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ORIGINAL RESEARCH

Current Testing Guidelines: A Retrospective Analysis of a Community-Based Hereditary Cancer Program

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

It is estimated that 5% to 10% of all cancers are related to a hereditary cancer syndrome. However, specific cancers, such as pancreatic and ovarian cancers, are related to hereditary cancer syndromes 15% to 20% of the time. Genetic testing guidelines for hereditary cancer syndromes are frequently reviewed and updated by the National Comprehensive Cancer Network (NCCN). The purpose of this retrospective analysis is to identify carriers of pathogenic variants or hereditary cancer syndrome who do not meet NCCN criteria for testing and compare the results with previous studies. The data obtained can be used to provide recommendations to assess current guidelines for testing and evaluate the benefit of comprehensive panel testing vs. standard testing for specific hereditary cancer syndromes. This project is a retrospective review of clinical histories of patients who had multigene panel testing between September 2015 and February 2019 through a cancer outreach and risk assessment (CORA) program. Frequencies analyses were performed to analyze results. A total of 233 individuals were included in the analysis: 171 met *BRCA1/2* testing criteria, 66 met Lynch syndrome criteria, and 4 met polyposis criteria. Of the individuals meeting established criteria for testing, 39 were identified with pathogenic variants. However, only 10 of these individuals were identified with a pathogenic variant associated with the criteria for which they met. Genetic testing that is limited to only those patients with genes associated with hereditary cancer syndromes may lead to exclusion of other potentially actionable genes, which may impair a patient's ability to receive additional screening or preventative measures.

Approximately 5% to 10% of all cancers can be related to germline pathogenic variants (Marta et al., 2019), although that number is expected to climb as more information on the genetic origin of cancers becomes available. At this time, up to 24% of ovarian cancers (Ring et al., 2017), 10% of pancre-

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atic cancers (Ohmoto et al., 2019), and 5% to 10% of breast cancers are hereditary (Göhler et al., 2017). The most commonly recognized germline pathogenic variants that increase one's risk for the development of cancer are *BRCA1/2* and Lynch-related genes (*MLH1, MSH2, MSH6, PMS2*, and *EPCAM*). However, more genes are being identified that increase one's risk for cancer development, and it is important to ensure that practitioners are utilizing the most up-to-date information when ordering testing. A critical mutation could easily be missed if testing is limited to only those genes in a basic genetic panel or those that a practitioner is familiar with (LaDuca et al., 2014).

BRCA testing was introduced in 1995 to evaluate patients for hereditary breast and ovarian cancer (HBOC) syndrome. Potential patients for testing included individuals diagnosed with a high-risk breast cancer or with strong family histories of breast cancer. A high-risk breast cancer is considered a diagnosis at or below the age of 45, triple-negative breast cancer under the age of 60, or multiple family members with a breast cancer diagnosis (Sankar et al., 2006). It was not until 2013 when the Supreme Court of the United States ruled that a gene could not be patented (Myriad Genetics held a previously acquired patent on *BRCA1/2* testing ["Association for Molecular Pathology v. Myriad Genetics, Inc," 2012]) that other labs were able to begin testing for pathogenic variants in *BRCA*, and panel testing came to the forefront of oncology care. Since then, multigene panel testing continues to grow, and practitioners' perceptions of appropriate testing is evolving (Hooker et al., 2017). Unfortunately, due to a lack of genetics knowledge and management guidelines for practitioners across the country, many individuals are undergoing limited genetic testing (Douma et al., 2016). This project will investigate the appropriateness of limited testing vs. comprehensive panel testing in individuals who meet criteria set by the National Comprehensive Cancer Network (NCCN).

LITERATURE REVIEW

Genetic testing for hereditary cancer syndromes allows for patients to identify potential lifetime risk factors for the development of a variety of cancers. Additionally, it allows practitioners to modify screenings and interventions to better serve the patient through early identification or cancer prevention. With the availability of multigene panel testing, more options are accessible to both practitioners and patients (Robson et al., 2015).

Current guidelines from the NCCN (2019) restrict recommendations for genetic testing to a few genes: *BRCA1/2*, *PTEN*, *TP53*, *MSH6*, *MSH2*, *MLH1*, *EPCAM*, *PMS2*, and *MUTYH*. In addition, the criteria for testing is significantly limited, requiring specific criteria for individuals to meet the standards dictated. However, research, as well as current practices, are beginning to show the importance of expanded testing outside of NCCN Guidelines, as actionable pathogenic variants are being identified in unexpected patients (Espenschied et al., 2017). Actionable pathogenic variants are defined as any pathogenic mutation that currently has a recommendation for alterations to management or screening options (Carr et al., 2016).

In 2019, The American Society of Breast Surgeons (ASBS) published their consensus guidelines on genetic testing for hereditary breast cancer. The consensus outlines the recommendation for genetic testing in all individuals with a personal history of breast cancer, regardless of age at diagnosis, family history, and hormone receptor status. Additionally, patients who previously underwent genetic testing for pathogenic variants only in *BRCA1* and *BRCA2* should be considered for updated or additional testing. Beitsch and colleagues (2019) outline the importance of testing patients outside of the guidelines due to the age restrictions. A patient diagnosed with triple-negative breast cancer at the age of 60 qualifies, but if the patient were diagnosed one day after their 61st birthday, they would not be recommended for testing.

A poster presentation at the 2019 San Antonio Breast Cancer Symposium further illustrated the importance of expanded testing through the retrospective review of 2,806 individuals. Within this cohort, 11.9% had an identified germline pathogenic mutation, only half of which were *BRCA1* or *BRCA2* (Hoste et al., 2019).

Evidence supporting comprehensive testing in cancers other than breast cancer is prevalent, too. In a cross-sectional study of 3,607 men with

a personal history of prostate cancer, 620 (17.2%) were found to have pathogenic germline pathogenic variants. 229 (37%) of these individuals did not meet NCCN criteria for testing (Nicolosi et al., 2019).

Testing for Lynch syndrome is also restricted by the Bethesda and Amsterdam guidelines (NCCN, 2019). However, studies suggest that due to the Guideline's limitations, Lynch syndrome is often undiagnosed. Approximately 3% to 5% of colon cancers are associated with Lynch syndrome. Of women who are later found to have a Lynch-related cancer, 50% of these are diagnosed with a gynecological cancer as the first primary (Kirkpatrick & Cotton, 2018).

Pritzlaff and colleagues (2017) performed a retrospective study of 715 male breast cancer patients who underwent multigene panel testing from March 2012 through June 2016. Per NCCN Guidelines, the presence of a male breast cancer is an immediate indication for germline testing for HBOC syndrome, although it is limited to *BRCA1* and *BRCA2*. Of these patients, 18.1% tested for a pathogenic mutation, with the most frequently identified pathogenic variants found in *BRCA2* and *CHEK2*. Additional variants were found in *PALB2*. These variants indicated an increased risk for male breast cancer in *BRCA2*, *CHEK2*, and *PALB2*. Additionally, pathogenic variants were also identified in *ATM*, *BARD1*, *NF1*, *RAD51D*, *NBN*, and *MRE11A*, although they were not as significant as the previously mentioned variants.

Churpek and colleagues (2015) performed an evaluation of 289 African American females with a personal history of invasive breast cancer in addition to other high-risk characteristics, such as tumor characteristics or family history. Recent studies found that breast cancers diagnosed in an African American female have a higher likelihood of being triple negative than in white or Hispanic women (Dietze et al., 2015). At this time, it is not known whether the difference in hormone receptor status is related to disparities or biology. Triple-negative breast cancer is more aggressive and an automatic indication for genetic testing if diagnosed at 60 years old or older (NCCN, 2019).

Based on the study by Dietze and colleagues (2015), it cannot adequately be attributed to the general population of African American women. However, the information is still valid, as a study was performed by utilizing a multigene panel test. 68 of the 289 subjects were identified to carry a pathogenic genetic variation, accounting for 23.5%, which is higher than the expected 5% to 10% within the general population. Of those identified with pathogenic variants, *BRCA1* and *BRCA2* were the most prevalent at 80%, while the other 20% consisted of pathogenic variations in *PALB2*, *CHEK2*, *BARD1*, *ATM*, *PTEN*, and *TP53*.

In a systematic review of eight different studies, Prapa and colleagues (2017) provided an intensive overview of the presence of additional pathogenic variants, outside of *BRCA1* and *BRCA2*, by investigating the results of 7,272 subjects with either breast or ovarian cancer. Additional genes identified through this study related to breast cancer susceptibility are *CDH1*, *PTEN*, *STK11*, *TP53*, *ATM*, *CHEK2*, *NF1*, *PALB2*, *BRIP1*, *NBN*, *RAD51C*, and *RAD51D*.

As depicted throughout retrospective studies, there are several genes being identified in patients meeting NCCN Guidelines for specific pathogenic variants, as well as in patients who do not meet current guidelines. Many of these pathogenic variants are considered actionable, and their presence may affect an individual's treatment. Therefore, consideration should be given for all patients undergoing genetic testing to have comprehensive panel testing performed instead of limited germline testing (Hoste et al., 2019; Nicolosi et al., 2019; Prapa et al., 2017).

PURPOSE

The purpose of this project is to assess the benefit of utilizing multigene panel testing over disease-specific testing for patients meeting NCCN Guidelines for HBOC syndromes, Lynch syndromes, and polyposis syndromes, and determine if NCCN Guidelines should be changed to include panel testing and be a resource to influence coverage by insurance companies.

This project attempts to answer the following questions: How many actionable genes were identified outside of the expected genetic pathogenic variants in patients meeting NCCN criteria for testing? How many patients who didn't meet NCCN Guidelines were identified to carry an actionable mutation? How many patients tested

positive for a pathogenic mutation outside of what was expected, such as Lynch syndrome when HBOC is suspected? Of all patients meeting NCCN criteria for testing, how many were identified with a pathogenic mutation?

METHODS

Study Population

Deidentified molecular results of patients seen within a community cancer outreach and risk assessment (CORA) program from September 1, 2015, through February 29, 2019, were evaluated. All patients had clinical histories reviewed for personal and family history of malignancy or other qualifying criteria per NCCN Guidelines. Patients under the age of 18 and older than the age of 88 were excluded from the study. Any patients whose testing was ordered by a different practitioner at an outside facility were not included. Pregnant patients were not included in the study.

Demographics

Demographics and clinical characteristics of the studied cohort are shown in Table 1. A total of 233 subjects were analyzed to see if they met NCCN criteria. Results of testing utilizing a 67-gene panel are shown. Patients were predominantly female (90%), and the mean age at testing was 51 years. A number of patients (73%) met NCCN criteria for *BRCA1/2* testing, while NCCN criteria for Lynch syndrome patients was met by 28%. Additional NCCN criteria evaluated include Li-Fraumeni syndrome (4%), Cowden syndrome (0%), Peutz-Jeghers (0%), polyposis (2%), and single-site or specific site analysis of previous identified gene within family (7%). Some patients met NCCN criteria for two or more syndromes (29%), while 40 (17%) patients met criteria for both *BRCA1/2* and Lynch. Of those tested, 14% did not meet any of the criteria set by the NCCN.

Table 1. Patient Demographics and Clinical Characteristics

	N	%
Female	210	90.1
Male	23	9.9
Age at testing, mean (range)	51 (22–87)	
Testing criteria met		
BRCA1/2	171	73.3
Lynch	66	28.3
Li-Fraumeni	9	3.9
Cowden	0	0.0
Peutz-Jeghers	0	0.0
Polyposis	4	1.7
Single-site	16	6.9
BRCA1/2 and Lynch	40	17.2
NCCN criteria not met	33	14.2

Both the clinical facility and university institutional review boards reviewed this research for exempt status. The database was maintained on an encrypted computer connected to an encrypted network and through a hospital network's technologies system. Within the database, no identifiable patient information was maintained. The database only included a study ID number, sex, age range, and testing results. The study identification number was linked to the original database maintained by the CORA program, which is password protected and only accessible by the program's manager/practitioner and the program's coordinator.

Data Collection

The database was created for the purpose of maintaining numbers of patients tested, number of positive, negative, and variant of uncertain significance results, and type of testing utilized. For this project, each patient was randomly assigned a study number and moved to a separate, password-protected spreadsheet. Within the database created for this project, only the study number, age of patient at time of testing, gender, results of testing (positive, negative, or variant of uncertain significance) and genes identified, if any, were recorded. A variant of uncertain significance is an inconclusive result. It indicates a mutation in one's gene—not the same mutation that is proven to be an increased risk of cancer, but a mutation separate from the expected DNA make-up (Greenblatt, 2015). Due to variations in panel sizes and genes tested, only those patients who underwent comprehensive testing through Ambry Genetics with the CancerNext-Expanded panel, analyzing 67 genes, were included.

All selected participants were retrospectively analyzed for NCCN criteria met or not met. The

criteria utilized were the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 3.2019, published on January 18, 2019, and the NCCN Guidelines for High-Risk Assessment: Colorectal, Version 1.2018, published on July 12, 2018. Patients were assessed for meeting the criteria for the following pathogenic variants/syndromes: HBOC (*BRCA1/2*), Li-Fraumeni syndrome (*TP53*), Cowden syndrome (*PTEN*), Peutz-Jeghers (*STK11*), Lynch syndrome (*MSH2*, *MSH6*, *MLH1*, *EPCAM*, *PMS2*), and polyposis syndromes (*APC*, *MUTYH*).

Data were downloaded to an Excel spreadsheet for data analysis. Frequencies procedures were performed for data analyses. The following comparisons were made:

- Patients positive for a pathogenic mutation meeting NCCN Guidelines vs. patients positive for a pathogenic mutation not meeting NCCN criteria.
- Patients who meet NCCN Guidelines and test positive vs. negative vs. inconclusive
- Patients positive for pathogenic mutation within the expected syndrome (e.g., HBOC, Lynch, etc.) vs. positive patients outside of expected syndrome.

Table 2. *BRCA1/2* Criteria Met, Pathogenic Variants

Gene	Total PV, n	% of PVs
BRCA2[a]	2	9.1
SDHA[a]	1	4.5
HOXB13	2	9.1
MUTYH	3	13.6
MSH6[a]	2	9.1
CHEK2[a]	2	9.1
MSH2[a]	1	4.5
POT1	1	4.5
RAD51C[a]	1	4.5
RET	1	4.5
FH	1	4.5
BMPR1A	1	4.5
CDKN2A	1	4.5
ATM[a]	1	4.5
TMEM127	1	4.5
RAD50	1	4.5

Note. One patient identified with both *MUTYH* and *CHEK2* pathogenic variants, and one patient identified with *RET* and *HOXB13* pathogenic mutations.
PV = pathogenic variant.
[a]Considered actionable per NCCN Guidelines.

RESULTS

Results of genetic testing were classified as negative, positive (pathogenic or likely pathogenic variant identified), and variant of uncertain significance. In comparison to the expected 5% to 10% findings of pathogenic variants, pathogenic or likely pathogenic variants were identified in 15.9% of patients, 44.2% negative for pathogenic variants, and 39.9% inconclusive.

BRCA1/2 Criteria Met

Patients meeting testing criteria for *BRCA1/2* accounted for 171 (73.3%) patients. Of these, 22 (12.9%) identified with pathogenic variants (Table 2), 78 (45.6%) tested negative, and 71 (41.5%) were classified as variant of uncertain significance. Only two of those individuals testing positive were found to have a pathogenic variant in *BRCA2*. All other individuals testing positive were found to have pathogenic variants outside of the expected *BRCA1* and *BRCA2* genes (specifically *SDHA*, *MSH6*, *CHEK2*, *MSH2*, *NF1*, *RAD51C*, *RET*, *HOXB13*, *FH*, *BMPR1A*, *MUTYH*, *CDKN2A*, *POT1*, *ATM*, *TMEM127*, and *RAD50*; see Table 2). One patient was identified to carry two pathogenic variants, *HOXB13* and *RET*, while another identified with pathogenic variants in *CHEK2* and *MUTYH*. Seven of these unexpected identified pathogenic variants are currently considered actionable by the NCCN.

Lynch Syndrome Criteria Met

Sixty-six (28.3%) of patients met Lynch syndrome testing. Negative results were classified in 28 (42.4%), variant of uncertain significance in 22 (33.3%), and positive or pathogenic variants in 16 (24.2%) patients, accounting for 18 total pathogenic variants (Table 3). Lynch-related variants were identified in seven of those individuals testing positive, four with *MSH6*, two with *MSH2*, and one with *EPCAM*. The patient testing positive for *EPCAM* also tested positive for a pathogenic variant in *CHEK2*. No pathogenic variants were identified in *MLH1* or *PMS2* for those meeting

Table 3. Lynch Syndrome Criteria Met, Pathogenic Variants

Gene	Total PV, n	% of PVs
BLM	1	5.6
BRCA1[a]	1	5.6
CDH1[a]	1	5.6
CDKN2A	1	5.6
CHEK2[a]	3	16.7
EPCAM[a]	1	5.6
HOXB13	2	11.1
MSH2[a]	2	11.1
MSH6[a]	4	22.2
MUTYH	1	5.6
RET	1	5.6

Note. One patient identified with *RET* and *HOXB1* pathogenic mutations, and one patient identified with *CHEK2* and *EPCAM* pathogenic mutations.
PV = pathogenic variant.
[a]Considered actionable per NCCN Guidelines.

Lynch syndrome criteria. Actionable pathogenic variants outside of the Lynch syndrome spectrum were identified in five patients, *CHEK2* in three patients, *BRCA1* in one patient, and *CDH1* in one patient. Additional pathogenic variants identified included *HOXB13*, *BLM*, *CDKN2A*, *RET*, and *MUTYH*.

Both *BRCA1/2* and Lynch Syndrome Criteria Met

Of the patients meeting both *BRCA1/2* and Lynch testing criteria (40), 17.5% were found to have pathogenic variants, 47.5% were negative, and 35% had inconclusive results. Of the pathogenic variants identified, only three (7.5%) were in the expected genes associated with *BRCA1/2* and Lynch syndrome, all three being Lynch related. One individual with a pathogenic variant of *CHEK2* was identified, which is associated with modified screening and management per NCCN Guidelines. The remaining pathogenic variants were considered nonactionable at this time by the NCCN (2019).

None of the individuals meeting Li-Fraumeni syndrome testing criteria (n = 9) were found to have a pathogenic variant in *TP53*, which is associated with the diagnosis of Li-Fraumeni. Of those tested, two (22%) tested negative, five (55.6%) identified to have a variant of uncertain significance, and two (22.2%) identified with pathogenic variants. One was a heterozygous for a pathogenic mutation in *MUTYH*. The other was identified with two pathogenic variants, one in *CHEK2* and one in *MUTYH*. A heterozygous mutation in *MUTYH* was nonactionable at the time.

Four (1.7%) patients met polyposis syndrome testing criteria. Two (50%) identified with variant of uncertain significance, one (25%) tested negative, and one (25%) tested positive for a pathogenic variant in *APC*, which is associated with the expected polyposis syndrome.

Those not meeting any NCCN criteria accounted for 33 (14.2%) of patients. Of those evaluated, three (9.1%) identified with pathogenic variants, two of which were considered actionable (*CHEK2* and *PALB2*). The other individual was found to have a pathogenic variant in *CDKN2A*, which is associated with a hereditary pancreatic-melanoma cancer syndrome. Fifteen (45.5%) tested negative and fifteen (45.5%) identified with variant of uncertain significance. Pathogenic and likely pathogenic variants are depicted in Table 4.

DISCUSSION

Within the sample population, 15.9% of patients tested were identified to carry pathogenic variants. Of the 53 patients meeting either *BRCA1/2*, Lynch syndrome, Li-Fraumeni syndrome, or polyposis syndrome criteria, only 10 (18.9%) of the positive results were consistent with the syndromes and associated genes. Therefore, if the ordering practitioner had limited testing related to only specific genes associated with criteria, over 80% of pathogenic variants would have been missed. Although not all of the identified variants are considered actionable, they may become actionable in the future. NCCN Guidelines are updated on a regular basis with expert panelists working together to update screening guidelines, including adding genes to actionable pathogenic variants.

Additionally, three patients who did not meet NCCN criteria were identified as having pathogenic variants. By limiting genetic testing to only those meeting criteria, the overall population may be missing potential risk factors. While population testing may not be indicated, expanding

guidelines for testing should include individuals with all breast cancer diagnoses or strong family histories of malignancy, regardless of cancer type. All of the groups identified, excluding polyposis, surpassed the 5% to 10% estimated presence of pathogenic variants, indicating the rate of pathogenic variants in the study group was higher than expected.

Limitations

Significant limitations exist within this analysis due to the small sample size. Additionally, all patients were within the same geographic area and tested through the same community program. A larger study evaluating criteria met and genes identified that utilizes a larger population size with diverse patients from all racial, social, and ethnic backgrounds should be considered.

Clinical Implications

Implications for clinical impact are based on the results of this analysis, as well as previously cited articles. Although many of the genes analyzed in the 67-gene panel are currently not actionable per NCCN Guidelines, there are still a number that are outside the spectrum of testing but may influence screening and management. For instance, while *CHEK2*, *ATM*, and *PALB2* are less penetrant than *BRCA1* and *BRCA2*, they are considered moderate risk and increased screening may be considered (Acevedo et al., 2018).

Advancements in cancer treatment are also influencing the need for genetic testing. With the introduction of poly(ADP-ribose) polymerase (PARP) inhibitors and the U.S. Food & Drug Administration's approval for use in prostate and ovarian cancer patients with *BRCA* pathogenic variants, genetic testing may directly influence treatment (Buchtel et al., 2018). In early stage prostate cancer patients, treatment will not immediately be affected by a *BRCA* mutation; however, delay in testing can result in a delay in treatment in the event of recurrence or metastasis (Giri et al., 2019).

Additional recommendations include:

1. All individuals, regardless of personal cancer history, should be evaluated by primary care physicians on an annual basis for cancer risk and risk of genetic pathogenic variants that increase the risk for cancer. The annual review is imperative due to the potential for new cancer diagnoses within the family.

2. Individuals tested prior to 2013 should consider additional, expanded panel testing, as a mutation may be present that was not previously tested for.

3. Expansion of NCCN criteria to promote panel testing instead of limited syndrome only–related pathogenic variants.

4. Education of primary care providers, oncologists, and advanced practitioners on assessments, what to look for, and appropriate testing.

Table 4. *BRCA1/2* and Lynch Syndrome Criteria Met, Pathogenic Variants

Gene	Total PV, n	% of PVs
APC	1	2.5
ATM	1	2.5
BLM	1	2.5
BMPR1A	1	2.5
BRCA1	1	2.5
BRCA2	2	5.0
BRIP1	1	2.5
CDH1	1	2.5
CDKN2A	3	7.5
CHEK	5	12.5
EPCAM	1	2.5
FH	1	2.5
HOXB13	2	5.0
MSH2	2	5.0
MSH6	5	12.5
MUTYH	3	7.5
NF1	1	2.5
PALB2	1	2.5
POT1	2	5.0
RAD50	1	2.5
RAD51C	1	2.5
RET	1	2.5
SDHA	1	2.5
TMEM127	1	2.5
Total	40	

Note. PV = pathogenic variant. Only genes identified with a pathogenic variant included in Table 2.

CONCLUSION

Further studies are indicated to evaluate patients meeting criteria compared with those who do not, as well as pathogenic variants identified outside of the expected spectrum. Additionally, concern should be given to the mental distress that genetic testing may put on an individual, especially when little to no information is available on newer or nonactionable genes (Harris & Hutson, 2019). Testing decisions should be individualized based on personal history, family history, and psychological mentality. Expanded panel testing may not be appropriate if a patient has a high level of anxiety and a variant of uncertain significance result. However, it is the responsibility of the practitioner to offer all options to the patient, providing the opportunity for a well-informed decision-making process.

Disclosure

The authors have no conflicts of interest to disclose.

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