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Current hereditary cancer reflex testing practices for Ashkenazi Jewish individuals, a large commercial laboratory's experience

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I. Introduction

Published guidelines are used to determine the best candidates for hereditary cancer genetic testing. Guidelines primarily take into account a patient's personal and family history of cancer, including cancer types and ages of diagnosis. It is well known that more individuals are at risk for a hereditary cancer condition than are identified by current testing guidelines.[1,2] Individuals with pathogenic variants in genes with well-established genetic testing criteria do not meet published criteria 21-50% of the time.[1,2] Published testing guidelines also take into account a patient's ethnicity. Three *BRCA1/2* founder variants (FV) account for up to 99% of *BRCA1/2* pathogenic variants identified in Ashkenazi Jewish (AJ) individuals.[3] For this reason, testing for the three FVs is often recommended as the first-tier test for AJ individuals with histories suggestive of hereditary breast and ovarian cancer (HBOC). However, emerging research is showing that testing AJ individuals for the *BRCA1/2* AJ FVs alone could miss 25-50% of pathogenic variants in any HBOC gene and suggests a broader approach to testing this population may be needed.[4,5] There is a lack of current research into the use of reflex testing after negative *BRCA1/2* AJ FV panel results in the AJ population in the context of multi-gene panels.

II. Methods

This study used a retrospective case review of 154 consecutive patient samples with negative results on a *BRCA1/2* AJ FV panel. Multiple published testing guidelines from the American Society of Breast Surgeons (ASBS) and the National Comprehensive Cancer Network (NCCN) were used to determine testing eligibility (**Table 1**). Laboratory genetic counselors called the ordering provider to discuss reflex testing on all negative *BRCA1/2* FV panel results. Uptake of reflex testing was documented to investigate ordering provider test reflex practices.

Table 1: Published testing guidelines used to determine testing eligibility.

Guideline	Source
The American Society of Breast Surgeons Official Statement: Consensus Guideline on Genetic Testing for Hereditary Breast Cancer	www.breastsurgeons.org/docs/ statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf
NCCN Genetic/Familial High Risk Assessment: Breast and Ovarian Cancer v.2.2019	www.NCCN.org
NCCN High Risk Colorectal Cancer v.1.2019	www.NCCN.org
NCCN Cutaneous Melanoma v.2.2019	www.NCCN.org

III. Results

- Of 154 patients negative on a *BRCA1/2* AJ FV panel, 70 (45%) were eligible for more comprehensive testing regardless of ethnicity (**Figure 1**)
  - 11/70 (15.7%) were eligible under more than one guideline
- Only 15/70 (21%) patients had reflex testing (**Figure 2**)
- One clinically significant finding as a result of reflex testing (**Figure 2**)
- Interestingly, 14 of the 70 patients eligible for more comprehensive testing were originally ordered for comprehensive *BRCA1/2* or a multi-gene panel, but were required to have a *BRCA1/2* AJ FV panel first due to insurance restrictions
  - Of these, only 3 (21%) reflexed to additional testing (**Figure 3**)
- A genetic counselor was involved in 27/154 (18%) cases
- Degree of AJ ancestry was not reported in the majority of cases

Figure 1. Reflex testing eligibility of cohort

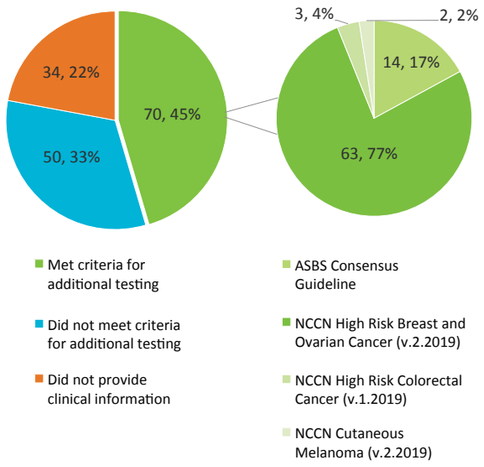


Figure 2. Reflex practices and outcomes among 70 patients eligible for additional testing

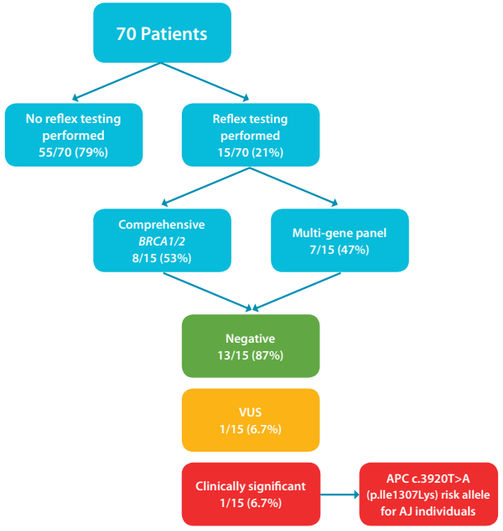
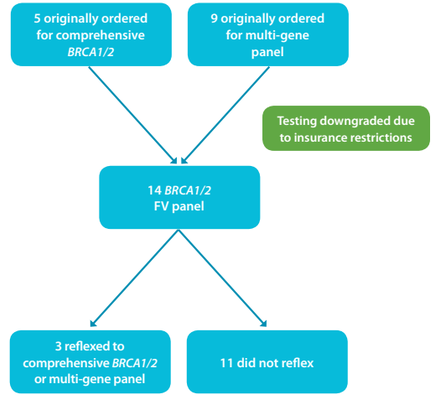


Figure 3. Insurance restricted cases and outcomes among 70 patients eligible for additional testing



The 3 cases that reflexed were approved by insurance after satisfying criteria for first tier *BRCA1/2* AJ FV testing.

IV. Conclusions

Many patients ordered for the *BRCA1/2* AJ FV panel at LabCorp/Integrated Genetics meet published guidelines for further hereditary cancer genetic testing. However, most of these individuals do not have reflex testing ordered despite laboratory genetic counselor outreach. Low uptake of reflex testing in the context of insurance restrictions reflects a possible barrier to considering reflex testing and warrants further study. Degree of AJ ancestry was often not provided, and also warrants further investigation into if providers and insurance companies are considering this information when selecting testing to order or approve.

Emerging data are showing the utility of testing beyond the *BRCA1/2* FVs in AJ individuals at risk for HBOC. This analysis builds on this topic by demonstrating the need for education for providers ordering hereditary cancer testing. Education could help encourage adherence to testing guidelines and ensure AJ individuals receive the most appropriate and comprehensive testing.

V. References

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