Genomic screening for hereditary cancer syndromes in 22,033 individuals

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ABSTRACT

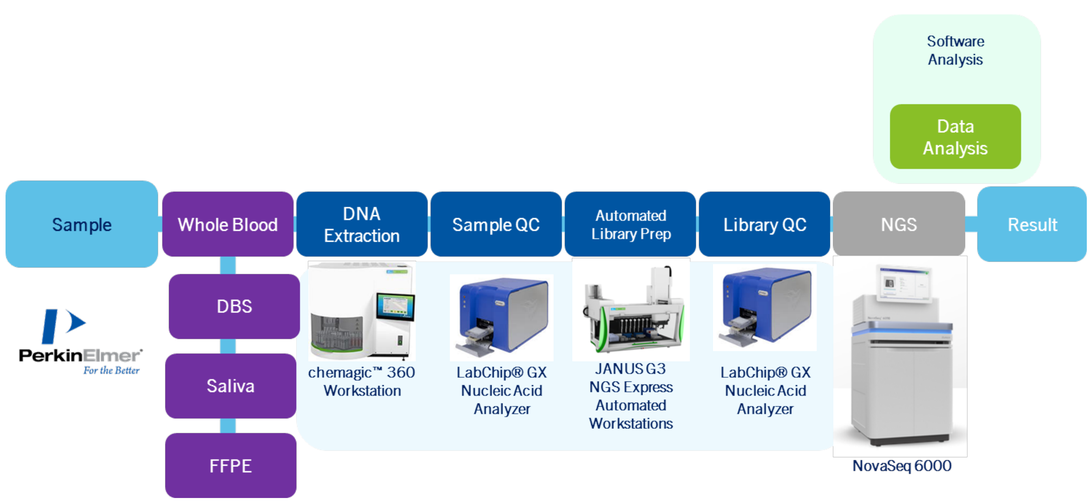
The timely diagnosis of a hereditary cancer syndrome is essential for increasing positive health outcomes for patients and their families. To date, more than fifty hereditary cancer syndromes have been described, which includes disorders such as hereditary breast and ovarian cancer, Li-Fraumeni syndrome, Cowden syndrome, Lynch syndrome, familial adenomatous polyposis, and multiple endocrine neoplasia. Screening guidelines have been established by professional societies to identify at-risk individuals that should be offered genomic/genetic testing. However, advances in next-generation sequencing have made genomic testing more affordable, leading to an increase in the amount of "elective" genomic testing ordered in clinical laboratories. For genomic testing of reportedly healthy individuals, evidence-based gene selection is integral to the gene panel design. Our laboratory offers next generation sequencing panels (27, 31, 33, 45, 102 genes) for hereditary cancer syndromes. Since October 2018, our laboratory has reported 22,033 hereditary cancer panels in individuals for whom many have no reported personal history of cancer. Of the cases reported, 4.1% had pathogenic or likely pathogenic variants identified. Pathogenic and likely pathogenic variants detected in these cases were identified in a variety of genes, including (but not limited to) *APC*, *BRCA1*, *BRCA2*, *CHEK2*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, and *POLE*. The identification of variants of uncertain significance in individuals with no personal history of disease is not clinically useful. Given the lack of clinical utility and literature which suggests that variants of uncertain significance should not be returned in individuals with no evidence of a phenotype (PMID: 30453057, 25232850), our laboratory has implemented a policy of returning only pathogenic and likely pathogenic variants for these hereditary cancer panels; variants of uncertain significance are not returned. These data provide further evidence that genomic screening of reportedly healthy individuals has clinical utility.

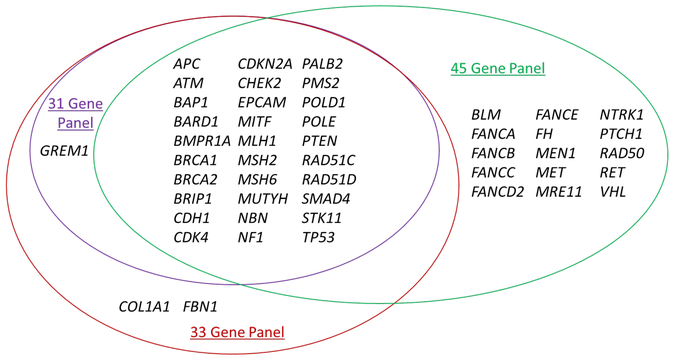
INTRODUCTION

- Given recent increases in the amount of elective genomic testing ordered, clinical laboratories will need to address the unique challenges inherent in this testing
- Identification of variants of uncertain significance in elective genomic testing is of minimal clinical utility, and therefore not reported by our laboratory
- Only pathogenic and likely pathogenic variants were reported due to the demonstrable clinical utility for this population
- **CHALLENGE**: Understand the clinical utility and diagnostic yield of genomic screening for hereditary cancer in an "allcomers" population, the majority of which have no reported personal or family history of cancer
- **APPROACH:** Multi-gene panel sequencing of an unselected population for genes associated with hereditary cancer

METHODS AND RESULTS

NGS sequencing workflow

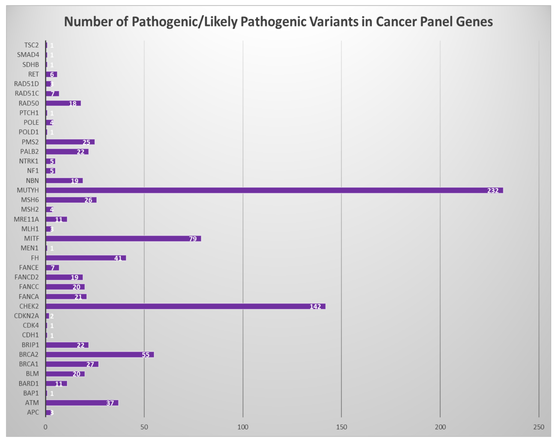




Gene Lists. Samples utilized for this analysis were run on different versions of the hereditary gene panel; however, there was a high degree of overlap for the genes assayed across these panels. For the 31, 33, and 45 gene panels, thirty genes are in common between the three panels. Gene panels were curated in collaboration with medical providers and ordering physicians.

Number of Genes in Panel	Number of Cases
27	55
31	3,311
33	7,669
45	10,982
102	16
Total number of samples	**22,033**

Samples run on multi-gene panels. A total of 22,033 samples were run on hereditary cancer panels consisting of 27, 31, 33, 45, and 102 genes. The 31, 33, and 45 gene panels were utilized for 21,962 (99.7%) samples tested.



Variant Type	Number of Cases
Pathogenic	787
Likely Pathogenic	118
Total number of samples	**905**

Number of samples with pathogenic/likely pathogenic variants detected. Of the 22,033 samples tested, 905 (4.1%) had a pathogenic or likely pathogenic variant detected. Twenty samples (0.09%) had two reportable (pathogenic or likely pathogenic) variants detected.

- 18/20 samples had 2 reportable variants in different genes
- 2/20 samples had 2 reportable variants in the autosomal recessive *MUTYH* gene

Genes with pathogenic and likely pathogenic variants detected. For the samples screened, pathogenic/likely pathogenic variants were identified in 39 of the genes assayed. A subset of these genes had the majority of reportable variants detected: *MUTYH* (232), *CHEK2* (142), *MITF* (79), *BRCA2* (55), *FH* (41), *ATM* (37), *BRCA1* (27), *MSH6* (26).

DISCUSSION/CONCLUSIONS

- Of the 22,033 samples tested, 905 (4.1%) had a pathogenic and/or likely pathogenic variant detected.
- Data strongly supports screening and reimbursement for inherited cancer panels for early identification and intervention.
- For genes with low or reduced penetrance, multiple pathogenic variants may be detected in a reportedly unaffected individual.
- Data help identify highly penetrant and low penetrance genes and variants.
- Modalities for VUS (variant of uncertain significance) reporting still need to be assessed carefully (PMID 30453057). Resources to evaluate VUS on periodic basis require significant effort.
- Careful return of result strategies need to be established for post-testing follow-up and education.
- Population based screening should be considered for other common inherited conditions.