Cancer risks associated with monoallelic MUTYH and NTHL1 pathogenic variants
Background

• Biallelic pathogenic variants (PVs) in MUTYH and NTHL1 are associated with adenomatous polyposis and increased risks for colorectal cancer (CRC); however, the spectrum of cancer risks for monoallelic carriers are not established.

• Limited evidence suggests an increased CRC risk for monoallelic MUTYH carriers and recent tumor signature data suggests a possible mild breast cancer risk for monoallelic NTHL1 carriers.

• We analyzed a large commercial laboratory dataset to assess cancer risks for carriers of monoallelic PVs in MUTYH and NTHL1.
Methods

• Results of individuals undergoing clinical analysis of MUTYH between 09/2013 and 05/2020 and NTHL1 between 03/2019 and 05/2020 as part of a multi-gene hereditary cancer gene panel were reviewed.

• Individuals with biallelic MUTYH or NTHL1 PVs, or PVs in hereditary cancer genes other than MUTYH and NTHL1 were excluded.

• Risks were estimated using multivariate logistic regression adjusting for multiple risk and ascertainment factors, including family history of cancer.

• Clinical information was obtained from the provider-completed test request form.

• Findings are reported as odds ratios (OR) with 95% confidence intervals (CI).
**Results**

A total of 14,459 individuals with a monoallelic \textit{MUTYH} PV and 625 individuals with a monoallelic \textit{NTHL1} PV were identified, of which, 486 (78\%) carried the \textit{NTHL1} p.Gln90* founder mutation.

Monoallelic \textit{MUTYH} PVs were associated with an increased risk for CRC [OR 1.24, 95\% CI 1.11-1.38] over non-carriers.

There was no evidence of increased risk for colon polyps or other cancers for \textit{MUTYH} heterozygotes.

There was no evidence of increased risk for CRC, colon polyps, breast or other cancers for carriers of monoallelic PVs in \textit{NTHL1} or the \textit{NTHL1} founder mutation.
Conclusions

• We confirmed that monoallelic MUTYH PVs are associated with a modestly increased risk for CRC.
  • Further studies to understand the clinical impact of this modest increase in CRC may be beneficial to help inform CRC screening guidelines.
• We found no significant cancer associations for monoallelic NTHL1 PV carriers in this sample, suggesting that increased cancer screening may not be warranted based on current evidence.