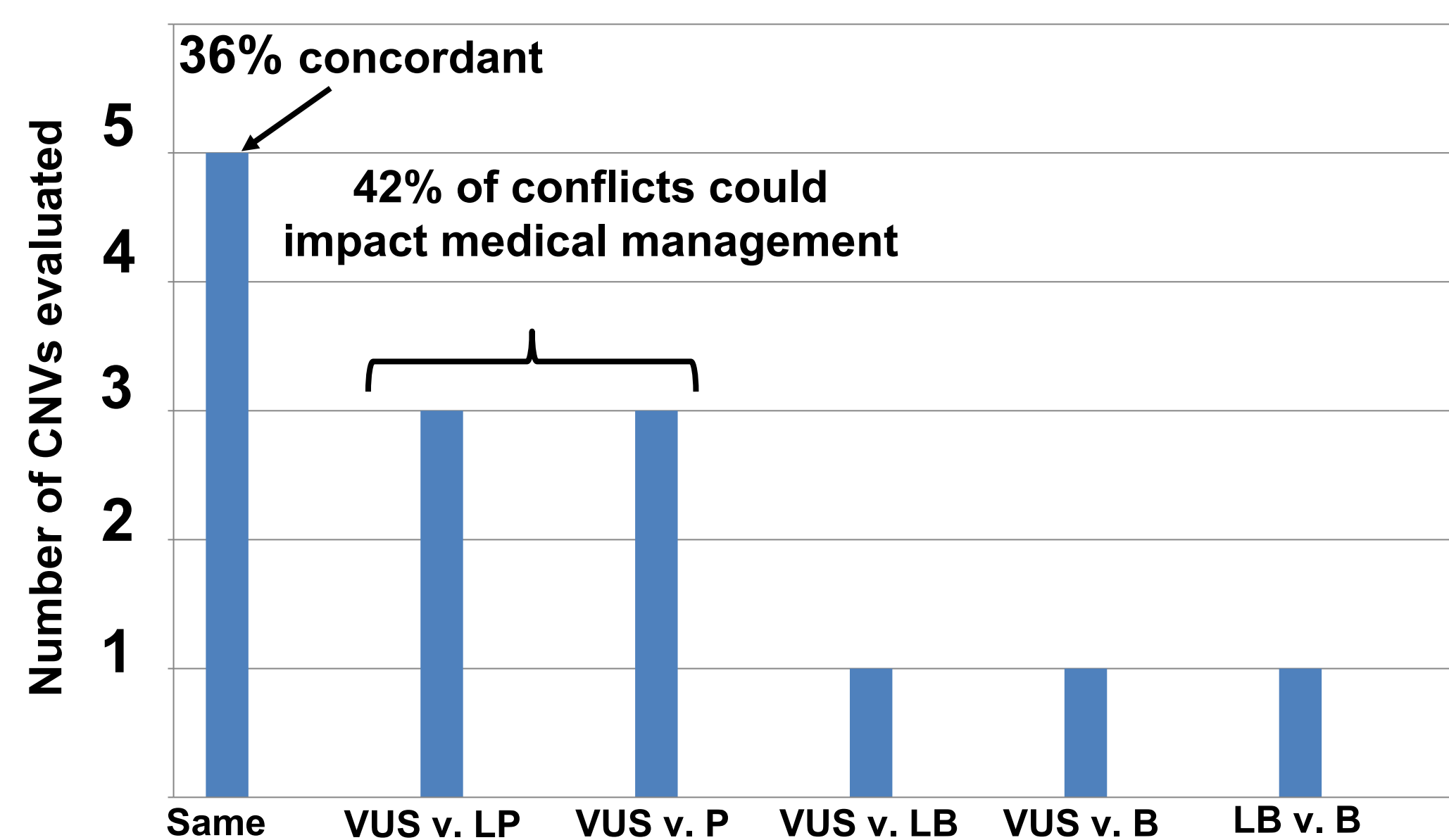


Introduction

Analysis of CNVs by chromosomal microarray analysis (CMA) is the first-tier genetic test in patients with neurodevelopmental disorders and/or multiple congenital anomalies. In addition, due to advancements in microarray and sequencing technologies, CNVs are now being analyzed at higher resolutions extending down to single-exon CNVs, extending their clinical scope to gene panels and whole exome sequencing.



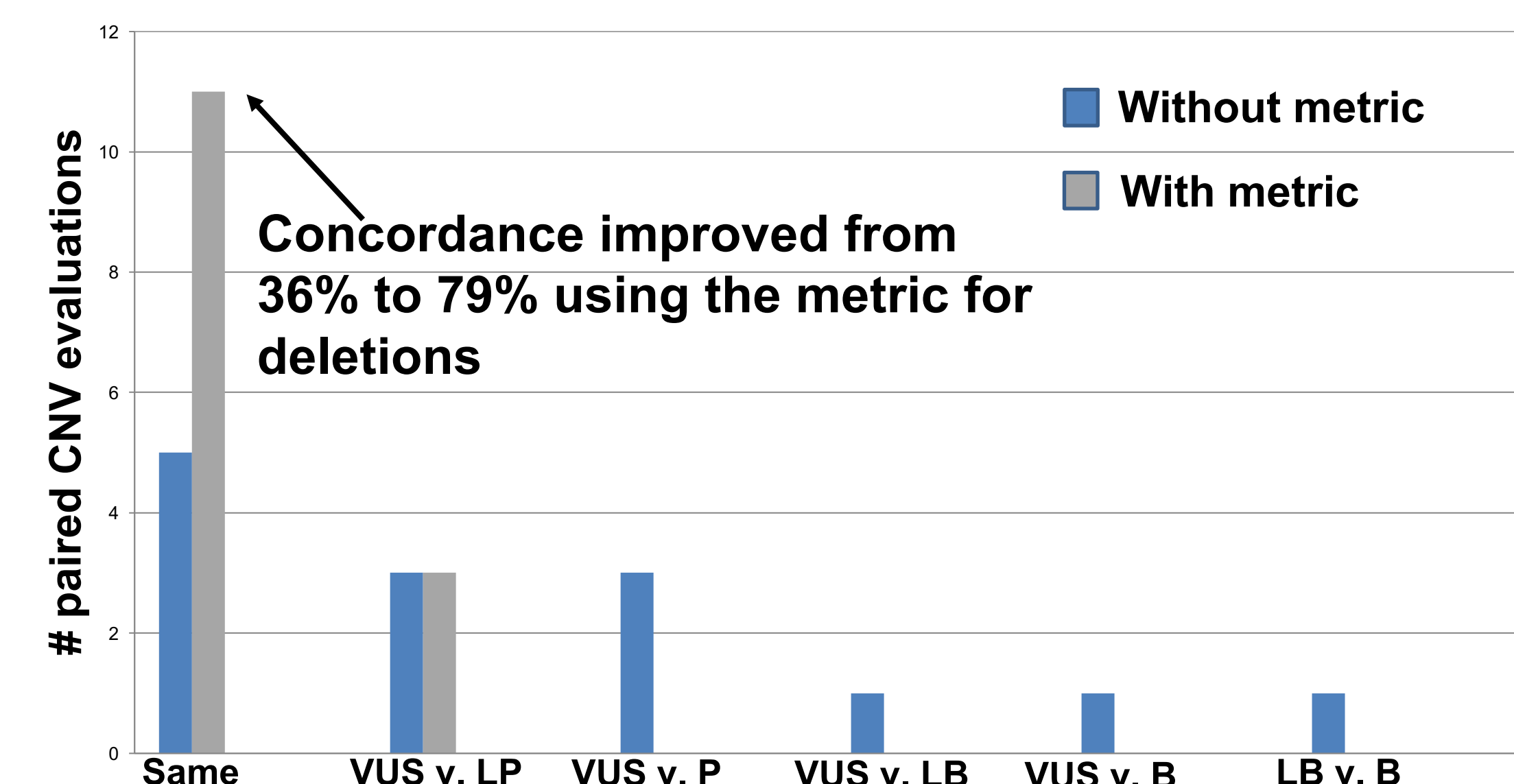
Despite the existence of CNV interpretation standards from ACMG and mounting experience from laboratories analyzing CNVs, inconsistencies in clinical interpretation persist due to differences weighing evidence used for classification.

In an effort to improve consistency, the ACMG and the Clinical Genome Resource (ClinGen) established a collaboration to update the existent CNV classification guidelines with a more standardized clinical classification framework.

Testing of the metric

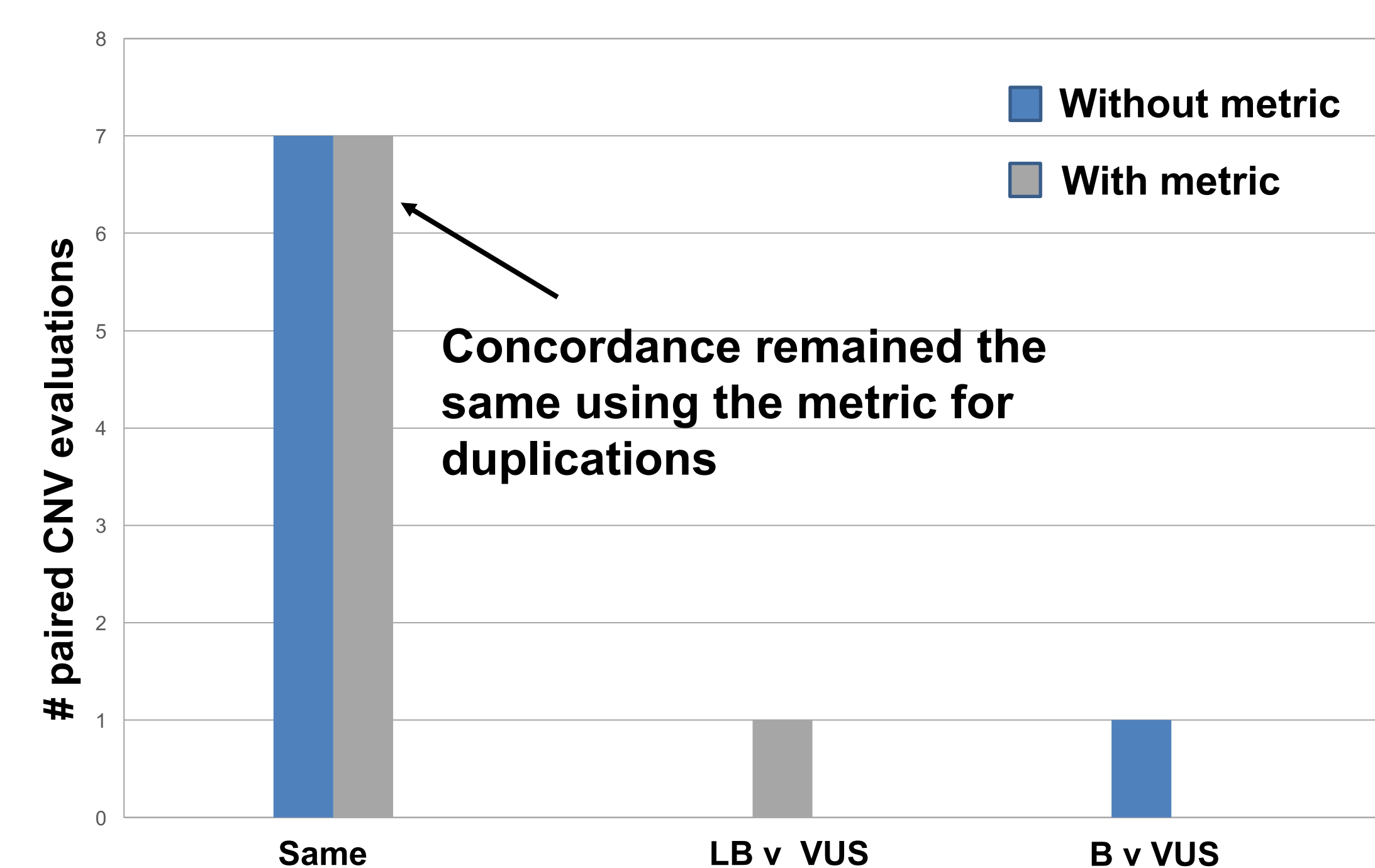
Thirty three (33) deletions and 28 duplications with defined clinical classifications from clinical laboratories were used to test the performance of the metric. All CNVs were evaluated independently by 2 geneticist. Fourteen (14) deletions and 8 duplications of the total of CNVs evaluated were also evaluated with the existing guidelines. Concordance between both rubrics was calculated.

Deletion metric



When the new rubric was used for evaluation of loss CNV, the concordance among reviewers significantly improved. Of the total number of evaluations (n=66), in 80%, the calculated clinical interpretation was deemed appropriate by an expert panel, 11% differed by a single-step classification difference (LP vs VUS or VUS vs LB), and 4% were confidence differences (P vs LP, LB vs B and vice versa).

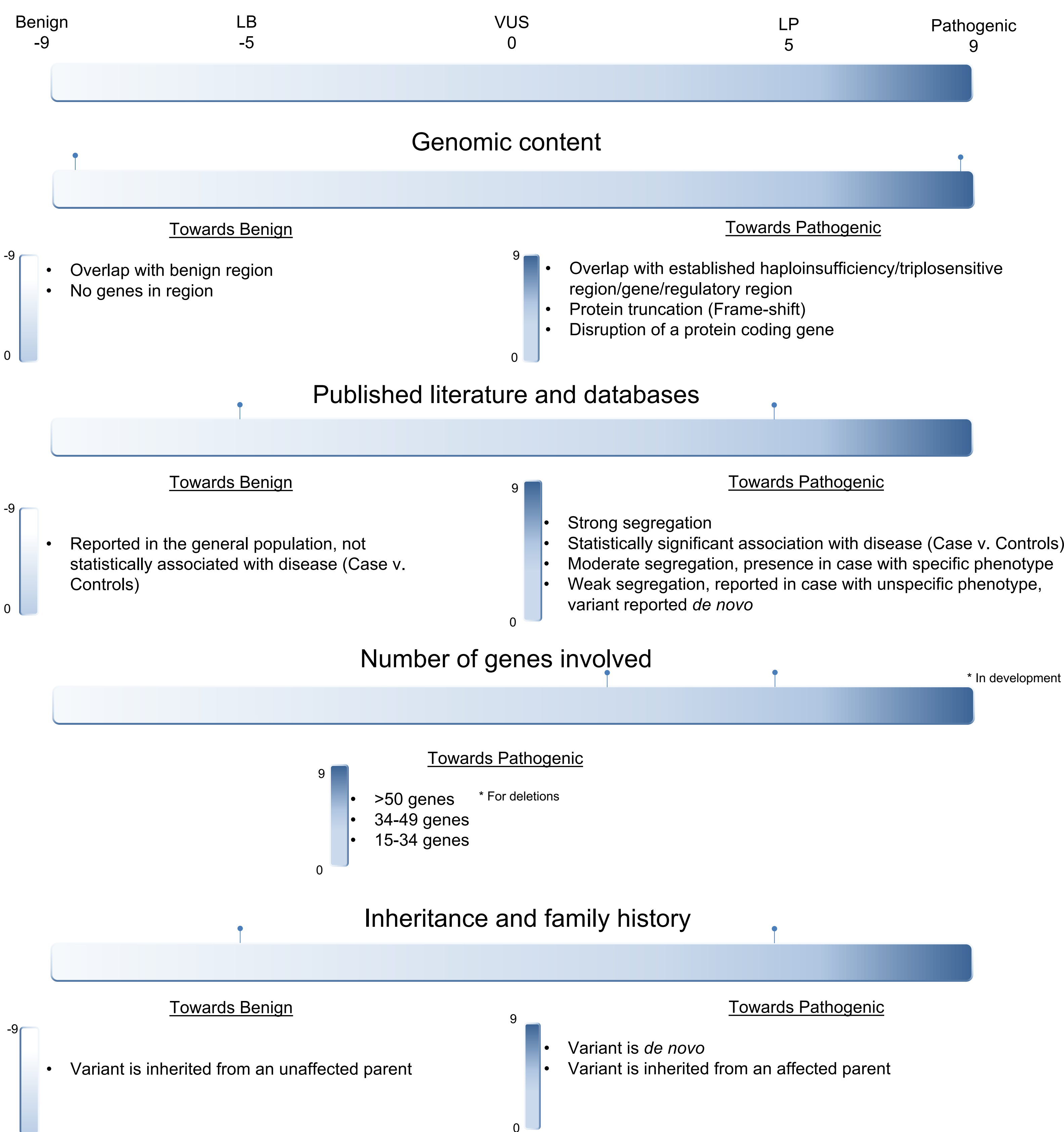
Duplication metric



Testing of the duplication metric is in progress. Preliminary data show that when the new rubric was used for evaluation of gain CNV, the concordance among reviewers was high, but did not improve. Of the total number of evaluations (n=62), in 90%, the calculated classification was deemed appropriate by an expert panel, and 8% differed by a single-step classification.

CNV clinical interpretation rubric

Point-based, hierarchical scoring system



Conclusion and future direction

- We devised a systematic framework for clinical interpretation of discrete CNV events, which is expected to have broad impact by providing a robust system to support the consistent interpretation across clinical laboratories.
- This rubric will be tested with a broader group of clinical laboratory geneticists to identify nuances and refine its guidance.

Disclaimers and funding

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- This work is in progress, and has not yet been reviewed or approved by the American College of Medical Genetics and Genomics' (ACMG) Board; ACMG has no formal or established position on the conclusions of this work at this time.