Detailed Review of Four Patients Affected with Cancer that were Previously Unaffected at the Time of Single Syndrome Testing and Subsequently had Pathogenic Variants Identified by a 25-Gene Panel

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BACKGROUND

- The advent of Next-Generation Sequencing has resulted in panel tests that often include genes associated with an increased risk of hereditary cancer not previously included in single-syndrome testing.
- Individuals who have previously received negative single-syndrome test results may benefit from the addition of these new genes.
  - This is especially true for individuals who were unaffected at the time of their previous single-syndrome testing, who would have been considered uninformative negatives if affected relatives had not received genetic testing.
- However, panel testing in this population may identify additional individuals who are at an increased risk for hereditary cancer and may be candidates for revised medical management.

AIMS

- Here, we assessed the utility of re-testing individuals who previously underwent single-syndrome testing by investigating individuals who were unaffected at the time of their negative single-syndrome testing, but later developed cancer.

METHODS

PATIENTS

- Results are presented from individuals who were re-tested using a 25-gene hereditary cancer panel that includes genes associated with an increased risk for breast, ovarian, colorectal, endometrial, melanoma, pancreatic, gastric, and prostate cancer.
- A commercial laboratory database was queried to identify patients who met the following selection criteria:
  - Previously tested negative by single syndrome testing for Hereditary Breast and Ovarian Cancer (HBOC), Lynch or Familial Adenomatous Polyposis (FAP) syndromes
  - Unaffected at the time of single-syndrome testing, but later developed one of the eight cancers covered by the 25-gene panel
  - Were re-tested with the 25-gene hereditary cancer panel

GENETIC TESTING

- Previous BRCA testing included *BRCA1/2* sequencing and deletion/duplication and, in some cases, 5-site rearrangement panel common in the Caucasian population.
- The 25-gene panel includes *APC*, *ATM*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK2NA*, *CDK4*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11* and *TP53*.
- Sequencing and large rearrangement (LR) analysis is performed for all genes on the panel, except for *EPCAM*, for which only LR analysis is performed.
- PVs are variants that received a laboratory classification of Pathogenic or Likely Pathogenic.

FAMILY HISTORY

- Family history information was collected from the test request form from the patient's order for 25-gene hereditary cancer panel with the exception of case 4, for which family history was only provided on their single syndrome test order.

BREAST CANCER RISK CALCULATION

- Breast cancer risk was calculated for four case studies using the Claus tables[1] using the age that patient presented for single-syndrome testing.

RESULTS

- Among the 106 individuals who met the selection criteria, 8 (7.5%) were identified as carrying a PV upon re-testing with the 25-gene panel.
  - This is similar to the positive rate for the overall 25-gene panel testing population over the same time period (6.8%).
- Four cases were chosen for a detailed review below based on the most common PVs identified in this population.
  - At the time of the single-syndrome testing, all four probands would have met 2015 NCCN testing guidelines[2] for HBOC based on their family history.
  - Three of these probands would not have met the 20% threshold for high risk screening breast MRI prior to the identification of their PV(s).

Review of Case Studies

Proband Genetic Testing and Cancer History

	BRCA Testing		Re-Testing with Panel		
	Age	Breast Cancer Risk*	Age	Diagnosis	PVs Identified
Case 1	37	15.3%	41	DCIS	*PALB2*
Case 2	43	28.7%	44	iBC and DCIS**	*ATM*
Case 3	53	10.9%	59	DCIS	*CHEK2*
Case 4	33	19.8%	37	iBC	*ATM* and *CHEK2*

Family Cancer History

	FDR	SDR	TDR
Case 1	iBC (Mother, 34 and 35)	Maternal Lineage: • Hodgkin's Lymphoma/Non-Hodgkin's Lymphoma (57) • PrCa/ Rectal Cancer (60/87)	Maternal Lineage • CRC (60) • CRC (60) • PrCa (age unknown)
Case 2	iBC (Mother, 44)	Maternal Lineage • iBC (44)	None
Case 3	Sarcoma (Mother, 94)	Maternal Lineage • iBC (35) • iBC (70) • CRC(75) • Endometrial Cancer (75) • Hematologic Cancer (60)	None
Case 4	None	Paternal Lineage • iBC (42 and 46) • iBC (42 and 48) • iBC, Leukemia and "Bone Cancer" (75)	Paternal Lineage • CRC (age unknown) • iBC (35)

*Risk calculated to age 79 **Diagnosis at age 43
Abbreviations: FDR - First Degree Relative; SDR - Second Degree Relative; TDR - Third Degree Relative; DCIS - Ductal Carcinoma *in situ*; iBC - Invasive Breast Cancer; CRC - Colorectal Cancer; PrCa - Prostate Cancer

CONCLUSIONS

- Re-testing with a hereditary cancer panel in this cohort resulted in the identification of PVs in 7.5% of individuals who were unaffected at the time of their single-syndrome testing.
- All of the cases reviewed here involved individuals who went on to develop breast cancer after testing negative for a PV in *BRCA1* or *BRCA2*.
- This shows that re-testing with a hereditary cancer panel may increase the number of individuals identified as candidates for increased screening, among those who were unaffected at the time of negative single-syndrome testing.

REFERENCES

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2. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V 2.2015. January 7. Available at http://www.nccn.org.

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