Germline Analysis from Tumor-Germline Sequencing Dyads to Identify Clinically Actionable Secondary Findings

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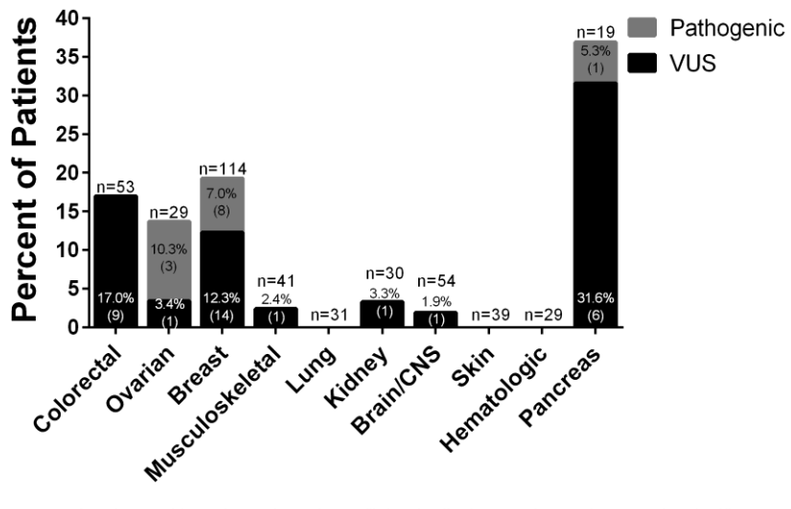
Abstract

PURPOSE: To evaluate germline variants in hereditary cancer susceptibility genes among unselected cancer patients undergoing tumor sequencing.
PATIENTS AND METHODS: Germline sequence data from 439 individuals undergoing tumor-germline dyad sequencing through the LCCC1108/UNCseq™ (NCT01457196) study were analyzed for genetic variants in 37 hereditary cancer susceptibility genes. Patients were unselected with respect to indicators of hereditary cancer predisposition.
RESULTS: Known Pathogenic or Likely Pathogenic variants indicative of a hereditary cancer predisposition were identified in 19 (4.3%) patients. For about half (10/19), these findings represent new diagnostic information with potentially important implications for the patient and their family. For the others, however, their hereditary cancer variants were previously identified through clinical genetic evaluation secondary to suspicion of a hereditary cancer predisposition. Genes with pathogenic variants included *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, and *CHEK2*. In contrast, a substantial proportion of patients (181, 41.2%) had Variants of Uncertain Significance (VUS), 24 of which had VUS in genes pertinent to the presenting cancer. Another 146 had VUS in other hereditary cancer genes, and 11 had VUS in both pertinent and non-pertinent genes.
CONCLUSION: Germline analysis in tumor-germline sequencing dyads will occasionally reveal pathogenic or likely pathogenic variants that were clinically occult. Return of these diagnostic findings could be beneficial for patients and their families. However, given the low yield for unexpected pathogenic germline variation and the large proportion of patients with VUS results, the evaluation and reporting of germline variants should be informed by established guidelines for incidental/secondary findings. Otherwise, the analysis and return of germline results could present an immense clinical burden with little net benefit. Hence, only Known Pathogenic or Likely Pathogenic variants would be returned to patients per the recommendations of the American College of Medical Genetics and Genomics.

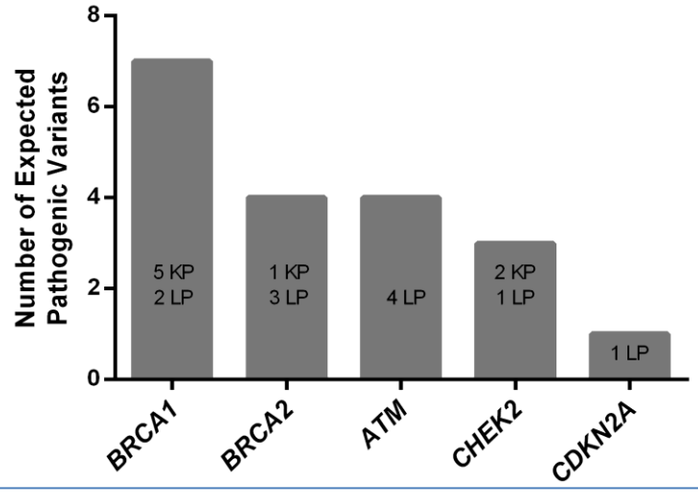
Cancer Type (Subtype)	Cases (% of Total)	Hereditary cancer susceptibility genes evaluated
Colorectal	53 (12.1%)	*MLH1, MSH2, MSH6, APC, PTEN, SMAD4, STK11*
Ovarian	29 (6.6%)	*BRCA1, BRCA2, MRE11A, TP53, MSH6, CHEK2*
Breast (Ductal, Lobular, Other)	114 (26.0%)	*BRCA1, BRCA2, ATM, CHEK2, CDH1, MRE11A, PTEN, STK11*
Musculoskeletal	41 (9.3%)	*TP53*
Lung (Non-small cell, Small cell, Other)	31 (7.1%)	*TP53*
Kidney	30 (6.8%)	*VHL, MET*
Brain/CNS (Astrocytoma, Glioma, Oligodendroglioma, Other)	54 (12.3%)	*NF1, NF2, TSC1, TSC2, TP53*
Skin (Melanoma, Non-melanoma, Other)	39 (8.9%)	*CDKN2A, PTCH1*
Hematologic (ALL, AML, CLL, Other)	29 (6.6%)	*RUNX1, CEBPA, TP53*
Pancreas	19 (4.3%)	*BRCA1, BRCA2, CDKN2A, ATM,TP53*
Total	439	
Other hereditary cancer genes	*AKT1, ATR, CBL, CDC73, CDKN1B, EGFR, MEN1 NTRK1, PIK3CA, RB1, RET, SMARCA4, SMARCB1,WT1*	

Germline findings across all UNCseq™ patients

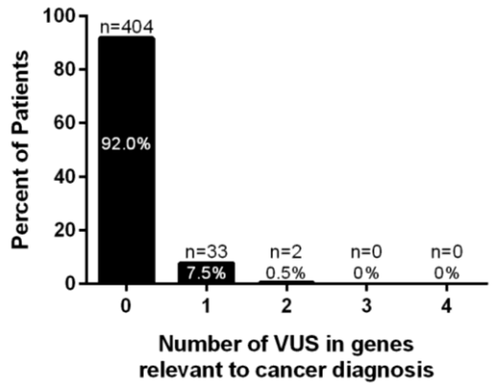


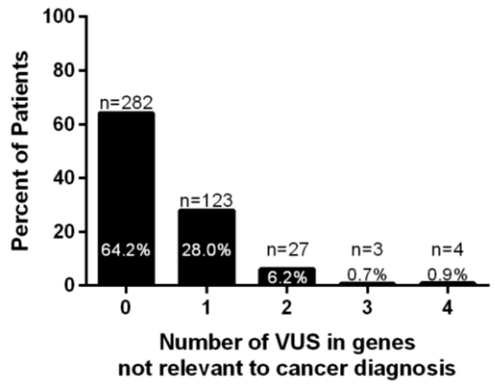
The percentages of patients with Pathogenic variants (light shading) or Variants of Uncertain Significance (VUS, dark shading) in genes relevant to the tumor type are depicted as stacked bar graphs. Numbers above the bars represent the sample size for the specific tumor type. Numbers in parentheses represent 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.

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



Germline Variants of Uncertain Significance





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 U01 HG006487 for financial support of the project. This work as been submitted to the Journal of Clinical Oncology for publication.