Families with a Known Mutation in a Cancer Predisposition Gene: Is Single Site Testing Always the Best Option for Relatives?

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BACKGROUND

- The current paradigm prescribes site-specific testing among family members when there is a known familial mutation in a cancer-risk gene.
  - Tested individuals are typically managed as true positives/negatives.
- Hereditary cancer panel testing has revealed that some individuals/families carry more than one mutation in cancer-risk genes.

OBJECTIVE

- Assess if multi-gene hereditary cancer panel testing may be appropriate even in the setting of a known familial mutation.

METHODS

Cohort

- Patients who reflexed to multi-gene hereditary cancer panel testing after testing negative for a known familial mutation between March 2005 and August 2017 (n=902) were assessed.

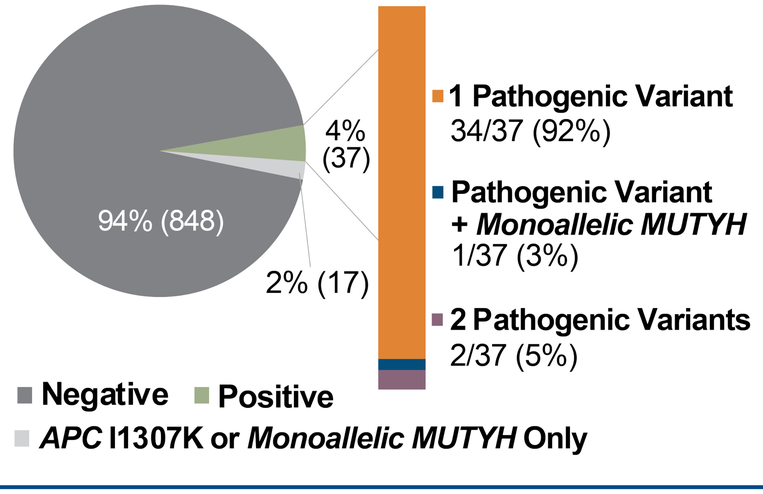
Genetic Testing

- The multi-gene hereditary cancer panel included *BRCA1, BRCA2, ATM, CHEK2, PALB2, NBN, BARD1, PTEN, BRIP1, RAD51C, RAD51D, MLH1, MSH2, EPCAM, MSH6, PMS2, APC, MUTYH, POLD1, POLE, GREM1, BMPR1A, SMAD4, TP53, STK11, CDH1, CDKN2A,* and *CDK4*.
- All genes on the panel were available for the full time period except for *POLD1, POLE*, and *GREM1*, which were included starting in July 2016.
- Sequence and large rearrangement analysis was performed for all genes except *POLD1, POLE* (sequencing only) and *EPCAM, GREM1* (large rearrangement only).
- Pathogenic variants are those that received a laboratory classification of Deleterious or Suspected Deleterious.

RESULTS

- 37/902 (4%) individuals who tested negative for a known familial mutation were found to carry ≥1 pathogenic variant upon panel testing (Fig 1).
  - 17/902 (2%) additional individuals carried only a low penetrant *APC* mutation (I1307K) or a single *MUTYH* mutation.

Figure 1. Cancer panel testing results (N=902)



- 16/37 (43%) individuals had panel testing ≥1 year after known familial mutation testing.
  - 2 individuals developed interim cancers.

Table 1. Cancer panel testing results

KFM	PVs Found with Panel Testing
***BRCA1* (15)**	*ATM* (2), *BRCA1* (2), *BRCA2* (4), *CHEK2* (3), *PALB2* (1), *PMS2* (2), *RAD51C* (1)
***BRCA2* (11)**	*APC* (2), *ATM* (2), *BRCA2* (2), *BRIP1* (1), *CHEK2* (2), *CDH1* (2), *PALB2* (1)
***MSH2* (4)**	*BRCA2* (1), *PALB2* (3)
***PALB2* (2)**	*PALB2* (2)
***ATM* (1)**	*CHEK2* (1)
***CHEK2* (1)**	*CDH1* (1)
***EPCAM* (1)**	*BRCA1* (1)
***MLH1* (1)**	*BRCA2* (1), *PALB2* (1)
***PMS2* (1)**	*ATM* (1)

KFM, Known Familial Mutation; PVs, Pathogenic Variants

Table 2. Selected case examples, which were negative for a known familial mutation, highlighting the difficulty in discerning additional familial mutations based on limited family history and/or syndromic overlap

	Initial Testing: Single-Site				Multi-Gene Cancer Panel Testing		
	Age	PHx	FHx	KFM	Age	Add'l PHx	PVs
Case 1	23	No cancer	**Mat**: BC (22)	*BRCA2*	26	CRC (26)	*APC*
Case 2	31	No cancer	**Pat**: CRCx3 (37, UNK, 47); SC (54); Other (58); BLC (unknown)	*MSH2*	32	BC (32)	*PALB2*
Case 3	53	BCx2 (38, 44) Other (53)	No Cancer Reported	*BRCA2*	53	None	*CHEK2 & CDH1*
Case 4	54	OC (54)	**Mat**: LC (77) **Pat**: CRC (67); BCx2 (26, 46); OC (47); LC (65)	*BRCA1*	54	None	*RAD51C*
Case 5	48	OC (47)	**Mat**: BC (32), OC (40); CRC (63) **Pat**: HC (75), BC (61)	*BRCA2*	48	None	*MSH6*

Add'l, Additional; BC, Breast Cancer; BLC, Bladder Cancer; CRC, Colon Cancer; FHx, Family History; HC, Hepatobiliary Cancer; KFM, Known Familial Mutation; LC, Lung Cancer; Mat, Maternal; OC, Ovarian Cancer; Pat, Paternal; PHx, Personal History; PVs, Pathogenic Variants; SC, Stomach Cancer; UNK, Unknown

CONCLUSIONS

- In this cohort, 4% of individuals who tested negative for a known familial mutation were found to carry a different pathogenic variant in a cancer-risk gene.
- An informative negative test result for a known familial mutation may give a false sense of security when there could be more than one mutation contributing to the family history of cancer.
- There may be added value to cancer panel testing among individuals with a known familial mutation.

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