclusion: Recent variant classifications from clinical testing laboratories have high overall concordance in many (but not all) clinical areas. ClinVar can be a reliable resource supporting variant interpretation, quality assessment, and clinical practice when factors uncovered in this study are taken into account. Ongoing improvements to ClinVar may make it easier to use, particularly for nonexpert users.

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Key Words: clinical genetic testing; ClinVar; concordance; data sharing; variant interpretation

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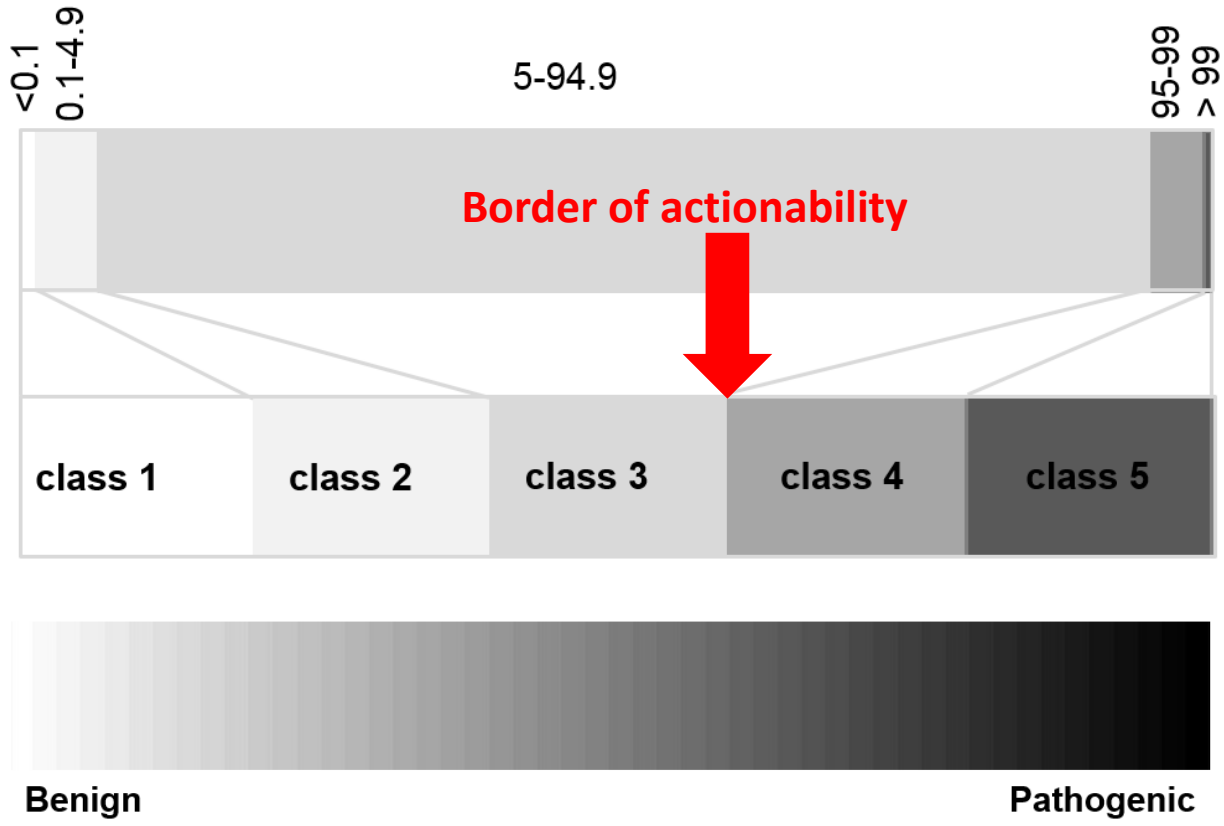

InSiGHT: posterior probability of pathogenicity derived by multifactorial likelihood analysis https://www.insight-group.org/

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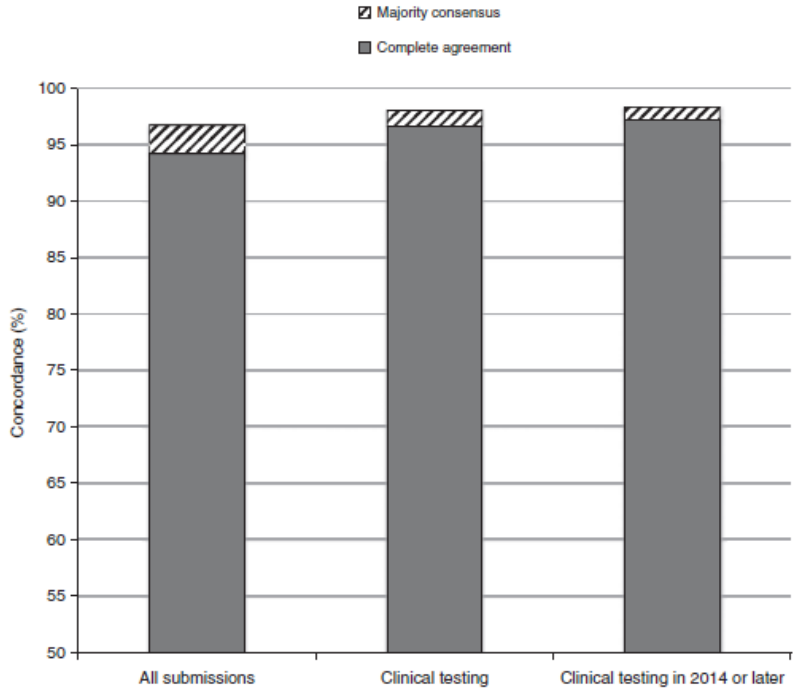

Figure 5 Concordance for ClinVar and subsets. Variant classification concordance measured as a fraction of variants for all of ClinVar and for subsets of ClinVar filtered by submission type and classification date. Concordance is calculated on an actionability basis (see text).

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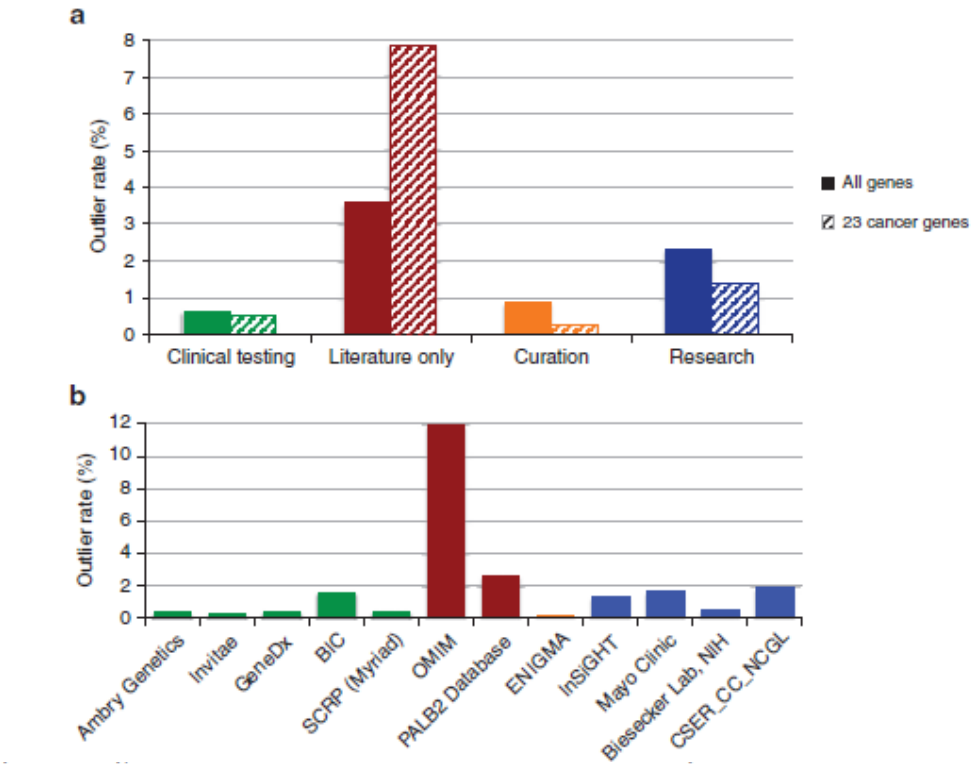

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