Introduction to cancer genetic susceptibility syndromes

Rose B. McGee and Kim E. Nichols

Division of Cancer Predisposition, St. Jude Children's Research Hospital, Memphis, TN

The last 30 years have witnessed tremendous advances in our understanding of the cancer genetic susceptibility syndromes, including those that predispose to hematopoietic malignancies. The identification and characterization of families affected by these syndromes is enhancing our knowledge of the oncologic and nononcologic manifestations associated with predisposing germ line mutations and providing insights into the underlying disease mechanisms. Here, we provide an overview of the cancer genetic susceptibility syndromes, focusing on aspects relevant to the evaluation of patients with leukemia and lymphoma. Guidance is provided to facilitate recognition of these syndromes by hematologists/oncologists, including descriptions of the family history features, tumor genotype, and physical or developmental findings that should raise concern for an underlying cancer genetic syndrome. The clinical implications and management challenges associated with cancer susceptibility syndromes are also discussed.

Learning Objectives

- Recognize the elements of a patient's family and medical history that should trigger consideration of an underlying cancer genetic susceptibility syndrome
- Understand the clinical implications resulting from the diagnosis of a cancer genetic susceptibility syndrome on the patient and family

Introduction

Cancer genetic susceptibility syndromes, including those that predispose to leukemia and lymphoma, have been increasingly identified during recent years. Through clinical studies of affected individuals and families and functional investigations of the associated germ line mutations, knowledge is emerging regarding the phenotypes of these syndromes, the biologic mechanisms of tumor formation, and the effects of mutations on treatment response and tolerance of therapy. The information gained is guiding development of tailored approaches to oncology care, including alterations in cancer treatment and incorporation of surveillance and risk-reducing measures, with the overall goal of lessening morbidity and mortality associated with hereditary neoplasms. Here, we provide an overview of the cancer genetic susceptibility syndromes, with an emphasis on aspects pertinent to hematopoietic malignancies.

The basis of cancer genetic susceptibility syndromes

Cancer is at its root a genetic disease resulting from the accumulation of mutations that deregulate cellular differentiation, proliferation, and/or survival. In the majority of human cancers, these mutations are believed to occur in a single postzygotic cell. Nonetheless, the existence of cancer-prone kindreds has suggested that some of human cancers have a hereditary basis. This possibility was first recognized more than 100 years ago, when in 1866, Paul Broca reported a large kindred with multiple members affected with breast cancer.[1] Subsequently, additional families characterized by distinctive patterns of occurrence of cancers, many early in onset or involving multiple primary tumors in the same individual, were described by Aldred Warthin and Henry Lynch (hereditary nonpolyposis colon cancer) and Frederick P. Li and Joseph Fraumeni (Li-Fraumeni syndrome [LFS]), among others.[1,2]

To explain development of the hereditary cancer retinoblastoma, Alfred Knudson proposed the "2 mutation" model of tumor formation in 1971.[3] According to his insightful model, individuals with hereditary retinoblastoma are at increased risk for tumor formation because they carry an altered copy of a growth regulatory gene (the first mutation) in the germ line; that is, in the noncancerous cells. Knudson proposed that if the remaining gene copy were to undergo inactivation within a susceptible cell (ie, the second mutation), that cell would then be prone to tumor formation. Because every cell in an individual with hereditary retinoblastoma carries the first mutation, cancers are more likely to occur at younger ages and in multiple locations. Knudson's prediction was confirmed in 1986 with identification of the retinoblastoma gene *RB1* as the first cancer susceptibility gene. In the decades after this seminal discovery, many other cancer-predisposing genes conforming to Knudson's model have been identified, including *NF1* in neurofibromatosis type 1 (NF1), *APC* in familial adenomatous polyposis (FAP), *TP53* in LFS, and *BRCA1* and *BRCA2* in hereditary breast–ovarian cancer. With the advent of high-throughput sequencing approaches, additional cancer-predisposing genes are being discovered, and now there are well more than 100 different genes and associated syndromes identified.[1] Notably, current large-scale sequencing studies reveal that at least 5% to 12% of all patients with cancer harbor germ line cancer-predisposing mutations.[4-6]

The majority of cancer susceptibility genes encode tumor suppressors, proteins that restrain cell growth by inhibiting cell cycle progression, promoting apoptosis, inducing senescence, and/or stimulating differentiation. Tumor suppressors also play integral roles in sensing DNA damage and promoting DNA repair. Less commonly, cancer

Conflict-of-interest disclosures: The authors declare no competing financial interests.

Off-label drug use: None disclosed.

Table 1. Genes associated with risk for hematopoietic plus other cancers

Gene(s)	Condition	Hematopoietic cancer(s)	Prevalence of hematopoietic cancers[36-39]	Other cancers	Other features
ATM	Ataxia telangiectasia	ALL, lymphoma	~30-40%	Breast Ovarian Gastric Others	Immunodeficiency Cerebellar ataxia, oculomotor apraxia Choreoathetosis Telangiectasias
BLM	Bloom syndrome	ALL, AML/MDS, lymphoma	15%	GI Breast Respiratory Skin Others	Pre- and postnatal growth deficiency Short stature Butterfly rash GERD Early-onset menopause Male infertility Early-onset diabetes COPD
FANCA-P	Fanconi anemia	ALL, AML/MDS	7-13% AML 500-fold increase in risk	H/N SCC Skin GI Genital Liver Brain	Bone marrow failure Short stature Hyper-/hypopigmentation Skeletal anomalies Ocular, renal, gonadal abnormalities DD Chemotherapy and/or radiation toxicity (Note: Absence of physical findings in 25-40%)
MLH1, MSH2, MSH6, PMS2	Constitutional mismatch repair deficiency	ALL, AML, lymphoma	~33%	Brain Colorectal/GI Endometrial Others	Cafe au lait macules Hypopigmentation Other NF1 signs Pilomatricoma GI polyps Mild immunoglobulin class switch defects
Multiple	Dyskeratosis congenita	AML/MDS	3-33%	H/N SCC Skin Anogenital	Dysplastic nails Lacy reticular pigmentation Other pigmentation Oral leukoplakia Premature graying/alopecia Pulmonary fibrosis Eye and dental abnormalities
Multiple	Diamond-Blackfan anemia	ALL, AML/MDS, lymphoma	~4-5%	Osteosarcoma	Macrocytic anemia Congenital malformations (craniofacial, limb, heart, genitourinary) Growth retardation

ACC, adrenocortical carcinoma; CMML, chronic myelomonocytic leukemia; COPD, chronic obstructive pulmonary disease; DD, developmental delay; GERD, gastroesophageal reflux disease; GI, gastrointestinal tract; GIST, gastrointestinal stromal tumor; H/N SCC, head/neck squamous cell carcinoma; JMML, juvenile myelomonocytic leukemia; MBL, medulloblastoma; MI, myocardial infarction; MPNST, malignant peripheral nerve sheath tumor; OPG, optic pathway glioma; RMS, rhabdomyosarcoma; TMD, transient myeloproliferative disorder.

Table 1. (continued)

Gene(s)	Condition	Hematopoietic cancer(s)	Prevalence of hematopoietic cancers[36-39]	Other cancers	Other features
NBN	Nijmegen breakage syndrome	ALL, lymphoma	40%	MBL Glioma RMS	Microcephaly Short stature Recurrent infections Characteristic facies Hyper- or hypopigmentation Premature ovarian failure Decline in intellectual ability
NF1	Neurofibromatosis 1	JMML, CMML, AML/MDS	AML/MDS: 11% JMML: 200-500-fold higher than general population	OPG Brain tumor MPNST GIST Breast	Cafe au lait macules Inguinal/axillary freckling Lisch nodules Neurofibroma Tibial dysplasia Vasculopathy Learning disabilities
PTPN11	Noonan syndrome	JMML, CMML, AML, ALL, TMD	~1%	RMS Brain	Characteristic facies Heart defect (especially pulmonary valve stenosis) DD Short stature Coagulation defects Skeletal and ocular abnormalities
RECQL4	Rothmund-Thomson syndrome	AML/MDS	Unknown	Osteosarcoma Skin	Poikiloderma Sparse hair Short stature Cataracts Skeletal/dental abnormalities Cataracts
TP53	Li-Fraumeni syndrome	ALL (especially low hypodiploid), AML/MDS lymphoma	2-4%	Breast Brain Sarcoma ACC Others	None
WRN	Werner syndrome	AML/MDS	Unknown	Sarcoma Melanoma Thyroid	Premature aging with onset in first decade Early-onset diabetes, osteoporosis MI

ACC, adrenocortical carcinoma; CMML, chronic myelomonocytic leukemia; COPD, chronic obstructive pulmonary disease; DD, developmental delay; GERD, gastroesophageal reflux disease; GI, gastrointestinal tract; GIST, gastrointestinal stromal tumor; H/N SCC, head/neck squamous cell carcinoma; JMML, juvenile myelomonocytic leukemia; MBL, medulloblastoma; MI, myocardial infarction; MPNST, malignant peripheral nerve sheath tumor; OPG, optic pathway glioma; RMS, rhabdomyosarcoma; TMD, transient myeloproliferative disorder.

Table 2. Genes associated primarily with risk for hematopoietic cancer

Gene(s)	Condition	Hematopoietic cancer(s)	Prevalence of hematopoietic cancers[36,40]	Laboratory features	Other features
ANKRD26	*ANKRD26*-related thrombocytopenia	AML, CML	Unknown	Thrombocytopenia	None
BTK	X-linked agammaglobulinemia	ALL, lymphoma	Unknown	B-cell deficiency, agammaglobulinemia	Recurrent infection
CBL	*CBL* syndrome	JMML	<1%		Neurological features Noonan syndrome phenotype
CEBPA	Familial AML	AML/MDS	Unknown		None
DDX41	Familial AML	AML/MDS	Unknown		None
ELANE, HAX1, G6PC3	Congenital neutropenias	AML/MDS	~10%	Neutropenia	Cardiovascular and/or urogenital abnormalities (*G6PC3*) Pulmonary hypertension (*G6PC3*)
ETV6	Familial leukemia	ALL, less commonly MDS/AML, CMML, T/myeloid mixed phenotype leukemia	Unknown	Thrombocytopenia, red cell macrocytosis	None
FAS, FASLG, CASP10	Autoimmune lymphoproliferative syndrome	Lymphoma	8-12%	Lymphoproliferation Autoimmune cytopenias	Autoimmune disease
GATA2	Familial AML and Emberger syndromes	AML/MDS	50% or greater	Neutropenia; dendritic cell, monocyte, B-cell and NK cell depletion	Primary lymphedema Warts Deafness
KLHDC8B	Lymphoma predisposition	Hodgkin lymphoma	Unknown		None
MPL	Congenital amegakaryocytic thrombocytopenia	AML/MDS	2%	Thrombocytopenia Megakaryocytopenia Bone marrow failure	Possibly CNS abnormalities
Multiple	Severe combined immunodeficiency	B-cell lymphoma	Unknown	Immunodeficiency	Failure to thrive Recurrent infection Autoimmunity Short stature
NPAT	Lymphoma predisposition	Nodular lymphocyte predominant, Hodgkin lymphoma	Unknown		None
PAX5	Leukemia predisposition	ALL	Unknown	Chromosome 9p loss in leukemia cells	None
RBM8A	Thrombocytopenia absent radius syndrome	ALL, AML/MDS	1%	Thrombocytopenia	Absent radii Other skeletal anomalies Heart defects, genitourinary defects Cow's milk intolerance
RUNX1	Familial platelet disorder with associated myeloid malignancy	AML/MDS, CMML	~35%	Thrombocytopenia	None
SBDS	Shwachman-Diamond syndrome	ALL, AML/MDS	5-36%	Bone marrow failure	Pancreatic insufficiency Short stature Skeletal abnormalities

CML, chronic myeloid leukemia; CNS, central nervous system; HbF, hemoglobin F; HLH, hemophagocytic lymphohistiocytosis.

Table 2. (continued)

Gene(s)	Condition	Hematopoietic cancer(s)	Prevalence of hematopoietic cancers[36,40]	Laboratory features	Other features
SH2B3	Leukemia predisposition	ALL	Unknown		Growth retardation, developmental delays Autoimmune disorders
SH2D1A	X-linked lymphoproliferative disease	NHL (B-cell)	~24%	HLH-associated EBV infection Dysgamma globulinemia	Aplastic anemia Vasculitis
SRP72	*SRP72*-associated familial aplasia and myelodysplasia	AML	Unknown	Aplastic anemia	Deafness
Trisomy 21	Down syndrome	ALL, AML, TMD	10% (TMD) ~2-3% (ALL, AML)		Multiple congenital anomalies Dysmorphic features Intellectual disability
Unknown	Familial monosomy 7 syndrome	AML/MDS, ALL	Unknown	Acquired monosomy 7 Bone marrow failure Red cell macrocytosis Increased HbF	None
WAS	*WAS*-related disorders (including Wiskott-Aldrich syndrome)	ALL, lymphoma	~2% (ALL) ~13% (lymphoma)	Thrombocytopenia neutropenia Immunodeficiency	Eczema Autoimmune disorders

CML, chronic myeloid leukemia; CNS, central nervous system; HbF, hemoglobin F; HLH, hemophagocytic lymphohistiocytosis.

susceptibility is conferred by the presence of activating mutations in growth-promoting oncogenes, including those encoding receptor tyrosine kinases and other intracellular signaling proteins. Regardless of the mechanism, mutations in these genes impair normal growth control, and thus increase the risk for cancer.

Genetic susceptibility syndromes that predispose to hematopoietic cancers

Leukemias and lymphomas are seen in association with a number of cancer genetic susceptibility syndromes, and at present, it is estimated that about 2% to 4% of patients with hematopoietic malignancies develop the disease as a result of an underlying predisposition[6,7] However, these numbers likely underestimate the true prevalence, as many hereditary cases are not ascertained. Furthermore, as the number of cancer genetic susceptibility syndromes in which hematopoietic malignancies are recognized as a component rises, it is plausible that considerably more cases will have a hereditary component than is currently appreciated.

In several cancer-predisposing conditions, hematopoietic malignancies are included among a spectrum of other neoplasms that can also develop (Table 1). Such is the case in conditions characterized by defects in DNA repair (ie, Fanconi anemia [FA], ataxia telangiectasia, constitutional mismatch repair deficiency [CMMRD], LFS), signal transduction (eg, NF1, Noonan syndrome), telomere maintenance (ie, dyskeratosis congenita [DC]), and lymphocyte development (eg, Wiskott Aldrich syndrome [WAS]). Less often, leukemia or lymphoma may be the primary oncologic manifestation of a genetic condition. Several of these conditions are shown in Table 2, including *ETV6*- and *PAX5*-related familial acute lymphoblastic leukemia (ALL)[8-11]; predispositions to acute myeloid leukemia (AML) as a result of germ line mutations in *RUNX1*, *CEBPA*, or *GATA2*[12-14]; and disorders associated with development of lymphoma, such as X-linked lymphoproliferative disease type 1. Because of space constraints, we direct the reader to several excellent recent reviews for a more comprehensive discussion of the cancer genetic susceptibility syndromes associated with development of these blood cancers.[15,16]

Factors to consider when evaluating for a cancer genetic susceptibility syndrome

When assessing a patient or family with hematopoietic cancers for the presence of an underlying cancer susceptibility syndrome, there are 3 key domains to consider, including the family cancer history, presenting features of the tumor and histology, and physical examination or cognitive/developmental manifestations. Hematologists/oncologists should consider each of these domains and refer to a cancer genetics specialist when there is a suspicion of an underlying syndrome.

Family cancer history

The presence of a positive family cancer history is one of the strongest and most well accepted indicators of an underlying cancer genetic susceptibility syndrome. In recognition of the integral role of family cancer information in the evaluation and management of patients, the American Society of Clinical Oncology published a statement outlining the approach and elements to be gathered when collecting a family cancer history.[17] It is recommended that the family history be taken at the first clinic visit and involve collection of data from at least first- and second-degree relatives. Family cancer histories evolve with time, and this is particularly true for pediatric patients, in whom close relatives may be young and not yet have developed the cancers indicative of an underlying predisposition syndrome at the time of the child's cancer diagnosis. Therefore, the

history should be periodically updated. Ideally, the family history should include collection of data on the type of cancer in relatives, age at cancer diagnosis, and whether the relative is from the maternal or paternal lineage. Genetic syndromes already identified or suspected in the family should be recorded, and test results for relatives who have had prior genetic testing should be obtained and documented. Patients should be asked about possible consanguinity, adoption, assistive reproductive technologies, and family ancestry.[2,17] Environmental exposures, details of cancer treatment, history of excessive toxicity to cancer treatment, and prophylactic surgical procedures to reduce cancer risk (eg, colectomy, mastectomy, or hysterectomy) should also be noted.[18]

When considering whether a leukemia or lymphoma predisposition syndrome might be present in a family or individual, there are several pieces of information to gather. First, it is important to assess whether 1 or more relatives developed a hematopoietic malignancy, and if so, to determine the lineage (lymphoid vs myeloid; non-Hodgkin's vs Hodgkin's) and tempo (acute vs chronic). Providers should inquire whether individuals with leukemia developed the disease as a primary or therapy-related neoplasm. For those with lymphoma, it is important to ask whether the cancer occurred in the setting of an immunodeficiency or in association with Epstein-Barr virus (EBV) infection. Information should be gathered regarding other hematologic and nonhematologic manifestations, such as a history of antecedent anemia, leukopenia and/or thrombocytopenia, or the presence of growth or developmental delays and congenital anomalies. Each of these pieces of data can facilitate identification of the relevant leukemia or lymphoma predisposition syndrome or syndromes, and thus guide subsequent genetic counseling and testing.

Family cancer history features that raise suspicion for an underlying genetic syndrome include multiple family members with the same or related types of cancer, cancers occurring in multiple generations along the same lineage, and presence of early-onset, bilateral or multiple primary solid cancers. For those with hematopoietic cancers, a history of prior cytopenias and/or myelodysplastic syndrome (MDS), or multiple or atypical infections, particularly in children and young adults, should spur further investigation into a possible hereditary basis. Although most syndromes follow an autosomal dominant inheritance, alternative genetic mechanisms (eg, autosomal recessive, polygenic), as well as shared lifestyles or environmental exposures, may explain certain familial cancer cases.[19]

Several recent studies document suboptimal collection and recording of family cancer history information.[6,20] Unfortunately, barriers exist that limit collection of good-quality family histories. Collection of these histories requires time and effort by providers and their patients alike. Patients may have poor knowledge of the family history, and thus provide limited or inaccurate data. This is particularly true for the hematopoietic malignancies, in which patients may not be aware of the lineage, chronicity, or associated hematologic or infectious manifestations. In such cases, strong consideration should be given to obtaining the records of affected relatives to gain better insight into the possibility of an underlying predisposing condition.

The interpretation of the family cancer history may be complicated by numerous factors, including the presence of de novo germ line mutations, autosomal recessive or other inheritance patterns, variable expressivity or reduced penetrance of a particular genetic condition, small family size or young families, adoption (with limited information about biological relatives), and noncancer-related early deaths.[17-19] In each case, the family cancer history may appear negative, and thus be falsely interpreted as not reflective of an underlying syndrome. Provider and patient education about the importance of the accuracy, collection, documentation, updating, and interpretation of the family cancer history are needed to facilitate identification of possible cancer genetic susceptibility syndromes.

Presenting features of the tumor and histology

Features of solid tumors that are suggestive of an underlying syndrome include bilateral involvement of paired organs, multifocal tumors, and multiple primary tumors. Specific solid tumor types should prompt consideration of a genetics evaluation even in the absence of a positive family history. Good examples include adrenocortical or choroid plexus carcinomas, which are caused by germ line *TP53* mutations in a high proportion of cases. Because of the increasing spectrum of cancer genetic susceptibility syndromes, it is becoming more and more challenging to know which patients with cancer warrant referral to a genetics specialist. To assist providers in these decisions, the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors have developed practice guidelines that incorporate family history and tumor information to reflect current clinical and scientific knowledge.[21] Additional resources have also been developed[22] (Table 3).

Similarly, certain cytogenetic, genetic and other features of cancer, including a hematopoietic malignancy may herald the presence of a predisposition syndrome. Up to 50% of children (but not adults) with hypodiploid ALL in which leukemia cells contain 32 to 39 chromosomes harbor germ line *TP53* mutations.[23] Seven percent of children and young adults with MDS and up to 72% with MDS and monosomy 7 carry germ line *GATA2* mutations.[24] Somatic mutations in *CEBPA*, which are often sought as part of leukemia prognostication, may signal presence of familial AML as a result of a germ line *CEPBA* mutation in 7% to 11% of cases.[24] Similarly, presence of somatic *RUNX1* mutations could herald the presence of familial platelet disorder/AML. Finally, B-cell non-Hodgkin lymphomas occurring in association with EBV should prompt consideration of an immunodeficiency disorder, such as X-linked lymphoproliferative disease type 1.

Secondary leukemia may be also associated with an underlying genetic predisposition, given the results of a recent study of 53 children and adults with an array of primary cancers who developed therapy-associated myeloid neoplasms. Nine patients (17%) were found to have germ line cancer-associated mutations, including 2 with *BRCA1*, 1 with *BRCA2*, 2 with *BARD1*, and 4 with *TP53* mutations.[25] Consistent with these data, a study of breast cancer survivors with therapy-related leukemia identified germ line mutations in *BRCA1*, *BRCA2*, *TP53*, *CHEK2*, and *PALB2* that collectively accounted for 21% of cases.[26] Interestingly, in this second study, there were 7 patients with therapy-associated ALL, with 2 (50%) of 4 tested harboring germ line *TP53* mutations.[26] Together, the data from these studies suggest that individuals with therapy-associated leukemia should be considered as candidates for a possible genetic evaluation.

Physical features

Many cancer genetic susceptibility syndromes are associated with nononcologic manifestations, including characteristic physical findings, cognitive or developmental delays, and presence of certain benign tumors. Some of these manifestations are summarized in Tables 1 and 2. For many of these conditions, it is important to note that the "defining" manifestations may precede a cancer diagnosis by

Table 3. Resources for genetic cancer susceptibility referral

Resource	Where to access
Breast, colon and pediatric cancer risk assessment tools: Web-based selection tools to identify patients who are appropriate for referral	https://www.radboudumc.nl/Pages/hereditarycancer.aspx
Familial cancer database: Web-based database to query tumors and nontumor features reported in cancer predisposition syndromes	http://www.familialcancerdatabase.nl
National Cancer Institute (NCI) Cancer Genetics Services Directory	http://www.cancer.gov/about-cancer/causes-prevention/genetics/directory
National Society of Genetic Counselors (NSGC) Find a Genetic Counselor Directory	http://nsgc.org/page/find-a-gc-search
American College of Medical Genetics and Genomics (ACMG) Clinic Services Search Engine	https://www.acmg.net/ACMG/Find_Genetic_Services/ACMG/ISGweb/FindaGeneticService.aspx

several years. Thus, clinicians should be attuned to the possible presence of these features and refer patients to a cancer genetics specialist once they are identified.

Dermatologic manifestations. The skin is often affected in cancer predisposition syndromes, and an initial evaluation by a dermatologist may be helpful in characterizing lesions and facilitating the associated diagnosis. One of the most common dermatologic manifestations is the cafe au lait macule, which can be seen in several cancer genetic syndromes, including those that predispose to hematopoietic cancers (NF1, Noonan syndrome, FA, and CMMRD). It is thus essential that hematologists be familiar with the appearance of cafe au lait macules, which exhibit distinct edges and are slightly darker than the surrounding skin. In isolation, cafe au lait macules are not diagnostic of NF1, Noonan syndrome, FA, or CMMRD, and must be considered in the context of other physical or medical history features. Other benign skin findings include freckling in the inguinal/axillary region (NF1), penile freckling (PTEN hamartoma tumor syndrome), mucocutaneous hyperpigmentation (Peutz-Jeghers syndrome, Carney complex), pilomatricoma (FAP, CMMRD), eczema (WAS), telangiectasias (ataxia telangiectasia, mothers against decapentaplegic homolog 4 [SMAD4]-associated juvenile polyposis syndrome), lipomas (phosphatase and tensin homolog [PTEN] hamartoma tumor syndrome), facial angiofibromas, Shagreen patches, ash leaf spots (tuberous sclerosis), and generalized warts (Emberger syndrome).[22] Dermatologic cancers seen in predisposition syndromes include squamous cell carcinoma (FA), melanoma (familial multiple mole melanoma syndrome, hereditary breast–ovarian cancer, LFS, CMMRD), and basal cell carcinoma (Gorlin syndrome, LFS).

Developmental anomalies. The etiologies of developmental delay, autism spectrum disorder, and intellectual disabilities are vast and often unknown. However, the occurrence of these manifestations in a patient with MDS or hematopoietic malignancy warrants further evaluation, as these abnormalities may signal the presence of conditions such as PTEN hamartoma tumor syndrome, tuberous sclerosis, NF1, FA, or Noonan syndrome.[22,27]

Congenital anomalies and other physical features. The presence of 1 or more congenital anomalies or other atypical physical features may also serve as an important clue for underlying cancer predisposition. For instance, differences in growth patterns such as short stature and/or microcephaly may suggest conditions associated with DNA repair, such as FA, Bloom, Nijmegen breakage, or Rothmund-Thomson syndromes. Sensorineural hearing loss can occur in familial MDS/AML caused by germ line *GATA2* or *SRP72* mutations. Primary lymphedema also can occur in individuals with *GATA2* mutations. Hair and nail abnormalities (eg, dysplastic nails, alopecia, premature graying) are seen in individuals with dyskeratosis congenita. Finally, skeletal anomalies are features of several cancer genetic syndromes, including FA, Gorlin syndrome, Shwachman-Diamond syndrome, and Diamond-Blackfan anemia.

Incidental discovery of cancer-predisposing mutations

Germline mutations in cancer-predisposing genes are increasingly being identified "by chance" as a result of the progressive incorporation of genomic approaches, such as array comparative genomic hybridization and WES, into clinical diagnostics. At this time, it is reported that 0.18% to 0.6% of germ line array comparative genomic hybridization results involve a known cancer predisposition gene.[28-31] Similar data on WES reveal that ~1% of cancer-unaffected individuals harbor germ line predisposing mutations.[32] Accordingly, these tests should be offered with pretest counseling, preferably by a genetic counselor or hematologist/oncologist familiar with these procedures and their outcomes, that includes discussion of the potential to uncover cancer-predisposing germ line findings, as well as a determination as to whether or not patients wish to receive this information.

Genomic sequencing of tumors can also uncover incidental germ line mutations that may be reflective of an underlying cancer genetic syndrome. Somatic genetic results should therefore be carefully interpreted in the context of tumor type, family history, and physical features. This scenario may be suspected when a tumor known to occur in individuals with a specific syndrome harbors mutations in the gene linked to that syndrome (eg, *TP53* mutations in adrenocortical carcinoma or hypodiploid ALL, *RB1* in retinoblastoma, and *SMARCB1* in rhabdoid tumor). If such a mutation is identified, it is important to examine the frequency of the mutation within the tumor sample. When the mutant allele frequency is considerably less than 50%, the mutation is most likely present within only a small proportion of cells (it is a subclonal event). In contrast, the identification of a mutation with an allele frequency of around 50%, particularly in a sample with high tumor purity, suggests it is present in the heterozygous state within the tumor cells. In these instances, it is important to distinguish whether the mutation is arising solely within the tumor cells or whether it is also present as a heterozygous event in the germ line. Finally, specific tumor mutational patterns may be suggestive of a predisposition. Such is the case in Lynch syndrome or CMMRD, in which tumors exhibit a very high mutation burden, also known as a "hypermutated" phenotype.[33]

Incorporation of germ line genetic information into clinical practice

In the 1990s, cancer genetic testing was rarely performed, as there was limited understanding of the clinical and functional effect resulting from most germ line mutations. Over time, knowledge of

the phenotypes associated with specific cancer susceptibility syndromes has improved, as has the ability to test for these conditions and use genetic information to guide clinical management. To facilitate evaluation, patients suspected of having a cancer genetic susceptibility syndrome should be referred to a professional with training in cancer genetics. These professionals may be identified via the National Society of Genetic Counselors, American College of Medical Genetics, and National Cancer Institute Cancer Genetics Services Directory (Table 3).

There are many potential benefits, both for the patient with cancer and his or her family, of making a diagnosis of an underlying cancer genetic susceptibility syndrome. For the patient with cancer or survivor, genetic information may inform therapy. For example, in some mutation carriers, certain chemotherapeutic agents may be dose-modified, organ-sparing surgical approaches may be indicated, radiation therapy may be reduced or even eliminated, or allogeneic stem cell transplantation (allo-SCT) should be considered. For patients with bone marrow failure, MDS, or leukemia, therapeutic choices may be informed by the presence of a predisposing mutation. For example, patients with hereditary bone marrow failure syndromes or MDS generally do not achieve sustained remission with immune suppression, and they are prone to infectious complications.[34] As a result, these patients should be treated with allo-SCT. However, these patients are often at increased risk of developing transplant-related complications. Careful consideration should be given to the choice of conditioning regimen, as patients with as FA, DC, and Shwachman-Diamond syndrome exhibit increased toxicity after myeloablative approaches.[34] Patients with DC are also at increased risk of developing graft failure and pulmonary complications after allo-SCT.[34] Importantly, patients with FA and DC exhibit a markedly increased risk of developing secondary tumors, in which 75% of patients with FA develop solid tumors by age 45 years, and 40% of patients with DC develop them by age 50 years.[34] Finally, it is important to screen relatives for the presence of a known familial mutation to exclude those who have the mutation from being a stem cell donor.

Patients with underlying cancer genetic susceptibility syndromes also become candidates for tumor surveillance. Surveillance is most suited for patients with solid tumors, where outcomes are more often linked to the initial stage of the tumor at diagnosis. In theory, solid tumors identified through surveillance may be smaller and require treatment with less-invasive surgical procedures, and possibly less or no chemotherapy or radiation therapy. Despite the theoretical benefits, there are many challenges related to cancer surveillance, including the choice of monitoring methods and timing of surveillance tests (ie, when to start, when to stop, intervals between surveillance tests). Surveillance is also complicated by the possibility of false-positive test results, which lead to increased anxiety, as well as increased follow-up imaging and invasive procedures. Finally, there are many unanswered questions related to the cost-benefit ratio of surveillance and whether the early detection of tumors really leads to significant enhancements in long-term outcomes. At this time, the area of tumor surveillance remains an active area of research investigation.

At present, consensus guidelines regarding the optimal methods of surveillance for individuals with hematopoietic cancer-predisposing genetic syndromes are lacking. Because of the rarity and relatively recent discovery of many of these syndromes, along with their variable penetrance and expressivity, there is limited understanding of how best to monitor for them. Some recommend that individuals undergo a baseline bone marrow aspirate and biopsy to assess for occult malignancy, followed by regular physical examinations and complete blood cell counts with differential.[16] If there are significant changes from baseline, it is suggested that the CBC be repeated. Should changes persist, a follow-up a bone marrow assessment could be performed.[16]

For some cancer genetic susceptibility syndromes, identification of at-risk individuals allows for cancer preventive measures, primarily prophylactic surgeries that can reduce or even eliminate the chances of developing cancer. Multiple endocrine neoplasia type 2 and FAP are excellent examples, in which early removal of the thyroid or colon, respectively, can prevent the development of cancer. Because of the morbidities associated with these procedures, alternative approaches are being sought. Toward this end, nonsteroidal anti-inflammatory medications have been shown to reduce polyp formation in individuals with FAP.[35] Despite this, it remains unclear whether use of these agents alters progression to adenocarcinoma, as case reports exist of patients developing malignancy despite use of chemoprevention.[35] At this time, the only way to prevent hematologic malignancies in individuals with conditions that predispose to blood cancers is via the pursuit of allo-SCT. However, there are many risks associated with allo-SCT, and accordingly, decisions about the timing of SCT are challenging and often driven by the need for repeated transfusions or acquisition of clonal cytogenetic abnormalities in the bone marrow.[16]

Conclusions

When faced with the diagnosis of cancer, patients and relatives will invariably question its cause. As we are learning, an increasing proportion of cancers are caused by an underlying genetic susceptibility. The identification of cancer susceptibility syndromes and their associated gene or genes is facilitating clinical and basic investigations into genotype-phenotype correlations and underlying disease mechanisms. Although many questions remain unanswered as to how best to incorporate the emerging information on heritable predisposition into the clinical setting, it is anticipated that ongoing and future discoveries will further increase knowledge of the host genetic factors that influence cancer risk and lay the groundwork for development of more effective cancer treatments, surveillance protocols, and risk-reducing measures.

Correspondence

Kim E. Nichols, Division of Cancer Predisposition, St. Jude Children's Research Hospital, Memphis, TN 38105; e-mail: kim.nichols@stjude.org.

References

1. Rahman N. Realizing the promise of cancer predisposition genes. *Nature*. 2014;505(7483):302-308.
2. Weitzel JN, Blazer KR, MacDonald DJ, Culver JO, Offit K. Genetics, genomics, and cancer risk assessment: State of the Art and Future Directions in the Era of Personalized Medicine. *CA Cancer J Clin*. 2011; 61(5):327-359.
3. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA*. 1971;68(4):820-823.
4. Parsons DW, Roy A, Yang Y, et al. Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors [published online ahead of print 28 Jan, 2016]. *JAMA Oncol*. doi: 10.1001/jamaoncol.2015.5699.
5. Schrader KA, Cheng DT, Joseph V, et al. Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA. *JAMA Oncol*. 2016; 2(1):104-111.
6. Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. *N Engl J Med*. 2015;373(24):2336-2346.

7. Kandoth C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. *Nature*. 2013;502(7471): 333-339.
8. Noetzli L, Lo RW, Lee-Sherick AB, et al. Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia. *Nat Genet*. 2015;47(5):535-538.
9. Topka S, Vijai J, Walsh MF, et al. Germline ETV6 mutations confer susceptibility to acute lymphoblastic leukemia and thrombocytopenia. *PLoS Genet*. 2015;11(6):e1005262.
10. Zhang MY, Churpek JE, Keel SB, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet*. 2015;47(2):180-185.
11. Shah S, Schrader KA, Waanders E, et al. A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia. *Nat Genet*. 2013;45(10):1226-1231.
12. Ostergaard P, Simpson MA, Connell FC, et al. Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome). *Nat Genet.* 2011;43(10):929-931.
13. Smith ML, Cavenagh JD, Lister TA, Fitzgibbon J. Mutation of CEBPA in familial acute myeloid leukemia. *N Engl J Med*. 2004;351(23):2403-2407.
14. Song WJ, Sullivan MG, Legare RD, et al. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. *Nat Genet*. 1999;23(2):166-175.
15. Churpek JE, Lorenz R, Nedumgottil S, et al. Proposal for the clinical detection and management of patients and their family members with familial myelodysplastic syndrome/acute leukemia predisposition syndromes. *Leuk Lymphoma*. 2013;54(1):28-35.
16. Godley LA. Inherited predisposition to acute myeloid leukemia. *Semin Hematol*. 2014;51(4):306-321.
17. Lu KH, Wood ME, Daniels M, et al; American Society of Clinical Oncology. American Society of Clinical Oncology Expert Statement: collection and use of a cancer family history for oncology providers. *J Clin Oncol*. 2014;32(8):833-840.
18. Riley BD, Culver JO, Skrzynia C, et al. Essential elements of genetic cancer risk assessment, counseling, and testing: updated recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2012;21(2):151-161.
19. Stadler ZK, Schrader KA, Vijai J, Robson ME, Offit K. Cancer genomics and inherited risk. *J Clin Oncol*. 2014;32(7):687-698.
20. Wood ME, Kadlubek P, Pham TH, et al. Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. *J Clin Oncol*. 2014; 32(8):824-829.
21. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL; Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med*. 2015;17(1): 70-87.
22. Jongmans MC, Loeffen JL, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. *Eur J Med Genet*. 2016;59(3):116-125.
23. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. *Nat Genet*. 2013;45(3): 242-252.
24. Churpek JE, Godley LA. How I diagnose and manage individuals at risk for inherited myeloid malignancies. *Blood*. 2016;128(14):1800-1813.
25. Schulz E, Valentin A, Ulz P, et al. Germline mutations in the DNA damage response genes BRCA1, BRCA2, BARD1 and TP53 in patients with therapy related myeloid neoplasms. *J Med Genet.* 2012;49(7):422-428.
26. Churpek JE, Marquez R, Neistadt B, et al. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. *Cancer*. 2016;122(2):304-311.
27. Knapke S, Zelley K, Nichols KE, Kohlmann W, Schiffman JD. Identification, management, and evaluation of children with cancer-predisposition syndromes. *Am Soc Clin Oncol Educ Book.* 2012;576-584.
28. Adam MP, Justice AN, Schelley S, Kwan A, Hudgins L, Martin CL. Clinical utility of array comparative genomic hybridization: uncovering tumor susceptibility in individuals with developmental delay. *J Pediatr*. 2009;154(1):143-146.
29. Adams SA, Coppinger J, Saitta SC, et al. Impact of genotype-first diagnosis: the detection of microdeletion and microduplication syndromes with cancer predisposition by aCGH. *Genet Med*. 2009;11(5):314-322.
30. Hamm JA, Mikhail FM, Hollenbeck D, Farmer M, Robin NH. Incidental detection of cancer predisposition gene copy number variations by array comparative genomic hybridization. *J Pediatr*. 2014;165(5):1057-1059.
31. Pichert G, Mohammed SN, Ahn JW, Ogilvie CM, Izatt L. Unexpected findings in cancer predisposition genes detected by array comparative genomic hybridisation: what are the issues? *J Med Genet*. 2011;48(8): 535-539.
32. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA*. 2014;312(18): 1870-1879.
33. Shlien A, Campbell BB, de Borja R, et al; Biallelic Mismatch Repair Deficiency Consortium. Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers. *Nat Genet*. 2015;47(3):257-262.
34. Babushok DV, Bessler M. Genetic predisposition syndromes: when should they be considered in the work-up of MDS? *Best Pract Res Clin Haematol*. 2015;28(1):55-68.
35. Kim B, Giardiello FM. Chemoprevention in familial adenomatous polyposis. *Best Pract Res Clin Gastroenterol*. 2011;25(4-5):607-622.
36. Malkin D, Nichols KE, Zelley K, Schiffman JD. Predisposition to pediatric and hematologic cancers: a moving target. *Am Soc Clin Oncol Educ Book*. 2014;e44-e55.
37. Wimmer K, Kratz CP, Vasen HF, et al; EU-Consortium Care for CMMRD (C4CMMRD). Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *J Med Genet*. 2014;51(6):355-365.
38. Chrzanowska KH, Gregorek H, Dembowska-Bagińska B, Kalina MA, Digweed M. Nijmegen breakage syndrome (NBS). *Orphanet J Rare Dis*. 2012;7:13.
39. Kratz CP, Franke L, Peters H, et al. Cancer spectrum and frequency among children with Noonan, Costello, and cardio-facio-cutaneous syndromes. *Br J Cancer*. 2015;112(8):1392-1397.
40. Stieglitz E, Loh ML. Genetic predispositions to childhood leukemia. *Ther Adv Hematol*. 2013;4(4):270-290.