

Patients Tested at a Laboratory for Hereditary Cancer Syndromes Show an Overlap for Multiple Syndromes in Their Personal and Familial Cancer Histories

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Key Words

Hereditary breast and ovarian cancer · *BRCA1* · *BRCA2* · Lynch syndrome · Hereditary cancer syndromes · Genetic testing · NCCN guidelines · Panel testing

Abstract

Objective: Hereditary cancer testing guidelines are based on the premise that the common hereditary cancer syndromes have distinct, recognizable phenotypes. However, many syndromes present with overlapping cancers. The aim of this analysis was to identify the proportion of patients tested for Lynch syndrome (LS) or hereditary breast and ovarian cancer (HBOC) who met testing criteria for the other syndrome. **Method:** We analyzed a commercial laboratory database of patients tested for LS and HBOC in a clinical setting from 2006 to 2013. Patient cancer histories were analyzed using the 2012 NCCN criteria for LS and the 2013 NCCN criteria for HBOC. **Results:** In all, 7% of the patients tested for HBOC met criteria for LS testing. The majority of these patients had a family history of colorectal (30.9%) and/or endometrial cancer (22.7%). Conversely, 29.5% of the patients tested for LS met criteria for HBOC testing. In this group, 30.5% of the patients had a personal history of breast cancer, and 12.6% had a personal history of ovarian cancer. **Conclusions:** Our data

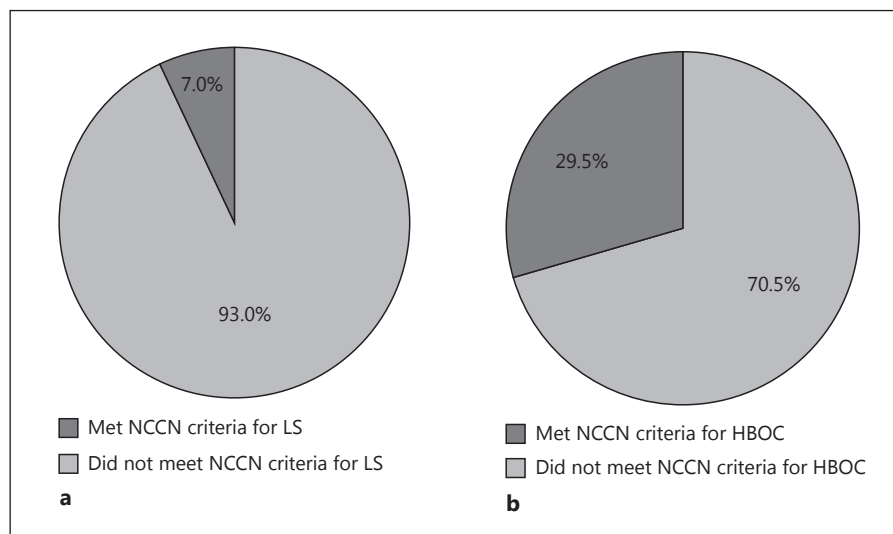
demonstrate a substantial phenotypic overlap among patients for multiple common inherited cancer syndromes, which likely complicates diagnosis and test selection. This supports the value of multigene panels to identify pathogenic mutations in the absence of a clinically specific phenotype.

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Introduction

Genetic testing is generally offered to individuals with strong personal and family histories of cancer. Professional societies and expert groups provide guidance for personal and family history screening criteria for clinicians to use in the identification of patients most likely to benefit from predictive testing for hereditary cancers. For hereditary breast and ovarian cancer (HBOC) syndrome, the National Comprehensive Cancer Network (NCCN) publishes guidelines outlining testing criteria for personal and family history of HBOC-associated cancers including breast, ovarian, pancreas, and prostate cancers [1]. The NCCN also publishes guidelines for Lynch syndrome (LS), which is generally suspected if there is familial aggregation of LS cancers such as colorectal and endome-

Fig. 1. a Percentage of patients tested for HBOC (n = 852,106) who met NCCN criteria for LS. **b** Percentage of patients tested for LS (n = 62,719) who met NCCN criteria for HBOC.



trial cancers, but also includes tumors of the ovary, stomach, urinary/renal pelvis, biliary tract, small bowel, pancreas, and brain [2–4].

These testing guidelines are based on the premise that the common hereditary cancer syndromes have recognizable and distinct phenotypes; however, as knowledge about these syndromes has increased, a considerable overlap in the spectrum of cancers has been observed. Notably, both HBOC and LS are associated with ovarian cancer. Of the ovarian cancers that arise in women with identifiable genetic susceptibility, women from HBOC and LS families account for 65–85% and 10–15%, respectively [5–8]. An increased risk of pancreatic cancer is also associated with both of the syndromes [9, 10]. There have been suggestions that the breast cancer risk is also increased in women with LS [11–13], and that the endometrial and colorectal cancer risk is increased in patients with *BRCA1* and *BRCA2* mutations [14].

Owing in part to the amount of cancer type overlap among the common hereditary cancer syndromes, there is increasing recognition that the use of risk criteria as the sole indicator for testing will miss a proportion of families [15]. Developments in next-generation sequencing platforms, which simultaneously assay multiple genes associated with a given spectrum of genetic disorders in a very cost-efficient manner, have shown promising results for overcoming the phenotypic heterogeneity seen with a wide range of genetic disorders, including congenital heart disease [16, 17]. In the work presented here, the extent of the phenotypic overlap between two common hereditary cancer syndromes was quantified to assess the

effectiveness of current strategies to appropriately test patients who meet NCCN criteria for both syndromes. To do this, we cross-referenced the testing criteria for HBOC and LS in patients referred for hereditary cancer testing at a large commercial laboratory.

Subjects and Methods

We conducted a retrospective analysis of personal and family cancer histories from a commercial clinical laboratory database of patients tested for LS or HBOC from January 2006 to December 2013. A subset of 9,000 patients tested for both syndromes either sequentially or in parallel was also analyzed. All patients tested for HBOC underwent comprehensive testing including full sequence analysis of *BRCA1* and *BRCA2*, with a subset of patients also receiving large rearrangement testing. All patients tested for LS underwent full sequence and large rearrangement analyses of *MLH1* and *MSH2*. The testing for some patients also included full sequence and large rearrangement analyses of *MSH6*, *PMS2*, and/or *EPCAM*. Patients tested for a specific family mutation, the three common Ashkenazi Jewish mutations in *BRCA1* and *BRCA2*, or a single mismatch repair (MMR) gene for LS were excluded.

For each patient, the clinical history was obtained from a test requisition form (TRF) provided by the referring health care provider. No individually identifiable patient information was acquired from the TRF. The patients were only placed in one category. Based on how clinical history was coded, patients might have met criteria based on their personal and family history, but since personal history was coded first, they would only have been counted in the personal history totals. The clinical history for patients tested for HBOC was compared to the 2012 NCCN criteria for LS, as these were the guidelines available at the time of analysis [4]. Patients were included as meeting criteria for LS if they, a first-degree relative, or a second-degree relative met revised Bethesda criteria [18] or had a diagnosis of endometrial cancer under the age

Table 1. Clinical history of the tested HBOC patients that met the NCCN LS criteria

LS criteria	%
<i>Family history only</i>	
CRC <50 years	30.9
EC <50 years	22.7
Two Lynch cancers in the same relative	16.4
CRC and a Lynch cancer <50 years	11.8
CRC and two other Lynch cancers	7.6
<i>Personal history only</i>	
EC <50 years	3.8
Two Lynch cancers	3.2
CRC <50 years	2.5
<i>Family and personal history</i>	
Personal history of CRC and family history of two Lynch cancers	0.8
Personal history of CRC and family history of Lynch cancers <50 years	0.4

Patients were only counted in one category. CRC = Colorectal cancer; EC = endometrial cancer.

Table 2. Clinical history of the tested LS patients that met the NCCN HBOC criteria

HBOC criteria	%
<i>Family history only</i>	
OC	32.8
BC ≤45 years	12.2
BC and OC	8.3
Three cases with BC, PC, and/or OC	2.6
Male BC	0.7
<i>Personal history only</i>	
OC	12.6
BC ≤45 years	5.4
TNBC ≤60 years	0.1
Male BC	0.1
<i>Family and personal history</i>	
Personal history of BC and one relative with BC ≤50 years	22.4
Personal history of BC and family history of OC	2.4
Personal history of PC and family history of two cases with PC, BC, or OC	0.3
Personal history of BC and family history of PC	0.1

Patients were only counted in one category. OC = Ovarian cancer; BC = breast cancer; PC = pancreatic cancer; TNBC = triple-negative breast cancer.

of 50 years. The clinical history for patients tested for LS was compared to the 2013 NCCN criteria for HBOC [1]. Patients were included as meeting criteria for HBOC based on their personal and family cancer history. The full NCCN criteria are listed in the supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000437307). The contribution of prostate cancer was excluded from these criteria, as we were unable to document the Gleason score.

Results

During the study period, we tested 852,106 patients for HBOC, excluding those patients tested for known inherited mutations and those tested for the common Ashkenazi Jewish founder mutations. Of the patients tested for HBOC, 59,908 (7.0%) had cancer histories that met 2012 NCCN clinical criteria for LS (fig. 1a). Table 1 identifies the reasons why they met NCCN criteria for LS. The majority of the patients who met criteria had family histories of colorectal (30.9%) and/or endometrial cancer (22.7%). Interestingly, 9.5% of these patients qualified based on a personal history of endometrial cancer under the age of 50 years, colorectal cancer under the age of 50 years, or a personal history of two Lynch cancers, making these patients obvious candidates for LS testing in addition to HBOC testing.

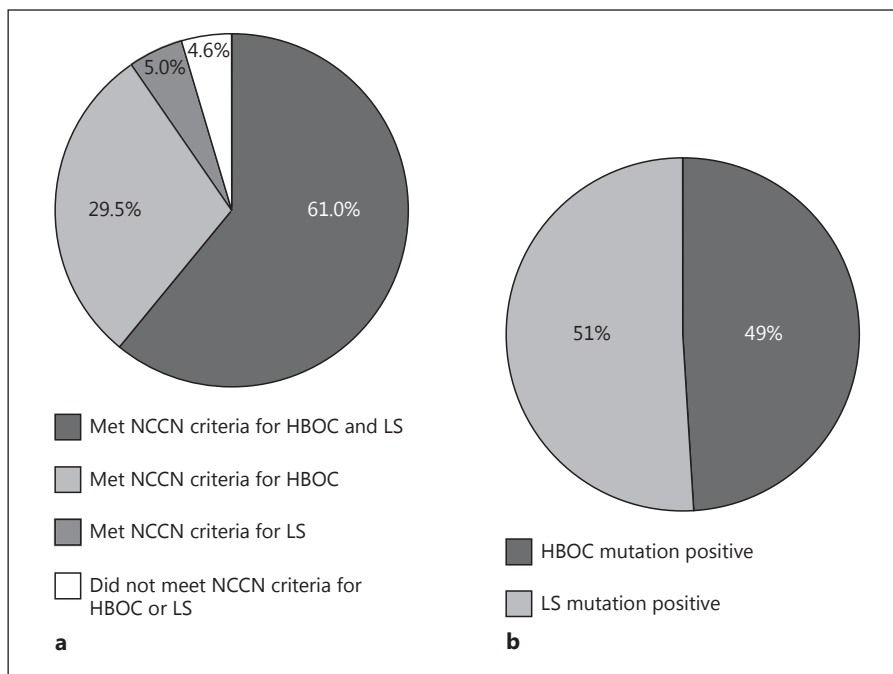
During the same study period, we tested 62,179 patients for LS, excluding those tested for a known family mutation or those tested for only one MMR gene. Of the patients tested for LS, 29.5% (18,339) met 2013 NCCN clinical criteria for HBOC (fig. 1b). Table 2 shows the reasons why they met NCCN criteria for HBOC. Strikingly, 30.5% of the patients had a personal history of breast cancer, and 12.6% had a personal history of ovarian cancer.

Of the 9,000 patients tested for both syndromes, 61% met criteria for both, 29.5% met criteria for HBOC only, 5.0% met criteria for LS only, and 4.6% met neither criteria (fig. 2a). After testing, 6.8% of these patients were shown to be positive for *BRCA1* or *BRCA2* (3.3%) and LS mutations (3.5%) (fig. 2b).

Discussion

The results presented here suggest that there is a phenotypic overlap among the cancer histories of patients tested for HBOC and LS based on the subset of patients who meet standard testing criteria for both syndromes. In all, 6.9% of the patients tested for HBOC met criteria for LS, 9.9% of whom qualified based on their personal his-

Fig. 2. a Percentage of patients tested for both HBOC and LS (n = 9,000) who met NCCN criteria for only HBOC, only LS, both HBOC and LS, or neither HBOC nor LS. **b** Mutation breakdown of the 6.8% of patients tested for both syndromes that were found to carry a mutation.



tory of cancer alone. This subset of patients is at a particularly high risk of testing positive for the other syndrome (LS) if testing is negative for the first (HBOC).

Although several studies have suggested there is no increased risk for breast cancer with LS, there has been no consensus to date on the correlation between breast cancer and LS [11–13, 19, 20]. This study revealed that 22.4% of the LS patients meeting NCCN criteria for HBOC had a personal history of breast cancer and a family history of early-onset breast cancer. These data could represent an ascertainment bias if having more cancers in a family increases the referral rate for genetic testing, even if those cancers are not known to be associated with the specific syndrome for which the patient is referred.

The overlap between patients tested for a single syndrome, either HBOC or LS, but meeting criteria for both syndromes is shown in figure 3. However, the number of patients actually tested for both syndromes (n = 9,000) was much smaller than the number of patients who met criteria for both syndromes (n = 78,247). While this could have been due to several reasons (patient dropout due to cost, lack of health care provider knowledge about other syndromes, or testing being performed in another laboratory), it certainly suggests an inherent weakness in the current guidelines and practices. Furthermore, the small subset of patients actually tested for both syndromes was as likely to test positive for LS as for HBOC (fig. 2b), il-

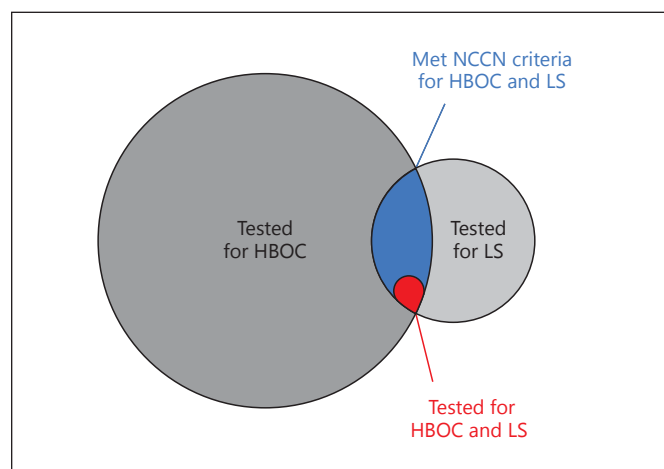


Fig. 3. Overlap of patients tested for only HBOC (dark gray) or only LS (light gray) with those who met criteria for both syndromes (blue). The percentage of patients actually tested for both syndromes (red) is also shown. Colors refer to the online version only.

lustrating the difficulty of predicting which syndrome fits best with a patient's cancer phenotype.

One limitation of this study is that personal and family cancer histories are assessed by patient report on the TRF. Since patients and providers are likely to report only the personal and family histories most relevant to the syn-

drome being tested for, it is possible that cancers perceived to be unrelated to the test order may be left off the TRF. Thus, our results may actually underrepresent the phenotypic overlap among the cancer histories in this testing population.

The reason for the phenotypic overlap for multiple syndromes among patients' personal and family cancer histories could be explained in a number of ways. Because *BRCA1*, *BRCA2*, and MMR mutations affect general genetic processes such as DNA breakage and repair, it is not surprising that different disorders have similar or overlapping phenotypes. Furthermore, cases of sporadic breast, colon, and endometrial cancers in the general population could be phenocopies and may confuse syndrome selection. In addition, the established phenotypes for the common inherited cancer syndromes are historically based on families with the most recognizable constellation of clinical features; professional society guidelines have consequently been informed by these phenotypes. Increased testing of patients with less overt phenotypes may reveal previously underappreciated clinical variability for the common inherited cancer syndromes.

Although it remains unclear whether the phenotypic overlap between HBOC and LS is the result of shared genetic pathways, inherent susceptibility to extra-syndromic cancers, or a background incidence of common cancers, the presence of shared clinical features among these common inherited cancer syndromes likely complicates testing selection by the health care provider. Single-syndrome hereditary cancer testing likely misses some patients who meet testing criteria for both syndromes due to inefficiencies in this testing strategy. For example, patients referred for clinical suspicion of HBOC based on their personal and family history may have LS. However, sequential testing increases the likelihood that patients will not continue with subsequent testing due to convenience or cost issues. In contrast, simultaneously testing for multiple genetic disorders – for example, with the use of multigene panels – would avoid the diagnostic odyssey of testing for, and ruling out, multiple disorders in sequence. Furthermore, multigene panels can identify additional gene mutations associated with cancer syndromes that have similar or overlapping phenotypes with HBOC or LS (e.g., Li-Fraumeni syndrome and *MUTYH*-associated polyposis, respectively). Such an approach is more cost-effective and timely, which is of particular relevance for inherited cancer syndromes in which definitive medical management such as prophylactic surgery or chemoprevention depends on an accurate diagnosis. Fi-

nally, early reports from cancer panel testing have shown that patients are sometimes positive for syndromes not even suspected based on the cancer history in their family – a concern that becomes more problematic with smaller families.

Conclusions

The data presented here suggest there is a phenotypic overlap between two of the most common inherited cancer syndromes, HBOC and LS, which likely complicates diagnosis in the clinic. Future investigations, including gene panels and prevalence studies, will be necessary to understand the significance of phenotypic overlap. Phenotypic variability and overlap among hereditary cancer syndromes supports the clinical utility of multigene panels that can identify pathogenic mutations in the absence of a clinically specific phenotype. Such multigene panels would be more efficient and provide more effective medical management. The use of multigene panels will help eliminate barriers to testing and allow more patients to be tested for hereditary cancer. This, in turn, will aid scientific knowledge about the phenotypic spectrum of well-known gene mutations in addition to those for which few patients have been identified.

Disclosure Statement

All authors were employees of Myriad Genetic Laboratories, Inc., during the study period. This analysis was funded by Myriad Genetic Laboratories, Inc.

References

- 1 National Comprehensive Cancer Network: Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology 2013 (1.2013). http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.
- 2 Vasen HF, Watson P, Mecklin JP, Lynch HT: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 1999;116:1453–1456.
- 3 Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, Lynch H, Perucho M, Smyrk T, Sobin L, Srivastava S: A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J Natl Cancer Inst* 1997;89:1758–1762.

- 4 National Comprehensive Cancer Network. Colorectal Cancer Screening. NCCN Clinical Practice Guidelines in Oncology 2012. http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf.
- 5 Lynch HT, Casey MJ, Snyder CL, Bewtra C, Lynch JF, Butts M, Godwin AK: Hereditary ovarian carcinoma: heterogeneity, molecular genetics, pathology, and management. *Mol Oncol* 2009;3:97–137.
- 6 Bewtra C, Watson P, Conway T, Read-Hippee C, Lynch HT: Hereditary ovarian cancer: a clinicopathological study. *Int J Gynecol Pathol* 1992;11:180–187.
- 7 Rubin SC, Blackwood MA, Bandera C, Behbakht K, Benjamin I, Rebbeck TR, Boyd J: *BRCA1*, *BRCA2*, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: relationship to family history and implications for genetic testing. *Am J Obstet Gynecol* 1998;178:670–677.
- 8 Malander S, Rambech E, Kristoffersson U, Halvarsson B, Ridderheim M, Borg A, Nilbert M: The contribution of the hereditary nonpolyposis colorectal cancer syndrome to the development of ovarian cancer. *Gynecol Oncol* 2006;101:238–243.
- 9 Goodenberger M, Lindor NM: Lynch syndrome and *MYH*-associated polyposis: review and testing strategy. *J Clin Gastroenterol* 2011;45:488–500.
- 10 Iqbal J, Ragone A, Lubinski J, Lynch HT, Moller P, Ghadirian P, Foulkes WD, Armel S, Eisen A, Neuhausen SL, Senter L, Singer CF, Ainsworth P, Kim-Sing C, Tung N, Friedman E, Llacuachaqui M, Ping S, Narod SA: The incidence of pancreatic cancer in *BRCA1* and *BRCA2* mutation carriers. *Br J Cancer* 2012;107:2005–2009.
- 11 Casey MJ, Bewtra C, Lynch HT, Snyder C, Stacy M, Watson P: Phenotypic heterogeneity of hereditary gynecologic cancers: a report from the Creighton Hereditary Cancer Registry. *Fam Cancer* 2013;12:719–740.
- 12 Watson P, Vasen HF, Mecklin JP, Bernstein I, Aarnio M, Järvinen HJ, Myrholm T, Sunde L, Wijnen JT, Lynch HT: The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer* 2008;123:444–449.
- 13 Buerki N, Gautier L, Kovac M, Marra G, Buser M, Mueller H, Heinimann K: Evidence for breast cancer as an integral part of Lynch syndrome. *Genes Chromosomes Cancer* 2012;51:83–91.
- 14 Segev Y, Iqbal J, Lubinski J, Gronwald J, Lynch HT, Moller P, Ghadirian P, Rosen B, Tung N, Kim-Sing C, Foulkes WD, Neuhausen SL, Senter L, Singer CF, Karlan B, Ping S, Narod SA: The incidence of endometrial cancer in women with *BRCA1* and *BRCA2* mutations: an international prospective cohort study. *Gynecol Oncol* 2013;130:127–131.
- 15 Drohan B, Roche CA, Cusack JC Jr, Hughes KS: Hereditary breast and ovarian cancer and other hereditary syndromes: using technology to identify carriers. *Ann Surg Oncol* 2012;19:1732–1737.
- 16 Dorn C, Grunert M, Sperling SR: Application of high-throughput sequencing for studying genomic variations in congenital heart disease. *Brief Funct Genomics* 2014;13:51–65.
- 17 Li X, Buckton AJ, Wilkinson SL, John S, Walsh R, Novotny T, Valaskova I, Gupta M, Game L, Barton PJ, Cook SA, Ware JS: Towards clinical molecular diagnosis of inherited cardiac conditions: a comparison of bench-top genome DNA sequencers. *PLoS One* 2013;8:e67744.
- 18 Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomäki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004;96:261–268.
- 19 Lotsari JE, Gylling A, Abdel-Rahman WM, Nieminen TT, Aittomäki K, Friman M, Pitkänen R, Aarnio M, Järvinen HJ, Mecklin JP, Kuopio T, Peltomäki P: Breast carcinoma and Lynch syndrome: molecular analysis of tumors arising in mutation carriers, non-carriers, and sporadic cases. *Breast Cancer Res* 2012;14:R90.
- 20 Win AK, Lindor NM, Jenkins MA: Risk of breast cancer in Lynch syndrome: a systematic review. *Breast Cancer Res* 2013;15:R27.