Utility of Adding Phenotypic Criteria Refinement to ACMG Guidelines

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Phenotype information is routinely used to determine the significance of rare variants identified through genetic testing. Although the ACMG guidelines for variant interpretation include PP4: “Patient’s phenotype or family history is highly specific for a disease with a single genetic etiology,” this guideline is vague and has been shown to be inconsistently applied (Amendola et al., 2016). To further build on the ACMG guidelines and address limitations, we developed a semiquantitative variant interpretation framework called Sherloc, which refines PP4 to systematically incorporate phenotype into variant interpretation. Within Sherloc, there are two evidence types that take into account phenotype and can be used in determining the pathogenicity of variants: case reports and pathognomonic criteria. Case reports indicate that an expected phenotype is present and that an individual is likely to receive a molecular diagnosis from genetic testing 25-75% of the time for the set of genes tested. Pathognomonic criteria can be applied if the phenotype is highly characteristic for a genetic disorder, and a molecular diagnostic yield of >75% is expected for the set of genes tested. In this study, we set out to evaluate the contribution of evidence from case reports or pathognomonic criteria to variant interpretation and the rate at which they supported a definitive molecular diagnosis. Concordance and discordance were assessed between classifications made using three approaches: the ACMG guidelines, Sherloc with case report criteria only (Case Only), and Sherloc with case report and

pathognomonic criteria (Computed). A total of 1,505 unique variants within 187 genes with established pathognomonic criteria had pathognomonic evidence applied during the original interpretation process and were re-interpreted for this study using the ACMG guidelines, Case Only criteria, and Computed criteria. When compared to the ACMG classification, Case Only and Computed criteria lowered the percentage of variants classified as a variant of uncertain significance (from 54% to 20%) or likely pathogenic (from 20% to 13%) while increasing the percentage of pathogenic classifications (from 26% to 67%). Moreover, 34% of the unique variants had a clinically significant upgrade with the potential to impact patient care when compared to the classifications based on the ACMG guidelines alone. Overall, these observations indicate that careful curation of case reports and pathognomonic criteria can provide useful evidence to support more informed variant interpretation and reduce uncertainty.