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Discussing and managing hematologic germ line variants

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With the introduction of genomic technologies, more hereditary cancer syndromes with hematologic malignancies are being described. Up to 10% of hematologic malignancies in children and adults may be the result of an underlying inherited genetic risk. Managing these patients with hereditary hematologic malignancies, including familial leukemia, remains a clinical challenge because there is little information about these relatively rare disorders. This article covers some of the issues related to the diagnosis and interpretation of variants associated with hereditary hematologic malignancies, including the importance of an accurate family history in interpreting genetic variants associated with disease. The challenges of screening other family members and offering the most appropriate early malignancy detection is also discussed. We now have a good opportunity to better define hereditary cancer syndromes with associated hematologic malignancies and contribute to clinically effective guidelines.

Learning Objectives

- Recognize the importance of family history in the interpretation of germ line variants
- Understand the different types of germ line variants found in genetic testing
- Become familiar with strategies for genetic screening and early malignancy detection

Introduction

The diagnosis of cancer is a life-changing event for families. The implications are compounded when that diagnosis also serves as a harbinger of a hereditary cancer predisposition, with implications for seemingly unaffected family members. Although the majority of hematologic malignancies are sporadic, growing evidence indicates that some of those malignancies are the result of an inherited predisposition. Identifying the subset of children and adults who have an inherited cancer risk is important for planning treatment, anticipating future cancer risks, and determining risks for family members.[1,2]

Leukemia predisposition is a component of many different genetic and familial conditions. Down syndrome, RASopathies (neurofibromatosis type 1, Noonan syndrome, and cardiofaciocutaneous syndrome),[3] and several inherited bone marrow failure syndromes (Diamond-Blackfan anemia, Shwachman-Diamond syndrome, severe congenital neutropenia, and congenital amegakaryocytic thrombocytopenia)[1] typically present early in childhood and can be diagnosed on the basis of multiple features. This article focuses on the role of genetic counseling and testing for rare hereditary hematologic syndromes, including nonsyndromic familial acute myeloblastic leukemia (AML)/myelodysplastic syndrome (MDS) and familial acute lymphoblastic leukemia (ALL).[1] These conditions present unique diagnostic and counseling challenges.

Starting the conversation: identifying risk factors for familial leukemia

Hereditary hematologic cancers are very likely underdiagnosed. Barriers unique to collecting family history in the setting of a new diagnosis of leukemia include the often acute nature of this blood cancer and the need for urgent treatment, perhaps compounded by the common perception that hereditary leukemia is rare and unlikely to be encountered.[1] However, awareness that cancer can be related to inherited factors is now increasing significantly in the general population, and rather than adding to the burden on families, discussing family history may be a welcomed chance to address concerns and questions.[4,5]

Key information to gather when collecting family history includes any occurrence of cancer in first-, second-, and ideally third-degree relatives. Documentation in the medical record should include all cancers and should also include the type, age at diagnosis, and parental lineage.[6] Inquiring about other hematologic diagnoses, such as cytopenia and congenital anomalies, can also be helpful because the presentation of many of these familial leukemia conditions remains quite variable.[1] A simple conversation with the patient and/or parents during the initial clinic visit can be the first step in collecting a family history. Collecting information on the types of cancer and ages of onset can help flag those patients with a pattern of cancer in the family who warrant referral for genetic counseling (Table 1). Earlier age of onset is often a feature of hereditary cancer predisposition, but history of multiple cases of late-onset MDS and AML has been associated with underlying *DDX41* germ line mutations.[7-9] Therefore family history is needed to accurately assess the risk for a genetic condition. However, the level of detail obtained

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Table 1. Red flags warranting a genetic evaluation for leukemia patients[1,17]

Red flag	Features
Personal history of congenital anomalies or comorbidities	Short stature; cutaneous features including café-au-lait spots, hypopigmentation, nail defects, premature graying; cardiac defects; skeletal defects (particularly radial anomalies); pulmonary fibrosis
Unusual response to chemotherapy or radiation treatment	
Prior diagnosis of squamous head, neck, or anogenital cancer	
Prior diagnosis of early-onset cancer (particularly those associated with Li-Fraumeni syndrome: breast, sarcoma, brain, adrenal, lung, and gastrointestinal)	
Certain somatic mutations	Fanconi anemia: gain of 1q, gain of 3q, monosomy 7, deleted 7q, gain of 13q, and deleted 20q Shwachman-Diamond syndrome: isochromoscome 7q *GATA2* germ line: monosomy 7, *ASXL1* *CEBPA* germ line: biallelic CEBPA, *GATA2, WT1* *RUNX1* germ line: biallelic RUNX1 *TP53* germ line: hypodiploid ALL *PAX5* germ line: PAX5 loss of heterozygosity and 9p deletion
Family history of any of these features	One or more first-degree relatives with a blood cancer; multiple cases of AML on the same side of the family regardless of age; congenital anomalies (particularly those features listed in first row of this table); cytopenias; early-onset cancer; individuals with multiple primary cancers

solely by patient report may not be sufficient for an accurate evaluation. Assessment of a family history of hematologic cancers ideally includes information about the specific cell lineage of the cancers, chronic vs acute, and the presence of cytopenia or other nonmalignant hematologic abnormalities. Accurate information about the diagnoses can help narrow down the possible underlying syndromes and also help in the selection of genetic tests. Although some types of cancers, such as breast cancer, tend to be quite reliably reported in both close and more distant relatives, laypersons are less familiar with the nuances of different hematologic malignancies and disorders. A study of the reliability of family history reports found that when compared with medical records, patient-reported history of hematologic cancers had a 0.38 (range, 0.30 to 0.40) sensitivity and a 0.99 (range, 0.98 to 0.99) specificity, whereas reports of breast cancer had a 0.72 (range, 0.69 to 0.74) sensitivity and 0.99 (range, 0.98 to 1.00) specificity.[10] Therefore, it is important to recognize that even though patients may share their family history with their practitioners, the patients themselves do not realize that their family histories are most likely incomplete.

Strategies for improving accuracy of family history reports include the use of paper or electronic questionnaires to guide patients through questions that they can ask their relatives, especially when trying to shed some light on their relatives' diagnoses and their own diagnosis.[11] Most family history collection tools are general, and it is likely that the creation of tools tailored to this population of patients with blood disorders would help ensure the most effective communication with relatives. Ideally, family members' diagnoses can be confirmed with medical records. These steps typically fall outside the scope of visits to the hematology or oncology clinic. Patients with suggestive histories should be referred to a cancer genetics clinic for a more thorough analysis of the family history. The genetic counselors and practitioners in the cancer genetics clinic can expand the family history and help validate the reported diagnoses.

Nonhematologic features associated with hereditary syndromes may be subtle and should be sought in the course of the initial evaluation of any hematology patient. Physical evaluation for skin features, including café-au-lait spots, hypopigmentation, premature gray hair, and nail dysplasia should be assessed, and the medical history should be reviewed for any history of congenital anomalies, pulmonary fibrosis, and prior cytopenias. Fanconi anemia (FA) and dyskeratosis congenita (DKC) are both inherited bone marrow failure syndromes characterized by distinctive phenotypes that can be diagnosed by careful physical examination. FA is associated with short stature, radial defects, other congenital abnormalities, and bone marrow failure presenting early in life.[12] DKC is classically defined by the triad of lacy reticular pigmentation of the skin, leukoplakia, and bone marrow failure.[13] An increasing amount of data now indicate that these classical nonhematologic findings have variable penetrance, and bone marrow failure, leukemia, or solid tumors may be the only presenting feature.[12-14]

Increasingly, the molecular features of the cancer provide clues about underlying germ line mutations. In some clinical scenarios, it may be that a hereditary cancer syndrome will first be considered after molecular results are returned. Biallelic mutations in *CEBP2A* and *RUNX1* have both been associated with germ line mutations in the same patient and their leukemia cells, respectively.[15-17] Additional chromosomal changes in the leukemia cells have been found to be characteristic of other inherited syndromes as well as other nonchromosomal indicators of familial cancer (Table 1).[1,17]

Genetic counseling and testing

The process of genetic testing begins with pretest genetic counseling.[18,19] The goal of this initial conversation is to help set the family's expectations about the type of information that can be gained, to prepare them for possible outcomes of testing, and to ensure that they are making an informed decision about pursuing the option of

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genetic testing. Ideally, this is a collaborative discussion that includes the oncology team, a genetic counselor, and the family to ensure a consensus plan for going forward on the basis of the test results.[20]

Multiple genes, each contributing to a small fraction of familial leukemia, have been identified and have clinical testing available. The phenotypes associated with these genes are overlapping. Therefore, in many situations, testing with a next-generation sequencing panel that includes multiple genes is often the most efficient approach for evaluating patients. A recent study of participants in the Canadian Inherited Bone Marrow Failure Registry, which used a 72-gene panel, detected causative mutations in 59% of patients. Use of the multigene panel changed 9% of the diagnoses that had been made on clinical history alone.[14] Despite these improvements in mutation detection, a significant number of patients with a clinical or family history suggestive of a hereditary condition will still have no identifiable cause. As comprehensive genomic testing in the clinical setting such as whole exome sequencing and whole genome sequencing becomes more widely available, it is expected that more genetic causes of familial leukemia and blood disorders will be recognized. Until then, the clinical risk management of such undiagnosed patients and their families remains clinically challenging.

Genetic testing of leukemia patients is complicated by the fact that, in many cases, it cannot be done with blood. In patients with active disease, testing with blood or bone marrow will not distinguish between germ line and somatic mutations. In patients who have had allogeneic bone marrow transplantation, their blood will be populated by donor DNA. Saliva and buccal samples have been shown to have high levels of lymphocytes and are not reliable alternative sources of host germ line DNA.[1,21] Ideally, DNA from cultured skin fibroblasts would be used in cases in which there is any possibility of residual disease or when an allogeneic bone marrow transplantation has been performed (although it may also be possible for lymphocytes to infiltrate the skin). In children, the need for a skin biopsy may add to the concern of parents who are considering testing for their child, especially when it may be occurring in the context of other invasive procedures. Discussion of the importance of having a source of DNA that will provide an accurate result and providing age-appropriate guidance for helping children through this procedure may help minimize the stress surrounding this decision.[22]

It should be noted that somatic mutation testing is being conducted more often as part of diagnosis, and treatment planning will identify features that suggest or confirm a germ line risk (Table 1). In these situations, there may have been little opportunity to address beforehand the potential familial implications of the testing. Evaluation of clinical and family history before diagnostic testing of leukemia will help flag patients who may have the greatest chance of harboring a germ line mutation. These individuals may be offered access to genetic counseling resources in preparation for receiving results from somatic mutation testing. In addition, including a genetic counselor as part of the team can help ensure that patients will have access to additional support and information as the need arises.

Interpreting outcomes from genetic testing

Genetic testing may result in the identification of a pathogenic mutation. The implication of that finding will depend on the specific gene harboring the mutation. Multigene panel tests, which are quickly becoming the standard in the field of cancer genetics, include genes with a range of risks for hematologic cancer and possibly other cancer risks. Identifying a genetic mutation will allow for testing for that specific mutation to be offered to at-risk relatives to determine who else in the family may have inherited that mutation and is at risk.

Even with the increasing number of genes identified in leukemogenesis, the actual etiology of most leukemias still remains unknown. A negative test result may help rule out some syndromes, but there still may be a residual risk for family members because of the possibility that unidentified genetic or environmental factors are still playing a role. Empiric risk estimates based on family history vary on the basis of the design of the study and cancers included in it. Estimates of the risk for hematologic cancer range from twofold to sevenfold for first-degree relatives of individuals with ALL and from approximately twofold to fourfold for those with AML.[23-26] However, at least 1 study has failed to confirmed any association between family history and ALL risk.[27] Ultimately, a negative test result in the affected patient should be evaluated in the context of the patient's personal and family history.[28] For families in which there is a strong pattern of leukemia and no mutation identified, enrollment in research to look for novel genetic factors would be appropriate.

Gene testing technology has outpaced our ability to determine the biological effect of all the genetic variants detected. Testing, particularly when it is performed as part of a multigene panel, frequently identifies a genetic variant of uncertain significance (VUS). These variants may be benign and only a marker of normal human variation, or they may affect the gene function and be related to the risk and onset of hematologic disease. The uncertain classification most often results from not having sufficient data to determine the effect (Table 2).[29] High levels of certainty are required to classify a variant as pathogenic or benign, which leaves a wide range of variants falling into an uncertain classification. VUSs should not be used for making medical decisions, and relatives should not be tested for a VUS unless it is part of research.[29] Several factors can be incorporated into the classification of a variant, including evolutionary conservation, modeling the predicted effect on protein function, co-inheritance with known pathogenic mutations, population frequency of the variant, frequency of the variant as a somatic change in cancers, segregation analysis in families, and functional assays.[30,31] Generally, data from multiple lines of evidence are needed to classify a variant and determine its clinical significance. One piece of evidence, such as a computer model that predicts how the variant will affect protein, may be suggestive but should not be considered sufficient by itself to classify a variant for decision making regarding a patient's care. The acceptable standard for labeling a variant deleterious is not standardized across testing laboratories, adding to the challenge of managing familial leukemia patients and interpreting the findings of their genetic testing. Another factor that complicates patient management is that many clinical laboratories have variations in policies regarding the data they use for classification, whether they will conduct additional research such as segregation analysis, and whether they will provide updated information if the variant is reclassified in the future.

Finding a VUS can be frustrating in any genetic disease testing setting. Studies of women found to have a VUS in *BRCA1* and *BRCA2* genes can cause distress, and some patients seek prophylactic surgery even though it is not indicated on the basis of the result.[32,33] At this time, there are no specific data regarding response to a VUS in individuals being tested for familial leukemia, but there is

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Table 2. Classification of genetic variants

Classification	Likelihood of being pathogenic	Implications for management	Implications for family members
Pathogenic	>0.99	Follow management guidelines for syndrome	Offer testing to at-risk relatives and related bone marrow donors
Likely pathogenic	0.95-0.99	Follow management guidelines for syndrome	Offer testing to at-risk relatives and related bone marrow donors
Uncertain	0.05-0.949	Do not consider in management planning	Do not test at-risk relatives or related bone marrow donors
Likely not pathogenic	0.001-0.049	Do not consider in management planning	Do not test at-risk relatives or related bone marrow donors
Not pathogenic	<0.001	Do not consider in management planning	Do not test at-risk relatives or related bone marrow donors

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a significant potential for misattribution of the significance of a VUS in these leukemia families. Genetic testing may frequently be initiated as part of the process of urgently planning treatment or selecting a bone marrow donor who is a family member.[15] There may be a strong desire to incorporate the VUS into these decisions, which is not appropriate on the basis of current guidelines. We encourage working with an experienced laboratory that can connect patients with experts in variant classification who can help ensure access to the most complete and up-to-date information possible about the variant. Discussion of the possibility of a VUS needs to be included in pretest counseling to ensure that everyone—treating physicians and family—is aware of the possibility of a VUS and that an agreed upon plan is established for addressing this finding if it occurs.

Unique considerations in counseling families about hereditary leukemia

Genetic testing for common hereditary cancer predisposition has been available for 20 years. Studies of outcomes of genetic testing for syndromes such as hereditary breast or ovarian cancer, Lynch syndrome, or Li-Fraumeni syndrome (LFS) have found that testing can improve management of patients and allow at-risk relatives to take preventive action, and tests for these syndromes have resulted in very few clinically significant psychological sequelae.[33,35,36] However, aspects of the biology of leukemia present unique challenges that may mean prior counseling strategies or previous experience with psychosocial outcomes may not apply to this population. First, conditions that may be associated with familial leukemia are very heterogeneous, and they vary in inheritance pattern, penetrance, and whether there is a risk for additional clinical features. Many of the genes included on multigene panels have been described in only a few leukemia families. Therefore, it is unlikely that these small numbers of patients with familial leukemia provide a full picture of the associated penetrance and disease spectrum. Prevention strategies for at-risk relatives have also not been well defined in many of these familial leukemia conditions.

Another aspect that makes leukemia unique is the occasional need for family members to serve as bone marrow donors.[37] Ideally, only bone marrow from mutation-negative family members should be used as donor bone marrow. The finding of a mutation in the patient may prompt urgent testing of family members as part of donor selection. The process of family donation, particularly when the donor is a child, is already associated with psychosocial implications, and we do not know if or how the addition of genetic testing might contribute to this.[34,38] The psychological impact of having a relative who tests positive for a germ line mutation may mean that another family member is at risk for leukemia and also that the individual family member is no longer a suitable donor for the current patient. Because of the lack of proven interventions for improving outcomes for at-risk relatives, some unaffected family members may prefer not to know whether they have inherited this risk. However, there may be pressure to have predictive testing to determine eligibility for being a bone marrow donor for the relative needing treatment. All of this can increase anxiety at an already very tense psychosocial time for the family. To date, guidelines for bone marrow donation do not yet specifically address how genetic testing for familial conditions in asymptomatic individuals should be incorporated into this process.[2,34,37,39] Research on the psychosocial implications of genetic testing for familial leukemia should be paired with ongoing research to understand genetic predisposition for hematologic cancer.

Long-term follow-up

Consensus management guidelines exist for some familial leukemia syndromes, particularly FA, DKC, LFS, and constitutional mismatch repair deficiency, but these focus predominately on screening for nonhematologic malignancies.[12,13,40-42] A study of 33 LFS patients found that following a comprehensive screening protocol improved survival compared with waiting for the onset of symptoms.[40] In this series, there were 3 cases of hematologic cancer: two AML and one MDS. The AML cases occurred in patients not undergoing surveillance; 1 died 6 months after diagnosis and the other survived for 16 years. The MDS case was detected with a screening complete blood count (CBC), and that patient was alive at 1.2 years of follow-up, but these few cases are insufficient to make any conclusions regarding the efficacy of hematologic cancer screening. Overall, hematologic cancer is a rare manifestation of LFS, occurring in an estimated 3% of patients.[17] However, rare families with *TP53* mutations have presented with only a hematologic cancer phenotype.[43] Although long-term outcomes of screening have not been studied in these families, patients with a significant family history of hematologic cancers may derive more clinical utility from screening. Until more evidence is compiled, patients with LFS should consider annual CBCs with manual differentials to assess their risk for hematologic malignancies. In addition, it is still unclear whether treatment regimens should be adjusted in the group of patients with LFS who have hematologic malignancies in the same way that DNA-damaging agents should be avoided in patients with FA. In the absence of evidence, we still encourage using the standard of therapeutic care for patients with LFS being treated for hematologic malignancies.

To date, there are few studies or guidelines for managing at-risk individuals who have the vast majority of the inherited syndromes with leukemia predisposition. Penetrance of hematologic malignancy risk, including any known associations with precursor hematologic abnormalities such as MDS that can be detected in the

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Table 3. Summary of familial hematologic cancer syndromes[1,7,12,13,15,17]

Condition	Gene name	Hematologic cancer	Nonmalignant hematologic features	Other cancer risks	Cancer screening for at-risk family members
Fanconi anemia	*FANC1*, *FANCB*, *FANCC*, *BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *BRIP1*, *FANCL*, *FANCM*, *PALB2*, *RAD51C*, *SLX4*	MDS/AML	Bone marrow failure	Head/neck and anogenital squamous cell cancers, liver cancer, esophageal cancer	CBC every 2 to 3 mo, bone marrow biopsy, annual gynecologic examination, oral cancer screening (at least annually), consider endoscopic examination of esophagus
Dyskeratosis congenita	*CTC*, *DKC1*, *TERC*, *TERT*, *TINF2*, *NHP2*, *POP10*, *WRAP53*	MDS/AML	Bone marrow failure, macrocytosis	Skin, head/neck, and anogenital squamous cell cancers	Annual CBC and bone marrow biopsy, dermatology examination, annual gynecologic examination, oral cancer screening (at least annually)
Familial AML with mutated *CEBPA*	*CEBPA*	AML	None	No other known cancer risks	No consensus; limited studies; consider periodic CBC, including baseline bone marrow biopsy
Familial AML with mutated *GATA2*	*GATA2*	AML/MDS	Monocytopenia and mycobacterial infection syndrome, Emberger syndrome, immune deficiencies	No other known cancer risks	No consensus; limited studies; consider periodic CBC, including baseline bone marrow biopsy
Quantitative and qualitative platelet disorders with propensity to myeloid malignancy	*RUNX1*, *ANKRD26*, *ETV6*	AML/MDS	Thrombocytopenia	No other known cancer risks	No consensus; limited studies; consider periodic CBC, including baseline bone marrow biopsy
DDX41-related AML	*DDX41*	AML/MDS (late onset), possibly others	No	No other known cancer risks	No consensus; consider periodic CBC
Familial mosaic monosomy 7	Monosomy of chromosome 7	AML/MDS	Bone marrow insufficiency, anemia	No other known cancer risks	Annual CBC, karyotype, and hemoglobin F
Familial aplastic anemia/MDS related to *SRP72*	*SRP72*	MDS	Aplastic anemia	No other known cancer risks	No consensus; consider periodic CBC
SH2B3-related familial ALL	*SH2B3*	ALL	Autoimmunity	No other known cancer risks	No consensus; consider periodic CBC
PAX5-related familial ALL	*PAX5*	ALL	No	No other known cancer risks	No consensus; consider periodic CBC
Li-Fraumeni syndrome	*TP53*	ALL, AML, MDS	No	Adrenal, breast, brain, and lung sarcoma, gastrointestinal cancers	Breast imaging every 6 mo, annual total body and brain magnetic resonance imaging scan, colonoscopy every 2 to 5 y; consider periodic CBC for hematologic cancer screening
Constitutional mismatch repair deficiency	*MSH2*, *MLH1*, *MSH6*, *PMS2*	ALL/AML	No	Brain tumors, gastrointestinal cancers	

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peripheral blood or bone marrow and the severity of other non-hematologic cancer risks and comorbidities, need to be considered together when deciding on the utility of screening at-risk relatives. Periodic checks of blood counts could be considered, but the limitations of screening options should be discussed with relatives who are considering testing for a familial mutation. Although it is intuitively appealing, especially given the recent understanding of subclonal evolution, little evidence has yet to be offered that early detection of leukemia through screening laboratory work in the peripheral blood will change clinical outcome compared with careful scrutiny for physical symptoms (eg, petechiae, bruising, pallor, and fatigue). Nevertheless, screening CBCs can still be considered as part of a comprehensive early-detection strategy for familial hematologic malignancies, along with baseline bone marrow biopsies (Table 3). Again, it is important to emphasize that the majority of these rare syndromes with leukemia predisposition lack consensus screening guidelines because of their rarity and the limited number of peer-reviewed publications.

Ideally, a relationship with a cancer genetics clinic will be part of the long term follow-up for families at risk for leukemia predisposition and other hematologic malignancies. Continued collaboration between the treating hematology team and cancer genetics experts can help ensure that families are kept up-to-date on new developments, including obtaining the latest information on interpreting mutation variants, testing other family members, and being made aware of the literature related to early malignancy surveillance. In addition, it is likely that the need for ongoing support for these families will continue as new health concerns arise, as relatives seek information about their risks, and as affected individuals consider implications for family planning. For clinicians and researchers, it will be important to form registries for hereditary hematologic syndromes to gain the kind of knowledge and experience necessary for managing such patients. For now, treating physicians can consider searching the ClinicalTrials.gov Web site for research studies enrolling patients with hematologic predisposition.

Conclusions

Familial leukemia and other hematologic hereditary conditions represent a diverse group of clinical diseases and pose unique issues for diagnosis, counseling, and clinical follow-up for early detection. A multidisciplinary team will be in the best position to plan care, interpret genetic test results, and ultimately communicate effectively with the family. In particular, genetic counselors will be extremely helpful in addressing the underlying fears and psychosocial concerns of families with a new diagnosis of a predisposition toward a hereditary blood cancer. There is little information about the clinical diagnosis and management of patients with familial leukemia and other hematologic malignancies, including penetrance of disease and other associated medical conditions. This lack of information represents an opportunity to learn more about the genetic basis of hematologic malignancies by studying families with inherited mutations and to develop and tailor genetic testing and counseling strategies to meet their unique needs.

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