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Strategies for clinical implementation of screening for hereditary cancer syndromes

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ABSTRACT

Hereditary cancer syndromes generally account for 5%–10% of malignancies. While these syndromes are rare, affected patients carry significantly elevated risks of developing cancer, as do their at-risk relatives. Identification of these patients is critical to ensure timely and appropriate genetic testing relevant to cancer patients and their relatives. Several guidelines and tools are available to assist clinicians. Patients suspected to have hereditary cancer syndromes should be offered genetic testing in the setting of genetic counseling by a qualified genetics professional. Germline testing ranges from testing for a known specific familial mutation to testing of a broad differential diagnosis using a pan-cancer multi-gene panel. Taking a family history, referring specific types of tumors with higher likelihood of heredity, implementing universal screening protocols such as microsatellite instability/immunohistochemistry (MSI/IHC) for specific tumors, and referring patients with somatic tumor testing that have potentially germline consequences are all important components to the identification of hereditary cancer syndromes in the oncology clinic.

Hereditary cancer syndromes account for 5%–10% of all malignancies. These syndromes are associated with significantly elevated risks of developing cancer and members of the patient's family may also be at risk to inherit the condition. Identification of these patients is critical to ensure timely and appropriate genetic testing, and potentially life-saving initiation of surveillance for secondary cancers in the individual tested, as well as in affected family members. Certain cancers by virtue of their tumor types alone should prompt further hereditary evaluation; however, for most patients this identification process will involve an in-depth exploration of the patient's personal and family cancer history. Guidelines for obtaining a family history and risk stratification tools have been developed. Patients suspected of hereditary cancer syndromes should be offered genetic testing in the setting of genetic counseling. This article outlines the critical elements for hereditary cancer risk assessment, genetic testing, and genetic counseling.

1. Collection of family health history

Gathering family history is the first step in assessing an individual's risk for a hereditary cancer syndrome. Discussion and documentation of a patient's family history of cancer should be performed at the initial visit and updated throughout the course of treatment. Ideally, a three-generation pedigree is used for an accurate genetic risk assessment. However, obtaining a full pedigree for each patient may be impractical in a busy clinical setting. The American Society of Clinical Oncology (ASCO) has put forth recommendations for the collection and use of family history for oncology patients [1]. The recommended elements for a minimum cancer family history are listed in Table 1 [1]. Patients should be asked about the type and age of onset of cancers in first- and second-degree relatives on both maternal and paternal sides of the family. Pertinent information regarding cancer in third-degree relatives, such as first-cousins, can also be gathered since this information is relevant in determining whether a patient meets National Comprehensive Cancer Network (NCCN) Criteria for Further Genetic Risk Assessment [2,3]. Ethnicity should be ascertained as certain populations have a higher incidence of hereditary cancer syndromes, eg, hereditary breast and ovarian cancer syndrome in Ashkenazi Jews. Asking whether family members have had genetic testing is also important as all patients with a family history of a known deleterious mutation in a cancer predisposition gene should be referred for genetic counseling [1–3].

Once the family history is collected and reviewed, the next step is interpreting the family history to determine if a referral for genetic counseling is indicated. In general, red flags for hereditary cancer syndromes include early onset (ie, under age 50) cancer,

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Table 1
Family history information that should be obtained for a hereditary cancer risk assessment.

First-degree relatives: siblings, parents, children
Second-degree relatives: grandparents, aunts, uncles, grandchildren, nieces, nephews, half-siblings
Both maternal and paternal sides
Ethnicity (eg, Ashkenazi Jewish ancestry)
For each cancer diagnosis: age at diagnosis, type of primary cancer
Results of any cancer predisposition testing in any relative

several relatives on the same side of the family affected with the same or related cancers (ie, breast and ovarian cancer; colon and endometrial cancer), and multiple primary cancers in the same individual. Detailed criteria for further genetic risk assessment for breast/ovarian cancer, as well as colorectal cancer are outlined in the NCCN Genetic/Familial High-Risk Assessment Guidelines [2,3].

Potential barriers for meaningful utilization of family history include limitations of both patients and providers. Many patients are not aware of their family history, or may have inaccurate information on the types of cancers or ages of diagnosis in the family. A population-based survey of cancer family history by Mai et al revealed that lung, prostate, colon, and breast cancers were accurately reported for first- and second-degree relatives 40%–60% of the time [4]. For providers, barriers include lack of adequate time for family history collection as well as lack of ability to perform an accurate initial risk assessment or provide recommendations for next steps according to family history. A vignette-based study surveying physicians' recommendations for genetic counseling demonstrated that many providers under- and over-refer patients that should and should not prompt a genetics referral, respectively [5].

A strategy to overcome family history barriers is the use of structured family history collection tools and risk assessment algorithms. Paper-based patient questionnaires may increase recognition of patients that would benefit from genetic counseling [6]. Several electronic resources are available to both patients and providers to collect family history. Some of these tools also incorporate risk assessment models which may assist in identifying high-risk patients. A list of currently available programs can be found in Table 2.

2. Tumors warranting a genetic evaluation, regardless of family history

While genetic risk assessment is largely based on an individual's family history of cancer, in some cases, a genetic counseling referral is indicated based on personal history alone. Patients with certain malignancies or benign tumor types such as epithelial ovarian cancer, triple-negative breast cancer, male breast cancer, diffuse gastric cancer, adrenocortical carcinoma, cerebellar hemangioblastoma, medullary thyroid cancer, paraganglioma, or pheochromocytoma should be offered genetic counseling due to the high incidence of hereditary mutations even in the absence of a contributing family history. Table 3 summarizes tumors that warrant genetic counseling, as well as the incidence of the related syndrome(s) in simplex cases.

3. Risk assessment models

Several risk assessment models have been developed to predict the likelihood of a patient or family harboring a germline mutation for the more common hereditary cancer syndromes. These tools are available online and are intended to be completed by a healthcare provider. As highlighted in Table 4, there are multiple tools for hereditary breast and ovarian cancer syndrome and Lynch syndrome risk assessment, but tools also exist for hereditary pancreatic cancer, hereditary melanoma, and the *PTEN*-hamartoma tumor syndrome.

Risk prediction tools for hereditary breast and ovarian cancer syndrome are based on the patient's ethnic background and personal and family history of female breast and ovarian cancer, although some models also account for male breast cancer, prostate cancer, and pancreatic cancer. BOADICEA and the Tyrer-Cuzik model not only offer risk prediction for *BRCA1* and *BRCA2,* but also calculate the lifetime risk of developing breast and ovarian cancer and breast cancer, respectively. In the early days of commercial *BRCA1* and *BRCA2* testing, patients with >10% pretest probability by a risk prediction model were recommended to undergo *BRCA1* and *BRCA2* genetic testing [7]. However, in modern practice, personal and family history testing guidelines, such as those offered by NCCN, have largely replaced this approach. Regardless, these tools still have utility in identifying patients appropriate for genetic counseling and/or as a genetic counseling to help patients understand the likelihood of harboring a *BRCA1* or *BRCA2* mutation [8].

Three models have been developed for Lynch syndrome: MMRpro, $PREMM_{1,2,6}$, and MMRpredict. $PREMM_{1,2,6}$ has the best sensitivity (90%) among the three models but the lowest specificity (67%), while MMRpredict is the most specific (90%) with a sensitivity of 69% [9]. MMRpro offers the advantage that it will predict the likelihood of identifying a germline *MLH1*, *MSH2*, or *MSH6* mutation as well as estimate the cancer risk for unaffected relatives. MMRpro and $PREMM_{1,2,6}$ have the greatest discriminatory power to identify patients with colorectal cancer from both average risk and clinic populations for tumor or germline-based

Table 2
Electronic family history collection tools.

Tool Name	Description	Risk assessment
Breast Cancer Genetics Referral Screening Tool [37]	Free web-based questionnaire available to patients and providers to assess for HBOC	Yes
Cancer Gene Connect [38]	Trademarked software utilizing patient entered data to assess for hereditary cancer syndromes; clinical documentation and follow-up features	Yes
Colon Cancer Risk Assessment	Cleveland Clinic's free web-based patient questionnaire to assess colon cancer risk	Yes
Family Health*Link* [39]	Ohio State University's free web-based patient questionnaire assessing cancer and cardiovascular risk	Yes
Health Heritage [40]	North Shore University's free web-based patient questionnaire assessing cancer and cardiovascular risk	Yes
Hughes RiskApps [41]	Trademarked software to identify patients at risk for HBOC	Yes
My Family Health Portrait [42]	Surgeon General's free web-based patient entered family health history collection tool	No
MeTree [43]	Genomedical Connection patient entered tool to collect family health history and performs clinical decision support	Yes

HBOC = hereditary breast ovarian cancer syndrome.
Adapted from National Society of Genetic Counselors Health Information Technology Special Interest Group [44].