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BRCA1/2 genetic testing ordering practices: A snapshot from a large commercial laboratory

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I. Background

The National Comprehensive Cancer Network (NCCN) recommends *BRCA1/2* testing for individuals meeting specific criteria following pre-test counseling by a genetic counselor, medical geneticist, surgeon, oncology nurse or other health professional with expertise and experience in cancer genetics.[1] Comprehensive genetic testing includes full gene sequencing and testing for large genomic rearrangements.[1,2]

Pathogenic BRCA gene variants are the most common genetic cause of hereditary breast and ovarian cancer but these cancers may also be associated with other hereditary cancer syndromes including Li-Fraumeni, Cowden, Peutz-Jeghers, Hereditary Diffuse Gastric Cancer, and Lynch.[2] NCCN and other published guidelines provide specific criteria for when genetic testing should be expanded beyond just *BRCA1/2*.[1-3] Targeted testing is recommended when a pathogenic variant has previously been identified in a family member.[1] Large genomic rearrangements are not detectable by most sequencing assays but are encompassed in recommendations for comprehensive *BRCA1/2* testing. Thus, this testing often requires separate methodology and can be offered as a unique test for individuals with previously negative sequencing results or with a known familial rearrangement; however, as a stand-alone-test, it is not sufficient for comprehensive testing. Ensuring a patient receives appropriate genetic testing tailored to their personal and/or family history of cancer is important and complex.[4]

II. Objective

This study aimed to analyze general trends in the hereditary breast and ovarian cancer ordering practices of providers by specialty, compare differences in tests selected following genetic counselor clarification of the order, and calculate rates of medically actionable results that would not have been identified without updated testing.

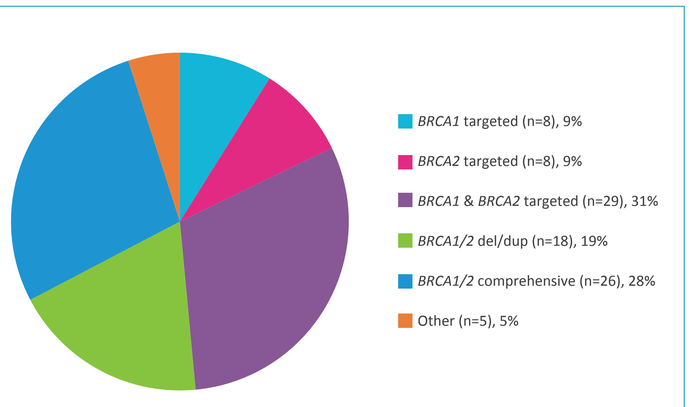
III. Methods

BRCA1/2 genetic testing orders received at Laboratory Corporation of America® Holdings ("LabCorp") for a period of four weeks in 2017 were analyzed for their clinical appropriateness. The ordering provider was contacted by a genetic counselor to offer alternative testing for one of several reasons:

- targeted testing could not be performed without documentation of a familial mutation
- only *BRCA1/2* deletion/duplication testing was ordered
- personal and/or family history suggested expanded testing was indicated

Testing was updated following standard LabCorp testing update procedures. These specimens were tracked and test updates were documented. Medical history and insurance were reviewed by LabCorp's Prior Authorization department. Patients and ordering physicians were provided the option of canceling testing if the testing was not a covered benefit. Finally, testing outcomes and results were recorded for each specimen.

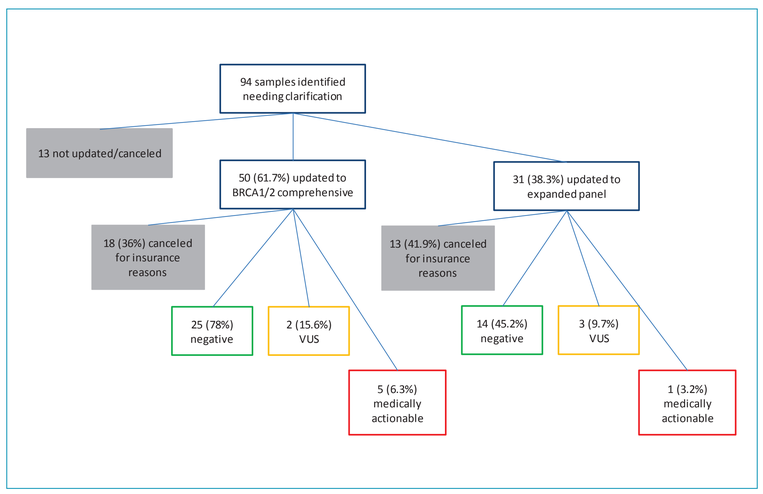
Figure 1. Initial test selection (n=94)



IV. Results

During the study period, 94 specimens were identified that required a discussion of alternative testing with the ordering provider by a LabCorp genetic counselor (GC). Of the tests that were able to be updated, the majority (61.7%) was updated to *BRCA1/2* sequencing and deletion/duplication testing (*BRCA1/2* comprehensive) from either an order of *BRCA1* targeted testing, *BRCA2* targeted testing, *BRCA1* and *BRCA2* targeted testing, or a deletion/duplication only order. Without GC clarification of these test orders, only 6% (n=3) were ordered such that *BRCA1/2* comprehensive testing would have been performed. Of these, the majority (80%) of medically actionable results identified in this group would not have been reported.

Figure 2. Flow chart of updated samples through reporting process



Orders that were not updated to *BRCA1/2* comprehensive testing were either canceled due to lack of ordering physician response (13.8%) or were updated to a more comprehensive cancer genetic testing panel (38.3%). More comprehensive genetic testing panels include expanded breast cancer panels (9.7%), breast and gynecological cancer panels (41.9%), general cancer panels (35.58%) or other testing. Of these samples, 18 (58.1%) received results and one was a medically actionable result in a gene other than *BRCA1/2*.

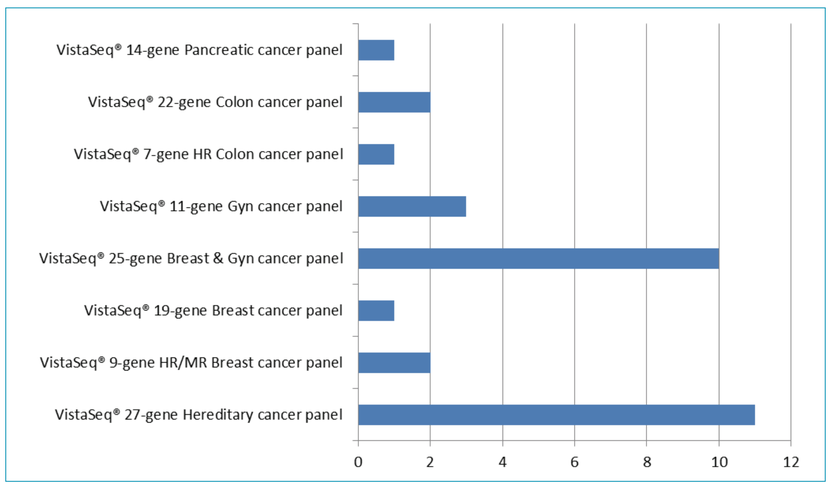
Overall, 53.2% (n=50) of samples included in this study were reported with most having no reportable finding (n=39, 78%). A smaller portion of results had a reportable finding, including a variant of uncertain significance (n=5, 10%) or a likely pathogenic or pathogenic variant (n=6, 12%). The majority of these test orders were received from primary care physicians and general internists (59.6%) and obstetricians and gynecologists (29.8%). Other specialists did place these test orders, but none involved a clinical genetic counselor.

Table 1. Specimens with medically actionable results (n=6)

Specimen	Initial Order	Clinical Indication	Updated Order	Medically Actionable Result	Classification
1	*BRCA1/2* deletion/ duplication	Personal history of breast cancer and family member with previously positive BRCA results (no report available)	*BRCA1/2* comprehensive	*BRCA1* c.5239C>T	Pathogenic
2	*BRCA2* targeted	Not provided	*BRCA1/2* comprehensive	*BRCA2* c.5946delT	Pathogenic
3	*BRCA1* targeted & *BRCA2* targeted	Family history of breast cancer	*BRCA1/2* comprehensive	*BRCA2* c.3264dupT	Pathogenic
4*	*BRCA1/2* Comprehensive & *BRCA1/2* deletion/ duplication	Family history of breast cancer	*BRCA1/2* comprehensive	*BRCA1* c.4386dupA	Likely pathogenic
5	*BRCA1* targeted	Family member with previously positive BRCA results (no report available)	*BRCA1/2* comprehensive	*BRCA1* c.3858_3861 delTGAG	Pathogenic
6	*BRCA1/2* comprehensive	Personal history of melanoma, family history of multiple cancers, and written order for alternative lab's expanded testing panel	VistaSeq® 27-gene Hereditary Cancer panel	*MUTYH* c.1187G>A	Pathogenic

*Medically actionable result would have been identified by initial order.

Figure 3. Breakdown of expanded testing selections (n=31)



V. Conclusions

These data were collected from a single four-week period but represent the larger testing trends of *BRCA1/2* ordering at LabCorp. Extrapolated to a full year of BRCA tests ordered at LabCorp, they suggest that laboratory genetic counselor (GC) review of complicated testing improves the clinical appropriateness of genetic testing ordered by non-genetic specialists in a significant number of patients. Previous analyses suggest that a substantial sum of health care dollars are spent on inappropriate genetic testing and this review of ordering practices of BRCA genetic testing supports these findings.[4,5] Without GC review of these cases, and intervention to update these orders to the recommended testing, a large number of medically actionable results would not be realized. The reasons for this may be varied, but these data suggest that non-specialist providers may experience challenges when selecting appropriately tailored BRCA testing within published guidelines, including both targeted and expanded testing. Laboratory GC review of genetic testing facilitates the increased availability of appropriate hereditary cancer genetic testing.

VI. References

1. Comprehensive Cancer Network. Breast Cancer. (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed March 25, 2018.
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