POLD1 and *POLE*: preliminary data from a laboratory-based multi-gene panel testing cohort

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Background
Putative pathogenic mutations in two candidate cancer predisposition genes, *POLD1* and *POLE*, have been identified in high-risk colorectal cancer (CRC) and polyposis families. Available clinical and co-segregation data primarily supports *POLD1* and *POLE* as causative of a dominantly-inherited, highly-penetrant colorectal phenotype; however, associations with extra-colonic tumors have been suggested. The majority of publications to date have focused specifically on amino acid substitutions impacting highly-conserved residues within the proofreading exonuclease domains of *POLD1* and *POLE*, while only rare reports of loss-of-function/null (LOF) alleles exist.

Methods
Beginning on May 18th, 2015 comprehensive analyses of *POLD1* and *POLE* were included in three of the clinically-available next generation sequencing multi-gene assays offered though our diagnostic laboratory. Retrospective data review yielded molecular and clinical details for individuals with identified *POLD1* and *POLE* alterations.

Results
At the time of submission, more than 1,700 individuals had undergone multi-gene panel testing including *POLD1* and *POLE*. The recurrent *POLD1* p.S478N and *POLE* p.L424V mutations were not detected in the patients analyzed; however, other rare amino-acid substitutions impacting highly-conserved residues within the exonuclease domains were detected in 6 individuals (0.35%). One of these 6 probands reported a personal and family history of early-onset (<50y) CRC significant enough to satisfy Amsterdam I criteria and did not carry a detectable CRC risk allele in any other gene analyzed. In addition, LOF alleles were identified in 4 cases (2 *POLD1*, 2 *POLE*, 0.25% combined). Of the probands carrying a LOF allele, none had a reported personal or family history including early-onset CRC or polyps.

Conclusions
Our data indicate that the highly-penetrant *POLD1* p.S478N and *POLE* p.L424V CRC and polyp risk alleles are rare in a laboratory-based cohort, while some cases of familial CRC/polyps may be explained by other variants within the exonuclease domains. Available clinical data for the limited number of LOF allele-positive families does not support association with the currently accepted *POLD1*- and *POLE*-associated phenotype. Our data support the hypothesis that LOF alleles in these genes do not confer the same cancer risk as functionally-relevant missense mutations, likely due to a mechanistic difference in pathogenicity compared to classic tumor suppressor genes. Continued investigation of *POLD1* and *POLE* findings will further clarify the associated phenotypic spectra, penetrance, and mutation detection rate in clinical cohorts. [Updated data to be presented]