Introduction
Approximately 5-10% of all breast cancers are thought to be hereditary. The identification of mutations in breast cancer susceptibility genes in healthy women may allow more personalized cancer risk management, surveillance, and/or prophylactic surgeries. For women already diagnosed with breast cancer, the identification of mutations may guide treatment decisions. Here, we describe the demographics and outcomes of 3,011 individuals with a self-reported diagnosis of breast cancer who received a multi-gene panel test for hereditary cancer risk.

Methods
These 3,011 patients were referred by physician order for a multi-gene, next generation sequencing panel for hereditary cancer risk. Analysis was limited to 19 genes associated with hereditary breast and ovarian cancer (ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53). Participants received genetic testing from Color Genomics (Burlingame, California), including both targeted next generation sequencing in a clinical CLIA and CAP accredited laboratory and whole genome sequencing in a non-clinical CLIA accredited laboratory. Self-reported demographics and health history information was collected via a self-reported online questionnaire.

Conclusions
• The overall mutation carrier rate amongst this breast cancer patient cohort was 17.7%.
• About half (48%) of mutations found were in BRCA1 or BRCA2. The age of breast cancer diagnosis was lower in BRCA2 or BRCA1 positives than in positives of other genes.
• CNVs accounted for 10% of mutations and were especially prevalent in BRCA1, emphasizing the importance of CNV detection in genetic testing for hereditary breast cancer.
• The identification of individuals with multiple mutations highlights a benefit of multi-gene panel testing.

Taken together, these data support the recommendation that all patients with breast cancer should undergo germline testing for hereditary cancer risk.

Results

Cohort demographics

Table 1: Self-reported demographics and personal history of cancer in the cohort. The cohort was almost entirely female and the positive rate of 11.7% for females, and 8.3% for males was both similar to previous reports. Also in line with previous data, the positive rate was highest for the youngest age group. While the majority of the cohort was Caucasian, the positive rate was highest amongst Hispanics.

Concurrent mutation carriers

Table 2: While 344 individuals were found to carry a single mutation, 8 individuals were found to carry two concurrent mutations in different genes. The identification of multiple mutations can have implications for the patient and influence cascade testing strategy for family members.

References

Methods

Figure 1: Age at breast cancer diagnosis, stratified by genetic test result. Overall, the median reported age at diagnosis was 49 years. The median age of diagnosis for individuals with a positive result in BRCA1 or BRCA2 (40 years) was lower than that of individuals with a positive result in one of the other 7 genes (46 years) and individuals with a negative result (52 years).

Figure 3: 173 of the 360 mutations identified in the cohort were in the BRCA1 and BRCA2 genes (48.1%), with 48.1% of mutations in BRCA1 and 51.9% in BRCA2. The mutation carrier rate of 5.7% was lower than what was expected. 60.8% of mutations were in CNVs (10.3%). The most prevalent mutations are highlighted in orange. The most prevalent CNVs are shown below the structure of the gene. All CNVs detected in this gene are highlighted in blue.

Figure 4: Top: single nucleotide variants (SNVs) and small insertions and deletions (indels) are displayed on a diagram of the BRCA1 protein, colored by effect of the mutation (yellow = stop, dark blue = splice, and light blue = missense), with frequency indicated by size. Bottom: CNVs are shown below the structure of the BRCA1 gene. All CNVs detected in this cohort are deletions, and each unique deletion is diagramed once (although some deletions were detected multiple times).