The Clinical Experience - Hereditary Cancer Testing by a 25-Gene Panel

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Background

- Prior to next generation sequencing (NGS) technology, genetic testing for hereditary cancer risk was gene and syndrome-specific.
- Fox Chase Cancer Center began offering a 25-gene panel, utilizing NGS, to patients through a commercial early access clinical program in September 2013.
- This panel includes *BRCA1/BRCA2* and other high/moderate risk genes for breast, colon, and other cancers.
- The utilization of this panel test compared to syndrome-specific testing has not been assessed in clinical setting.
- Here we describe our clinical experience with this new testing option.

Methods

- Patients were given the choice, as appropriate, between syndrome-specific (*BRCA1/BRCA2* only) and panel testing from Myriad Genetic Laboratories.
- Analysis included tests ordered from September 4, 2013 to April 23, 2014.
- All tested patients met NCCN criteria for genetic testing or were deemed appropriate for testing after assessment by a certified genetic counselor.
- The 25 gene panel includes *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, *MUTYH*, *CDKN2A*, *CDK4*, *PALB2*, *CHEK2*, *SMAD4*, *BMPR1A*, *STK11*, *TP53*, *CDH1*, *PTEN*, *ATM*, *NBN*, *BARD1*, *BRIP1*, *RAD51C*, and *RAD51D* analyzed by next generation sequencing and deletion/duplication testing.

Results

Figure 1: Panel Versus Syndrome-Specific Testing

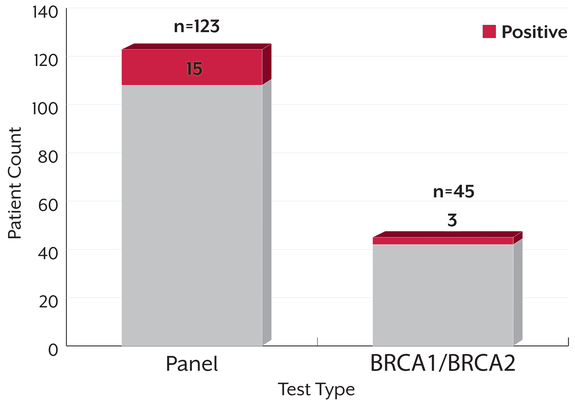
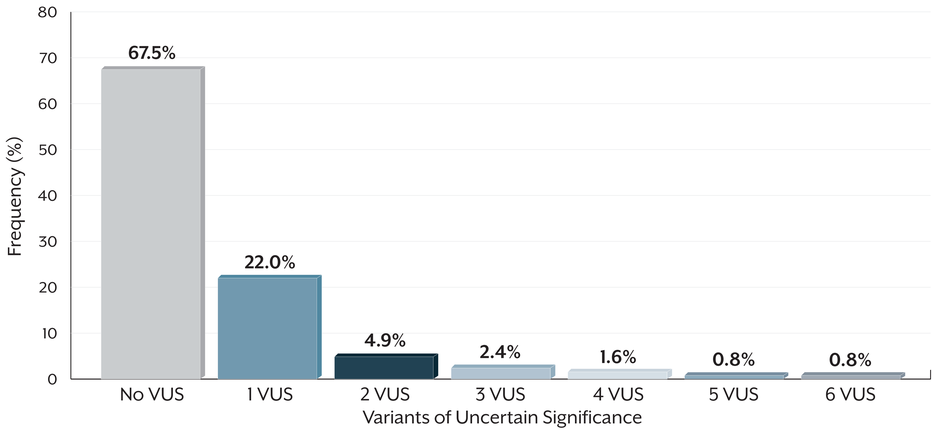


Table 1: Gene Mutations Identified with Panel Testing

- 16 mutations found in 15/123 patients

Gene	# of Patients (% of Total)
BRCA1	2 (13.3%)
BRCA2	2 (13.3%)
MSH2	1 (6.7%)
PMS2	1 (6.7%)
APC	1 (6.7%)
ATM	1 (6.7%)
NBN	1 (6.7%)
RAD51D	1 (6.7%)
Monoallelic *MUTYH*	5 (33.3%)
APC and *ATM*	1 (6.7%)
TOTAL	**15**

Figure 2: VUS in Panel Tested Patients



Results

- Of 168 patients tested, 123 had 25-gene panel testing and 45 had syndrome-specific testing.
- For patients tested with the 25-gene panel (n=123):
  - Fifteen had positive results for a deleterious gene mutation (12.2%)
    - 5/15 (33.3%) were unanticipated test results that influenced clinical management (mutations in *ATM*, *APC*, *PMS2*, *NBN* and *RAD51D*)
    - 5/15 (33.3%) had a monoallelic *MUTYH* mutation
    - 11/15 individuals were affected with cancer
    - One *MSH2* mutation was found in a patient at 50% risk for a known familial *MSH2* mutation. This patient pursued panel testing due to additional personal and family history of breast cancer.
  - 40/123 had a variant of uncertain significance (VUS) (32.5%)
- For patients with syndrome-specific testing for *BRCA1/BRCA2* (n=45):
  - A deleterious mutation was identified in 3/45 (6.7%)
  - 4/45 had a variant of uncertain significance (8.9%)
- Of patients who opted for syndrome-specific testing (n=45):
  - 22/45 patients declined panel testing after discussion of limitations
  - 14/45 were treatment decision patients who needed results as quickly as possible

Conclusions

- Multi-gene panel testing yields results that would not otherwise be discovered through syndrome-specific testing, and may provide additional clinical guidance.
- Some patients preferred syndrome-specific testing due to concerns over the panel test limitations, including the following:
  - Potential findings for which there is no clear medical management at the present time.
  - Higher VUS rate with panels. (Patients with uncertain variants should be managed based on their personal and family history).
- Despite pre-test education regarding potential limitations of gene panel testing, patients strongly favored panel testing over syndrome-specific testing when there were no other mitigating factors such as surgical decisions.

Presented at ASCO - June 1, 2014