Reduced Risk *BRCA1* and *BRCA2* variants: Insight into Classification of Concordant Variants Between Two Commercial Laboratories

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Introduction: The identification and reporting of reduced risk *BRCA1* and *BRCA2* (RR-*BRCA*) variants is complex and poses challenges for patient counseling. We sought to compile and compare data for RR-*BRCA* variants reported by two clinical diagnostic laboratories.

Methods: A list of RR-*BRCA* variants provided by two laboratories were compared for concordant interpretations. Rationale and data supporting a reduced-risk interpretation were compiled, including unpublished functional and clinical data (where available), and publicly available information including population-, predictive-, and functional data.

Results: Laboratories had different but complementary approaches in identifying RR-*BRCA* variants. Considerations included 1) the identification of biallelic Fanconi Anemia-affected patients; 2) variant type; 3) incomplete aberrant splicing; 4) identification of NMD-escaping, in-frame splice events; 5) laboratory-validated cancer history weighting models; 6) published reduced risk data; and 7) extrapolation of a reduced-risk interpretation onto close match variants that are expected to have the same effect. A total of 30 variants were listed by the two laboratories as RR-*BRCA* and 13 variants overlapped both laboratories' lists. For *BRCA1,* variants included c.5096G>A (p.R1699Q) and variants impacting the canonical c.671 splice acceptor site. For *BRCA2,* variants included three frameshift (c.658_658delGT, c.9672dupA, c.9699_9702delTATG); two spliceogenic (c.8488-1G>A and c.8488-1G>T); and two missense [c.7878G>C (p.W2626C), c.9302T>G (p.L3101R) variants.

Conclusions: Despite differences in interpretation strategies across two laboratories, consistent results were obtained for 13 RR-*BRCA* variants providing evidence for a less severe phenotype. As such, these variants may require less stringent management strategies compared to traditional pathogenic *BRCA* variants depending on individual and family history. Further work to define risk thresholds and categories for reporting RR-*BRCA* variants will be of great clinical value to personalize cancer risks in conjunction with other clinical and genetic risk factors, including polygenic risk scores. Opportunities to harmonize variant interpretation and standardized reporting will be of great benefit for patients and care teams.