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Hereditary Cancer Syndrome Recognition and Testing: Beyond BRCA

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A B S T R A C T

Hereditary cancer syndromes, resulting from mutations of tumor suppressor genes, can significantly increase the risk for breast cancer. Although hereditary breast and ovarian cancer syndrome caused by *BRCA1/2* mutations is well-known, less well-known hereditary cancer syndromes also exist. This article focuses on 3 other syndromes, including Li-Fraumeni, Cowden, and Peutz-Jeghers. This article will help prepare nurse practitioners to recognize key clinical features of these syndromes and understand testing criteria. Additionally, this article discusses barriers to diagnosing hereditary cancer syndromes and the role of primary care nurse practitioners in ordering genetic tests and making genetic referrals for optimal patient care.

More than 50 hereditary cancer syndromes (HCSs) have been identified and contribute to the development of 5% to 10% of all cancers.[1] Most clinicians have a basic knowledge and awareness of *BRCA1* and *BRCA2* gene mutations as major causes of the HCS known as hereditary breast and ovarian cancer syndrome. However, other gene mutations leading to other HCSs also increase the risk for breast cancer. Examples of these syndromes include Li-Fraumeni syndrome (LFS), Cowden hamartoma tumor syndrome or Cowden syndrome (CS), and Peutz-Jeghers syndrome (PJS)[2] (Table 1). Although uncommon, each of these syndromes poses risks to individuals who inherit related mutations. Because they are uncommon, many patients may go undiagnosed for years, minimizing their ability to reduce risk.

Primary care providers (PCPs), including nurse practitioners (NPs), are gatekeepers in health care. Patients depend on PCPs' expertise to guide them through the network of specialties and resources needed to treat and prevent diseases. Primary care NPs must be prepared to identify patients at risk for HCSs, order genetic testing when appropriate, and properly refer patients to genetic counselors.

Patients rely on PCPs for guidance about genetic risk and testing; however, PCPs' knowledge of HCSs may be limited because many are rare diseases only recently discovered and described. PCPs have been found to both under- and overtest. For example, in the years after the discovery of BRCA-related HBOC, PCPs have struggled to correctly identify, test, and refer at-risk patients.[3-6] Although many PCPs are aware of BRCA testing, few have ordered it.[5] Approximately 90% of high-risk women meeting United States Preventive Services Task Force criteria for counseling referral and testing have reported sharing their risk factors with their PCPs, yet only 20% were actually referred, and 8% were tested.[3] In contrast, many average-risk women not meeting criteria for genetic counseling or BRCA testing have been offered counseling and/or testing.[6]

Both under- and overtesting and referral for counseling can be problematic. The lack of understanding about HCSs is an additional problem. In a study published in 2017, 44% of PCPs reported routinely referring patients for genetic counseling; despite making referrals, most of them showed deficits in their understanding of HBOC.[4]

Despite knowledge limitations, 81.5% of PCPs reported high interest in HBOC education.[4] Researchers have called for educational programs to "focus on narrowing the knowledge gap between basic genetics and clinical medicine, because identification of individuals at risk for HBOC [and other HCSs] is a critical first step to ensuring access to cancer genetics services and risk reducing interventions."[4] The aim of this article was to inform primary care NPs about clinical characteristics and testing criteria for 3 HCSs associated with breast cancer and to encourage early recognition, appropriate genetic testing, and referral for genetic services.

Li-Fraumeni Syndrome (LFS)

LFS is a rare autosomal dominant HCS associated with germline mutations in *TP53*, a cancer suppressor gene, which codes for the p53 tumor suppressor protein.[15] LFS was originally described by Li and Fraumeni in 1969 while analyzing families with childhood rhabdomyosarcoma. *TP53* mutations are highly penetrant, with a cumulative lifetime risk for developing some type of cancer at nearly 100% by 70 years old and an 85% cumulative lifetime risk of developing breast cancer by 60 years old.[2,9]

LFS predisposes individuals to soft tissue sarcomas, osteosarcomas, breast cancer, colon cancer, gastric cancer, adrenocortical

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Table 1
Comparison of Autosomal Dominant Hereditary Cancer Syndromes Associated With Breast Cancer

Syndrome	Associated Tumor Suppressor Gene	Lifetime Risk for Breast Cancer with Syndrome	Other Malignancies/ Conditions in Syndrome	De Novo Rate
Hereditary breast and ovarian cancer syndrome	*BRCA1*	46%-87%[7]	Ovarian Prostate Pancreatic	< 5%[7]
	BRCA2	38%-84%[7]	Ovarian Prostate Pancreatic Melanoma[8]	< 5%[7]
Li-Fraumeni syndrome	*TP53*	85%[9]	Soft tissue sarcomas Osteosarcomas Colon cancer Gastric cancer Adrenocortical carcinoma Brain tumors[9]	7%-20%[10]
Cowden syndrome	*PTEN*	85%[11]	Thyroid disease Thyroid cancer Macrocephaly Paired organ cancer Endometrial cancer Brain tumors Vascular malformations Mucocutaneous lesions[2]	10.7%-47.6%[12]
Peutz-Jeghers syndrome (PJS)	*STK11*	45%[13]	Gastrointestinal hamartomatous polyps Gastrointestinal cancer Pancreatic cancer Cervical cancer Ovarian cancer[2]	Unknown, approximately 45% of affected individuals have no family history of PJS[14]

carcinoma, and brain tumors. Approximately 1% of all hereditary breast cancer cases are attributed to the presence of a *TP53* gene mutation.[16] The syndrome is characterized by the development of certain cancers at ages earlier than expected. For example, of all breast cancers and soft tissue sarcomas associated with LFS, 80% develop before 45 years old.[17] Women appear to be more prone to any early cancer with a 50% chance by 31 years old and 90% to 100% by 60 years old. In comparison, men exhibit a 50% chance of any cancer development by 46 years old and a 73% lifetime risk.[9]

In some cases, cancer onset occurs especially early. Frequently, children with LFS are found with soft tissue sarcomas, brain tumors, and adrenocortical carcinomas.[2] Studies have suggested a higher prevalence of individuals with germline *TP53* mutations than previously thought, between 1 in 5,000 and 1 in 20,000.[18,19] It is suspected that there are other mutations that may also be responsible for LFS characteristics.

Identifying Patients for LFS Genetic Testing

The National Comprehensive Cancer Network (NCCN) recommends using a combination of 2 sets of criteria to select patients for LFS testing: classic LFS criteria and Chompret criteria[2] (Table 2). Chompret criteria can be met regardless of family history, allowing for the detection of de novo *TP53* germline variants that would be missed using classic LFS criteria alone.[20,21] When both sets of criteria are used together, sensitivity increases to 95% from the estimated 40% that is seen with the use of classic LFS criteria alone.[18]

Testing may also be considered for patients who do not meet classic LFS or Chompret criteria. *TP53* germline mutations are commonly found in women with early-onset breast cancer; 3% to 8% of those with breast cancer before 30 years old with no family history have *TP53* mutations.[18] Thus, the NCCN recommends that women who develop breast cancer before 30 years old be considered for testing.[2] Cancer survivors should be tested because if they carry a harmful mutation, having this knowledge will qualify them for intensive cancer surveillance so that future cancers may be caught at earlier stages. Similarly, any person having a first-degree blood relative with a known *TP53* mutation should be considered for testing.

Cowden Syndrome (CS)

CS is a disorder inherited in an autosomal dominant pattern that predisposes individuals to a number of conditions and cancers, including breast cancer, thyroid disease, thyroid cancer, macrocephaly, paired organ cancer, endometrial cancer, brain tumors, vascular malformations, and various mucocutaneous lesions.[2] Lloyd and Dennis[23] were the first to identify CS based on the unique clinical findings of a 20-year-old woman with the surname of Cowden.

The syndrome most often stems from a germline pathogenic mutation in the *PTEN* tumor suppressor gene (approximately 85% of the time), but other gene mutations are also suspected to cause CS.[1] *PTEN* germline mutations do not always result in CS. Rather, CS is 1 of multiple syndromes associated with *PTEN* mutations, including Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, adult Lhermitte-Duclos disease, and autism spectrum disorders with macrocephaly. However, these other syndromes are not typically associated with breast cancer. Collectively, this spectrum of disorders is known as the *PTEN* hamartoma tumor syndrome (PHTS).

CS itself is understood to occur in about 1 in 200,000 people; however, considering the challenge of accurate clinical diagnosis, this figure is likely an underestimate.[2,24] Penetrance is usually high at 80%. Multiple tumorlike hamartoma lesions with an associated increased risk for multiple cancers characterize CS. Breast cancer is the most frequently found malignancy in CS.[24] Women with CS have an 85% lifetime risk of developing breast cancer, with an average age of 38 to 46 years at diagnosis.[11] Hamartomas form most frequently on the skin and mucous membranes. Other common

Table 2
Li-Fraumeni Syndrome (LFS) Testing Criteria

Classic LFS Criteria[22]	Chompret Criteria[20,21]	Additional NCCN Recommendations[2]
Any individual diagnosed with sarcoma under age 45 years with • One first-degree relative diagnosed with cancer under age 45 years AND • One additional first- or second-degree relative diagnosed with cancer under age 45 years or sarcoma at any age	Any individual with multiple primary tumors under age 36 years, including at least 2 of the following • Sarcoma • Breast cancer • Adrenocortical carcinoma • Brain tumor OR adrenocortical carcinoma at any age	Any individual with breast cancer before 30 years old Any individual with a blood relative diagnosed with p53 mutation

NCCN = National Comprehensive Cancer Network.

sites include the breast, thyroid, endometrium, and brain.[2] Benign mucocutaneous lesions occur in an estimated 99% of individuals with CS, and most often manifest in patients in their 20s.[25] Gastrointestinal polyps occur in most patients. Patients with CS may present with a number of different lesions (Table 3); thyroid disorders like multinodular goiter, adenomatous nodules, and follicular adenomas are common, and lifetime risk for thyroid cancer is approximately 3% to 10%.[2]

Macrocephaly, defined as having a head circumference in the 97th percentile, or 58 cm for females and 60 cm for males, is an especially common manifestation in CS, occurring in 80% to 100% of patients.[26,27] Strong associations have been found between CS and Lhermitte-Duclos disease and autism spectrum disorder characterized by macrocephaly.[28] Patients with CS exhibit some risk of developing endometrial cancer, brain tumors, vascular malformations, and colon cancer.[2] The cumulative risk for developing any cancer and/or Lhermitte-Duclos disease by 60 years old is estimated to be 56% for men and 87% for women.[29]

Identifying Patients for CS Genetic Testing

The NCCN[2] suggests the use of 3 sets of criteria and various combinations of each to evaluate the need for genetic testing for CS (Table 3). The first criteria set includes individuals meeting diagnostic criteria for CS with a history of certain diagnoses or a family history positive for a known *PTEN* mutation. The second and third criteria sets include identified “major” and “minor” features of CS.[2] Patients may meet different combinations of these categorized criteria and are considered to meet threshold criteria if they meet any of the conditions listed in Table 3. Testing may also be considered for those not meeting criteria with symptoms of concern, suggestive personal cancer histories, or suggestive family histories.[2]

Peutz-Jeghers Syndrome (PJS)

PJS is an autosomal dominant HCS most often caused by a mutation in the *STK11* tumor suppressor gene. Few cases characteristic of PJS have been identified without this mutation. Gastrointestinal hamartomatous polyps, most frequently in the stomach and intestines, are characteristic of PJS. Hamartomas are benign tumors made of an abnormal mixture of tissue that are normally found in the area where they grow. In children, darkly pigmented spots can often be found on the oral mucosa and around the eyes, nostrils, and anus. These spots often fade with age. When asked, young adults may recall the presence of these spots during childhood.

PJS greatly increases an individual’s risk for gastrointestinal, pancreatic, cervical, ovarian, and breast cancers. The prevalence of PJS is estimated to be between 1 in 25,000 and 1 in 300,000.[30] Penetrance in affected individuals is high. The risk for developing any first cancer has been shown to be 2% by age 20 years and increases gradually with age to reach 85% by 70 years old.[13] In addition, women with PJS have an increased risk for developing breast cancer (ie, 8% by 40 years old and increasing to 45% by 70 years old).[13]

Identifying Patients for PJS Genetic Testing

PJS should be suspected in individuals presenting with 2 or more PJS-type intestinal polyps, mucocutaneous macules, gynecomastia in males as a result of estrogen-producing Sertoli cell testicular tumors, or a history of intussusception (especially in a child or young adult).[14] Testing for PJS is recommended when an individual meets any 1 of 4 conditions in listed in Table 4. Additionally, testing may be considered when patients present with other concerning symptoms or histories under circumstances in which these criteria are not met.

Barriers to Identification of HCS

Beyond the need for further PCP education, other barriers to HCS patient detection and counseling exist. These include incomplete collection and assessment of family histories, time constraints, patient perceptions and beliefs, limited patient knowledge, and financial concerns. Although most providers collect family histories with all patients, family histories are often incomplete and not routinely assessed for genetic risk factors. It is important to recognize that family history collection should not be a 1-time event because family histories are ever changing.[32] Time constraints and other pressures may limit complete collection and assessment. Even with electronic family history-taking tools that allow patients to electronically enter their own family history information and give providers organized pedigree and risk information, providers have been found to only refer 54% of those for whom a genetic counseling referral is recommended.[33]

Although providers experience barriers to making genetic referrals, patients also experience barriers to receiving genetic counseling and testing after being referred by a PCP. Only 8% of women identified by family history as high risk for hereditary breast cancer went to a genetic counseling appointment within 1 year of receiving a referral.[34] Among women who did not go through with a genetic counseling appointment, 3 main barriers were identified. First, patient-held perceptions may prevent follow-through with referrals. For example, patients might not perceive urgency or benefit to undergoing counseling; patients may not believe they are at risk or believe that breast cancer in their families was due to genetic causes. Second, women lacked knowledge about genetic counseling and its purpose. Women worried about the complexity of genetic services and feared the possibility of a positive test. Third, women worried about financial challenges. They feared genetic counseling would bring high costs of testing and management, cause challenges dealing with insurance companies, and result in insurance discrimination.[34] Many women of this study also discussed the fact that their PCP, when presented with a letter

Table 3
Cowden Syndrome (CS) Testing Criteria

Individuals meeting any of the following warrant testing:
- Meets at least 1 stand-alone criteria
- 2 or more major criteria with 1 being macrocephaly
- 3 or more major criteria without 1 being macrocephaly
- 1 major criterion and 3 or more minor criteria; if 2 or more major criteria are met without one being macrocephaly, then 1 may be counted as 1 of the 3 minor criteria in this case
- 1 or more major criteria or 2 or more minor criteria AND a relative diagnosed with CS/PHTS or Bannayan-Riley-Ruvalcaba syndrome

Stand-alone Criteria	Major Criteria	Minor Criteria
Meets diagnostic criteria for CS	Breast cancer	Autism spectrum disorder without macrocephaly
History of Bannayan-Riley-Ruvalcaba syndrome	Macrocephaly	Colon cancer
History of adult Lhermitte-Duclos disease	Endometrial cancer	Esophageal glycogenic acanthosis, 3 or more lipomas
Autism spectrum disorder with macrocephaly	Follicular thyroid cancer	Intellectual disability
2 or more biopsy-proven trichilemmomas	Multiple gastrointestinal hamartomas or ganglioneuromas	Papillary thyroid cancer, papillary or follicular variant
Family history with a known *PTEN* mutation	Macular pigmentation of glans penis	Other thyroid structural lesions (adenoma, nodules, goiter, etc)
	Mucocutaneous lesions (trichilemmomas, palmoplantar keratoses, oral mucosal papillomatoses, cutaneous facial papules)	Renal cell carcinoma
		One gastrointestinal hamartoma or ganglioneuroma
		Testicular lipomatosis
		Vascular anomalies

Individuals not meeting testing criteria should be followed according to his or her personal cancer history and family history.[2]

PHTS = PTEN harmatoma tumor syndrome.

Table 4
Peutz-Jeghers Syndrome (PJS) Testing Criteria

Individuals meeting any 1 of the following criteria should be tested[31]:
- More than 2 histologically confirmed PJS-type hamartomatous gastrointestinal polyps
- Any number of PJS-type polyps with a family history of PJS in close relatives
- Characteristic mucocutaneous pigmentation with a family history of PJS in close relatives
- Any number of PJS-type polyps along with characteristic mucocutaneous pigmentation

identifying high risk based on family history taken during screening mammograms, were often dismissive of the letter or ignored it completely and did not recommend genetic counseling.[34]

Although patients experience multiple barriers, certain factors have proven to motivate and facilitate their decision to seek genetic counseling and testing. Most importantly, more verbal discussion with PCPs, along with more written information and a strong recommendation for counseling, encourage the uptake of counseling and testing.[34] Thus, PCPs play an important role in helping high-risk women receive genetic counseling services and testing. They must be thorough in collecting and assessing family histories, well versed in basic genetics, ready to educate and provide information, and highly encouraging of genetic counseling services.

PCP-NP Role in Genetic Testing

Genetic counselors are experts in reviewing pedigrees, selecting genetic tests, and providing pre- and posttest counseling. However, relying exclusively on genetic counselors to recommend genetic testing presents a dilemma. Currently in the US, there are only 4,000 genetic counselors, less than 1 counselor per 80,000 people living in the US.[35] Because of challenges finding a counselor and wait times for visits, individuals needing services may opt not to follow through with referrals. If they decide to be seen, they may wait months for an appointment. Another option is for PCPs to provide appropriate pretest counseling and order genetic testing for high-risk individuals before meeting with genetic counselors. Patients with positive findings could then attend genetic counseling appointment with results in hand, allowing for much faster adoption of risk-reducing and screening interventions.

A process intervention study assessing the integration of routine hereditary cancer risk assessment, counseling, and genetic testing in obstetrics/gynecology practices found it is feasible to incorporate hereditary cancer risk assessment, education, and testing into community obstetrics and gynecology practices.[36] In this study, obstetrics/gynecology providers were appropriately trained and acted competently in assessing risk and ordering tests. Both providers and patients reported high levels of confidence and satisfaction with the process, and the number of patients who underwent genetic testing increased 8-fold over the previous year.[36] This finding implies that during the previous year many patients who would have qualified for genetic testing and would have accepted it did not receive that option. As PCPs develop knowledge and skills in assessing family pedigrees for genetic risk and ordering genetic tests with appropriate pretest counseling, more patients will benefit from receiving personalized risk information.

Multigene Panel Testing

PCPs should consider the utility of ordering multigene panel testing as opposed to single-gene testing. Previously, single-gene testing has been standard practice. However, multigene panel testing can be more efficacious for several reasons. Primarily, less common HCSs, such as the 3 discussed in this article, may go undetected for great lengths of time if PCPs order single-gene tests. Multigene panel testing has the ability to identify significant cancer risks that otherwise would not be recognized, and it enables appropriate risk-reducing medical management decisions.[36] In studies of women already diagnosed with breast cancer, half of all

pathogenic variants identified among individuals meeting HBOC criteria were in genes other than *BRCA1/2*. In other words, panel testing revealed twice as many women with genetic risk for breast cancer than single-gene testing for *BRCA1/2* would have.[37,38] Panel testing allows for quicker diagnosis of HCSs and thus greater opportunity for risk-reducing surveillance and potentially greater uptake of genetic counseling services.

Resources for PCPs and Patients

Many online resources are available for PCPs and patients to help them understand HCSs. The NCCN can be accessed at www.nccn.org. Practitioners must register for a free account. Once registered, practitioners have access to many guidelines. The guideline titled "Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic" has information about all cancer syndromes discussed in this article and more. The NCCN website also has patient education resources. Another online resource is Cancer.Net published by the American Society of Clinical Oncology. A search on hereditary cancer-related syndromes will bring up a list of syndromes including those discussed in this article. Both of these organizations use expert panels to compile information and update their publications regularly.

Conclusion

Various HCSs beyond *BRCA*-related HBOC predispose many individuals to breast and other cancers. As gatekeepers of health care, primary care NPs must be prepared to identify patients at risk for HCSs and guide them through genetic testing, referral, and follow-up care. Multiple provider and patient factors act as barriers to the use of genetic resources. Among other barriers, limitations in provider knowledge and understanding of genetic disorders prove to be a prominent barrier, but most providers express high interest in learning more about genetic principles and HCSs. Because of barriers, many high-risk patients who have inherited an HCS may be currently undiagnosed, thus inhibiting the ability to initiate risk-reducing measures. In this article, 3 less common HCSs, their etiologies, and recommended testing criteria have been reviewed in an effort to inform provider practice. Because genetic counselor availability is limited, PCPs have the opportunity to be a valuable genetics resource for many individuals. Primary care NPs should identify patients with presentations and family histories consistent with HCSs and either offer pretest counseling and order multigene panel testing or refer at-risk people to genetic counseling. Finally, all patients with positive findings should be referred for genetic counseling for support and recommendations on prevention and screening.

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