Title: Specification of frequency criteria for secondary findings genes to improve classification concordance

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ACMG policy recommends that secondary findings (SF) from clinical sequencing be offered to individuals. Toward standardizing this process, the ACMG Secondary Findings Working Group curates a list of genes for variant return, v3.2 contains 81 genes. In 2015, the ACMG/AMP put forward criteria for classifying the pathogenicity of variants applicable to mendelian disease. Prior work has shown discordance in variant classification amongst laboratories using these classification criteria. To increase concordance, ClinGen is providing additional guidance through the Sequence Variant Interpretation group and Variant Curation Expert Panels (VCEPs). However, 57 genes suggested for SF return do not currently have published specified criteria. Having specified criteria for SF genes is important as laboratories are expected to classify variants in these genes for SF return whether or not they have specialized expertise in the gene. Classification concordance could be increased by providing basic specified criteria. Our goal is to provide thresholds for BA1 (stand-alone benign) and BS1 (allele frequency greater than expected for disorder) along with guidance for application of PVS1 (loss of function) prior to VCEP criteria publication. The Whiffin-Ware calculator was used to define BA1 (wBA1) with disease frequency, gene contribution and penetrance values identified from the literature. It is reasonable, for genes without a VCEP, to define a more stringent BA1 (sBA1) at ten times the wBA1 value. We have compared calculated wBA1 and sBA1 values with popmax filtering allele frequencies (FAF) of the most common pathogenic/likely pathogenic (P/LP) variants in gnomAD v4.1.0. P/LP variants were defined as variants with a ClinVar classification of P/LP or novel loss of function variants in the MANE transcript for genes with evidence supporting haploinsufficiency. For 15 genes without published VCEP BA1 values, the popmax FAF of the most common P/LP variant was higher than the calculated wBA1, none were higher than the calculated sBA1. For BS1, we suggest using a value three times wBA1 (sBS1) when published VCEP criteria are not available. Four genes, BTD, CACNA1S, RET, and TTR, had a known P/LP variant with a popmax FAF higher than the calculated sBS1. One additional gene, SDHAF2, had a novel LoF variant with a FAF higher than the calculated sBS1. For PVS1, we have used the ClinGen dosage sensitivity data and variant information from HGMD and ClinVar to determine if loss of function variants

contribute to disease. Specification of basic criteria should allow for improved classification concordance for the return of secondary findings.