**Box 1 Genomics England tiering overview and assignment of all RIPD alleles (*n*=25) to Tiers by PanelApp.**

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|  | Number of RIPD alleles in Tier |
| **Tier 1**: Should be clinically assessed by GMCs. Includes high impact variants (e.g. likely loss-of function) and *de novo* moderate impact variants (e.g. missense) within a curated list of Green genes available through PanelApp with sufficient evidence associating them with the patient’s phenotype(s). | 1a |
| **Tier 2**: Should be clinically assessed by GMCs. Includes moderate impact variants (e.g. missense) within a curated list of Green genes available through PanelApp with sufficient evidence associating them with the patient’s phenotype(s). | 1a |
| **Tier 3**: It is not expected that GMCs will review all of the variants in Tier 3. For plausible candidate variants identified in genes *outside* of known disease gene panel(s), caution should be used during clinical assessment and interpretation. Includes high and moderate impact variants outside of the curated list of genes that are associated with the patient’s phenotype(s). Although most Tier 3 variants will *not* be pathogenic, sometimes the causal variant will lie within Tier 3. This could occur because there is insufficient evidence to support the inclusion of the gene within the relevant panel(s) at the time of analysis, or because the relevant panel was not applied. | 12 |
| **Tier A**: CNV calls identified by Canvas, >10 kb size and with a call quality score >10, overlapping with a diagnostic-grade gene in a panel applied to the patient. | 1 |
| **Tier null/untiered**: All variants not belonging to one of the categories above. | 10b |

aThe biallelic variants in *MAN2B1* comprised one classified as Tier 1 and one as Tier 2.

bBoth *MEGF8* alleles were untiered.