Cancer Genetics 218-219 (2017) 58–68

Cancer Genetics

Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories

Eric T. Rosenthal *, Ryan Bernhisel, Krystal Brown, John Kidd, Susan Manley
Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA

Genetic testing for inherited cancer risk is now widely used to target individuals for screening and prevention. However, there is limited evidence available to evaluate the clinical utility of various testing strategies, such as single-syndrome, single-cancer, or pan-cancer gene panels. Here we report on the outcomes of testing with a 25-gene pan-cancer panel in a consecutive series of 252,223 individuals between September 2013 and July 2016. The majority of individuals (92.8%) met testing criteria for Hereditary Breast and Ovarian Cancer (HBOC) and/or Lynch syndrome (LS). Overall, 17,340 PVs were identified in 17,000 (6.7%) of the tested individuals. The PV positive rate was 9.8% among individuals with a personal cancer history, compared to 4.7% in unaffected individuals. PVs were most common in *BRCA1/2* (42.2%), other breast cancer (BR) genes (32.9%), and the LS genes (13.2%). Half the PVs identified among individuals who met only HBOC testing criteria were in genes other than *BRCA1/2*. Similarly, half of PVs identified in individuals who met only LS testing criteria were in non-LS genes. These findings suggest that genetic testing with a pan-cancer panel in this cohort provides improved clinical utility over traditional single-gene or single-syndrome testing.

Keywords Hereditary breast and ovarian cancer syndrome, Lynch syndrome, melanoma, prostate cancer, genetic testing, pan-cancer panel

Introduction

Genetic assessment and testing for inherited cancer risk is now a widely used tool in cancer prevention and treatment. Identification of individuals carrying pathogenic variants in hereditary cancer genes allows for targeted interventions for the prevention of cancer through lifestyle and environmental modification, chemoprevention, and/or preventative surgeries. These individuals can also benefit from interventions aimed at early detection of cancer through screening initiated at younger ages, more frequent intervals, and with more sensitive technologies than would be recommended for individuals in the general population (1,2). Additionally, there is growing evidence that many cancers arising as a result of hereditary cancer syndromes are candidates for targeted therapies (3).

Genetic testing strategies across all areas of medical genetics are evolving in response to expanded knowledge about gene associations and the widespread availability of technologies that allow for cost-effective, high throughput screening. This has led to the development of multi-gene, multi-syndrome panel tests for the assessment of inherited cancer risk as an alternative to the historic strategy of testing a single or limited set of genes based on an analysis of the individual's personal and family history. Panel testing provides a mechanism to address overlap in the clinical presentation of numerous hereditary cancer conditions as well as growing awareness of the limitations of family history as a predictor of genetic risk.

Although panel testing is becoming more common in clinical practice, there is still considerable debate surrounding the best strategies for utilization and design. One option is to use

Received June 26, 2017; received in revised form September 5, 2017; accepted September 18, 2017.

* Corresponding author.
E-mail address: erosenth@myriad.com

https://doi.org/10.1016/j.cancergen.2017.09.003

panel testing as the front-line test for all individuals. Alternatively, panels may be selectively utilized for individuals whose personal and family histories are not a good fit with a single gene or syndrome, or as a second-line option for those who have tested negative for a pathogenic variant as part of single-syndrome testing but whose histories remain highly suspect for an inherited condition. Additionally, questions remain regarding the clinical utility of different approaches to panel design. Many of the panels now available for clinical use are targeted at specific cancers, i.e. breast, ovarian or colorectal cancer. Other "pan-cancer" panels take a broader approach and include genes associated with multiple cancer types, usually focusing on those that are substantial contributors to disease burden in the population and are known to have a significant hereditary component. Although there is an ongoing debate about the best strategy for panel design and the choice of individual genes to be included, there is limited evidence available to support an objective evaluation based on outcomes.

Beginning in September of 2013, our laboratory has offered a single pan-cancer panel test targeted mainly, but not exclusively, to individuals at risk for the two most common hereditary cancer syndromes: Hereditary Breast and Ovarian Cancer (HBOC) and the hereditary colorectal/endometrial cancer condition, Lynch syndrome (LS). The 25 genes included are known to be significant contributors to risk for one or more of the following eight cancers: breast, ovarian, colorectal, endometrial, pancreatic, gastric, melanoma, and prostate. The panel is heavily weighted toward genes for which findings have concrete clinical relevance. The National Comprehensive Cancer Network (NCCN) and other professional societies currently provide medical management guidelines for individuals with PVs in all but one of the 25 panel genes (1,2).

Here we report on the outcomes of testing with this 25-gene panel for the first 252,223 individuals for whom results were reported. This summary provides insight into the distribution of pathogenic variants identified among the 25 genes and clinically significant findings. This is the largest study to date reporting on the outcomes of clinical testing for hereditary cancer risk in a diverse population with a single pan-cancer panel. This analysis provides valuable information to inform comparisons of panel testing versus the targeted single-syndrome or single-cancer testing, as well as the evaluation of different strategies for panel design.

Materials and methods

Cohort characteristics

This analysis includes a consecutive series of the first 252,223 individuals tested with a 25-gene hereditary cancer panel from September 2013 through July 2016 (Myriad Genetic Laboratories, Inc., Salt Lake City, UT). Testing was performed in a Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathology (CAP) approved laboratory. All individuals provided informed consent for clinical testing. Only data collected as part of clinical testing is utilized here. Ordering providers indicated that the majority of individuals were ascertained for suspicion of Hereditary Breast and Ovarian Cancer (HBOC-Panel) or for suspicion of Lynch syndrome (LS-Panel), and 92.8% of the tested individuals met NCCN criteria for one or both of those conditions. The same panel was run for all individuals.

For the purposes of this analysis, only results of testing with the full 25-gene panel were included. Specifically excluded were: 1) single-site tests for known familial gene mutations and 2) tests ordered for individuals who previously had genetic testing for inherited cancer risk, including comprehensive testing for mutations in *BRCA1* and *BRCA2* or the Lynch syndrome genes, or previous testing for the three common Ashkenazi Jewish founder mutations in *BRCA1* and *BRCA2*. Ashkenazi Jewish individuals for whom the 25-gene panel was ordered as the initial test were included in the analysis.

Panel composition and categorization of genes

The 25 genes included in the panel are listed in Table 1 along with all of the cancers for which there is sufficient evidence to support a significant association as of July 2016 (4). To facilitate analysis, the genes are grouped into seven categories, based on their primary cancer/syndrome associations, focusing on the cancers widely regarded as most distinctly associated with each gene. Table 1 also includes the source of professional society recommendations for the management of individuals with findings in each gene. *BARD1* is the only panel gene for which management guidelines are not yet available.

NGS assay and variant classification

The details of the Next Generation Sequencing (NGS) assay used have been described previously (5–7). Briefly, this assay consists of sequencing and large rearrangement detection, followed by data review and reporting. All tests were performed on genomic DNA extracted from whole blood or saliva by QIAsymphony using the DSP DNA Midi kit (Qiagen, Venlo, The Netherlands). Sequencing was performed on an Illumina HiSeq2500 or MiSeq platform (Illumina, Inc., San Diego, CA) and long-range PCR was incorporated to address the highly homologous pseudogenes in the *CHEK2* and *PMS2* genes. Large rearrangements identified with quantitative dosage analysis of the NGS data were confirmed with microarray CGH and multiplexed ligation-dependent probe amplification (MLPA) analysis. All data were reviewed to assess zygosity and quality metrics. Only those variants detected at allele frequencies between 30% and 70% were regarded as germline in nature, as allele frequencies outside of this range are highly suspicious for representing somatic mosaicism rather than germline inheritance.

Variants were classified according to current guidelines from the American College of Medical Genetics and Genomics (8), as previously described (9). For the purposes of the analyses performed here, variants with a laboratory classification of Deleterious or Suspected Deleterious were considered to be a Pathogenic Variant (PV). Variants with a laboratory classification of Polymorphism or Favor Polymorphism were considered to be Benign (clinically insignificant). Variants for which the clinical significance could not be determined were classified as a Variant of Uncertain Significance (VUS). A small proportion of large rearrangement variants were not counted as PVs if they were reported as Inconclusive findings after