Germline Pathogenic/Likely Pathogenic variants identified in all UNCseq™ patients

Germline findings across all UNCseq™ patients

Cancer Type (Subtype) Cases (% of Total) Hereditary cancer susceptibility genes evaluated

Colorectal 53 (12.1%) MLH1, MSH2, MSH6, APC, PTEN, SMAD4, STK11

Ovarian 29 (6.6%) BRCA1, BRCA2, MRE11A, TP53, MSH6, CHEK2

Breast (Ductal, Lobular, Other) 114 (26.0%) BRCA1, BRCA2, ATM, CHEK2, CDH1, MRE11A, PTEN, STK11

Musculoskeletal 41 (9.3%) TP53

Lung (Non-small cell, Small cell, Other) 31 (7.1%) TP53

Kidney 30 (6.6%) VHL, MET

Brain/CNS (Astrocytoma, Glioma, Oligodendroglioma, Other) 54 (12.3%) NF1, NF2, TSC1, TSC2, TP53

Skin (Melanoma, Non-melanoma, Other) 29 (8.9%) CDKN2A, PTCH1

Hematologic (ALL, AML, CLL, Other) 29 (6.6%) RUNX1, CEBPA, TP53

Pancreas 29 (4.3%) BRCA1, BRCA2, CDKN2A, ATM, TP53

Total 439

Other hereditary cancer genes ATRX, ATM, BCL1, CDH3, CDKN1B, ESR1, MEN1, PTCH1, PHD3, RB1, RET, SMARC A4, SMARC B1, WT1

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The percentages of patients with Pathogenic variants (light shading) or Variants of Uncertain Significance (VUS, dark shading) in genes relevant to the tumor type are depicted as stacked bar graphs. Numbers above the bars represent the sample size for the specific tumor type. Numbers in parentheses represent the number of patients with Variants of Uncertain Significance or Pathogenic variants. Here, Pathogenic variants include both Likely Pathogenic (LP) and Known Pathogenic (KP) variants. In both the ovarian and breast cancer groups, one patient in each group had a Variant of Uncertain Significance and a Pathogenic variant.

Discussion

- While 19 (4.3%) patients had pathogenic findings, ~2% of them were previously undetected, supporting germline analysis to provide critical information for both patients and their families, and enabling potentially lifesaving interventions.
- When tumor-germline sequencing is performed for prognostic or therapeutic implications, only Known Pathogenic or Likely Pathogenic germline findings should be reported to patients per the recommendations of the American College of Medical Genetics and Genomics.
- With Variants of Uncertain Significance existing in almost half (41.2%) of the patients, returning such results to patients would produce a significant clinical burden, and may result in potentially unnecessary surveillance, testing, or procedures for the patient and family members erroneously presumed to be "at risk”.

Acknowledgments

We wish to thank members of the Lineberger Comprehensive Cancer Center for support of the work. We also wish to thank the University Cancer Research Fund and National Institutes of Health grant U54 HG006487 for financial support of the project. This work has been submitted to the Journal of Clinical Oncology for publication.