Unexpected germline mutations in a pan-cancer analysis including sarcoma, renal, and other cancers.

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Background

Multi-gene testing for cancer predisposition is being utilized more frequently in clinical care. Technological advances in next-generation sequencing have allowed broader panels of genes to be tested in diagnostics settings. The testing of more genes results in the reporting of in a greater number of variants of uncertain significance (VUS); however, more actionable pathogenic or likely pathogenic variants may be found in genes other than those traditionally analyzed based on a patient's clinical presentation.

In this study, we retrospectively analyzed de-identified data from 39,147 patients referred for hereditary cancer syndrome testing for pathogenic germline variants in 80 cancer risk genes across multiple types of cancers. We report an initial estimate of the prevalence of positive findings in the genes in a pan-cancer panel in this patient population.

Although the diagnostic yield and management implications of broader testing in breast, ovarian, and colorectal cancer have been addressed in previous studies, data for other cancer types are still emerging. In this study, we focused specifically on patients with renal cancer, sarcoma, paraganglioma, melanoma, and pancreatic cancer.

Methods

1. A sequential series of de-identified patients with genetic testing orders for genes strictly within the pan-cancer panel (80 in total) were included. The study was approved under a research protocol approved by the Western IRB.

2. Positive findings (pathogenic [**P**] or likely pathogenic [**LP**] variants in the clinical reports) and personal/family history information were extracted.

3. Variants were considered P/LP if:
a) They were computationally predicted to cause loss of function (LOF) in genes implicated in dominant cancer syndromes or were present in a homozygous or compound heterozygous state in genes implicated in recessive cancer syndromes.
b) They had been previously clinically interpreted as P/LP variants in other patients.

4. Cancer types were assigned based on the personal cancer history description provided by the patients' physicians.

*** Gene list of panels used in the study.**
Renal/Urinary Track Cancer Panel includes primary genes: BAP1,CDC73,CDKN1C,DICER1,DIS3L2,EPCAM,FH,FLCN, GPC3, MET,MLH1,MSH2,MSH6,PMS2,PTEN,SDHB,SDHC,SMARCA4,SMARCB1,TP53,TSC1,TSC2, VHL, and WT1; and preliminary-evidence genes: BUB1B,CEP57,MITF,PALB2,SDHA, and SDHD

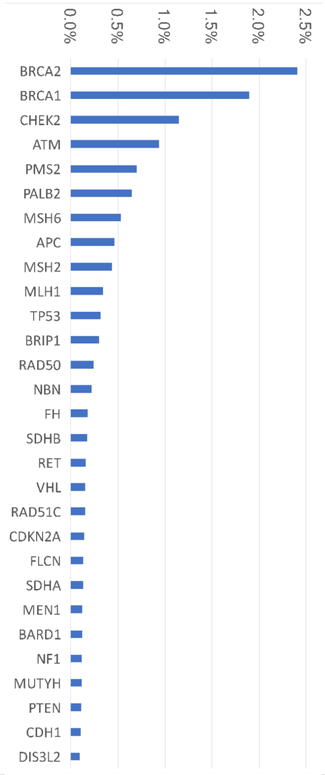
Sacorma Panel including primary genes: APC,BLM,CDKN1C,DICER1,EPCAM,FH,HRASKIT,MLH1,MSH2,MSH6, NBN, NF1,PDGFRA,PMS2,PRKAR1A,PTCH1,RB1,RECQL4,SDHA,SDHB,SDHC,SDHD,SUFU,TP53, and WRN and preliminary-evidence genes: CDKN2A,POT1,PTCH2,TSC1, and SC2

Melanoma Panel including primary genes: BAP1,BRCA2,CDK4,CDKN2A,MITF,POT1, PTEN,RB1, and TP53 and preliminary-evidence genes: BRCA1,MC1R, andTERT

Paraganglioma-Pheochromocytoma Panel including primary genes: MAX,NF1,RET,SDHA,SDHAF2,DHB,SDHC,SDHD, TMEM127, and VHL and preliminary-evidence genes: EGLN1,FH,KIF1B, and MEN1

Pancreatic Cancer Panel including primary genes: APC,ATM,BMPR1A,BRCA1,BRCA2,CDKN2A,EPCAM,MEN1,MLH1, MSH2,MSH6,NF1,PALB2,PMS2,SMAD4,STK11,TP53,TSC1,TSC2, and VHL and preliminary-evidence genes: CDK4,FANCC, and PALLD

Results
Overall prevalence of positive results in pan-cancer genes



Overall, 14.3% of patients (5,589) carried germline P/LP mutations in 80 cancer risk genes. Among them, 12.3% (686) had pathogenic/likely pathogenic variants in the genes initially requisitioned by the ordering provider.

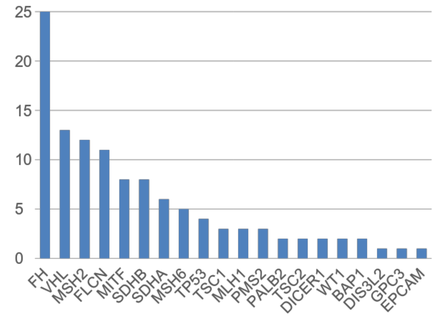
These 5,589 patients carried positive germline findings totaling 5,840 P/LP variants in 67 cancer genes.

P/LP variants in BRCA2 were the most prevalent, with a 2.4% positive rate, followed by BRCA1, CHEK2, ATM, PMS2 and PALB2. The high prevalence in BRCA1 and BRCA2 in the patient population was likely driven by the large number of HBOC patients included.

We found that 0.68% of patients (266) had two or more P/LP variants in the 80 pan-cancer genes.

Fig 1. Positive rate for genes with rates of ≥ 0.1% in our patients.

Results:
Unexpected findings in renal/urinary tract cancers patients



Among these positive findings, 44% (90) were "unexpected", meaning that they appeared in genes not commonly requisitioned in renal cancer patients.

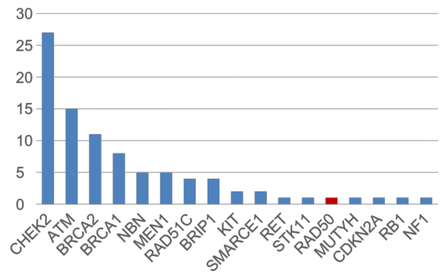
All of these variants except for one in RAD50, have no published management recommendations.

Fig 2b. Unexpected positive findings in renal patients. (right)

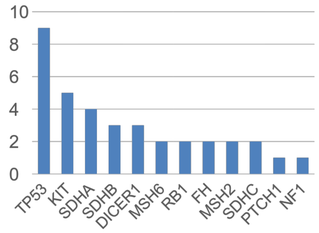
Of the 949 patients with personal histories of renal/urinary tract cancer, 20% (190) were positive with 204 P/LP variants.

Among these 204 variants, 56% (114) are included in our Renal/Urinary Tract Cancer Panel*.

Fig 2a. Expected positive variants in renal/urinary tract cancer patients (left).



Results:
Unexpected findings in sarcoma patients

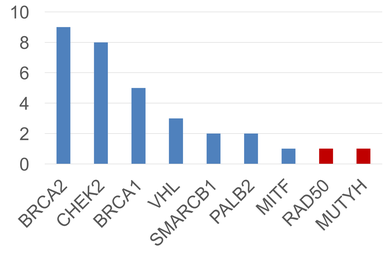


Among the 423 sarcoma patients, 16% (68) had positive findings. There were 71 P/LP variants, among which 45% (32) were unexpected.

Fig 3a. Positive findings in expected genes in Sarcoma Panel* (left).

Among unexpected findings, 94% (30) were in genes with published management recommendations. The only genes without such guidelines were RAD50 and MUTYH.

Fig 3b. Unexpected positive findings in sarcoma patients (right).



Results:
Melanoma, Paraganglioma and Pancreatic Cancer

Similar results were observed in melanoma, paraganglioma and pancreatic cancer patients. Between 20-40% of P/LP variants were in unexpected genes, the majority of which have published management recommendations.

Cancer Type	total patients	total positive patients	total P/LP variants	expected	unexpected	unexpected with recommendations
Melanoma	933	115 (12%)	122	69 (57%)	53 (43%)	50 (94%)
Paraganglioma	223	67 (30%)	71	50 (70%)	21 (30%)	20 (95%)
Pancreatic cancer	693	96 (14%)	101	83 (82%)	18 (18%)	18 (100%)

Conclusions

In this series of patients, we show that the yield of positive findings (pathogenic or likely pathogenic variants) in less common cancer types is comparable to, if not higher than, that seen in cancers often associated with hereditary risk. This result suggests that germline genetic testing is warranted in patients with renal cancer, pancreatic cancer, sarcoma, melanoma, or paraganglioma.

We estimate that ~12% of P/LP variants are unexpected—i.e., in genes other than those commonly tested for these cancer types. The variants we observed most frequently (CHEK2, ATM, BRCA2, and PMS2) are common in both breast and colon cancer patients. These variants may be generally common and unrelated to the indication for testing, or they may correlate to additional tumor types in the family history.

Given that most of the results were associated with actionable medical management — independent of whether the gene was associated with the tumor indication — clinicians should consider germline testing using expanded panels for patients with personal histories of rare tumors.