Tumor sequencing with germline genetic testing: identification of patients with hereditary cancer and precision treatment eligibility.

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BACKGROUND
- Cancer is a fundamentally genetic disease, as such, somatic and germline mutation analysis is used in the comprehensive assessment of patients with cancer.
- Studies report that approximately 10% of patient’s tumors have clinically significant variants known to predispose to hereditary cancer, with medical implications for both patients and family members.
- We retrospectively reviewed a series of patients where providers suspected a somatic variant also existed in the germline and followed up with clinical germline genetic testing.
- We report the rate of concordance between germline and somatic results and their clinical impact.

METHODS
- An IRB-approved retrospective study was performed on 1043 consecutive patients who underwent somatic genetic testing followed by germline genetic testing with a Next Generation Sequencing–based hereditary cancer panel.
- Individuals undergoing testing and test ordered were not selected by the ordering clinician.
- Clinical information was collected and reviewed form test requisition forms and medical records when provided.

RESULTS
- Somatic results most frequently prompting germline testing included variants in BRCA2 (20%), BRCA1 (17%), TP53 (15%), ATM (70%), MLH1 (65%), APC (65%), PMS2 (61%), MSH6 (58%), PTEN (54%) and CDH1 (42%).
- In 364/1043 cases (35%) the variant was detected as likely pathogenic or pathogenic (LP/P) in the germline.
- Variants were never confirmed in the germline for: AKT1, ALK, BARD1, CDK4, CDKN1B, CDKN2A, CEBPA, EPCAM, EZH2, FANCN, FLCN, HRAS, KIT, MAX, MET, MSH3, NBN, NF1, NF2, PDGFR, PIK3CA, POLE, PIK3R1, PTCH1, RAD51C, RB1, SDHC, SMAD4, SMARCA4, STK11, TERT, TSC1, TSC2.

PATIENTS
- Approximately 3% of patients suspected to have hereditary risk after tumor testing had LP/P germline variants.
- Notably, some genes had a high probability of variants occurring in the germline, while others were primarily seen in tumors.
- Interestingly, 6% of the germline variants were not included on the somatic report due to technical and gene content differences in either assays or due to differences of clinical classification between somatic and germline testing.
- Adding germline results to somatic testing may inform options for precision treatment, prevention, or early detection of, secondary malignancies and guide genetic counseling of family members.

CONCLUSIONS
- Genes with variants detected in the tumor and confirming on germline testing greater than 40% of the time included: RAD50, FANCA, AXIN2, MUTYH, BLM, PALB2, CHEK2, SDHB, MITF, FANCQ2, FH and BRCA2.
- In 24 (2%) cases a LP/P germline variant was detected but not reported in the tumor. 19/24 occurred in genes with medical management implications for hereditary cancer risk (ie. imaging, prophylactic surgery)