THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Hereditary Myeloid Malignancy and Inherited Bone Marrow Failure

Clinical Features and Molecular Genetics:

Hereditary myeloid malignancies were considered rare, but have been increasingly recognized in recent years [1-3]. Hereditary myeloid malignancies can occur in the context of familial myeloid dysplastic syndrome/acute leukemia (MDS/AL) that have MDS/AL as the principal clinical feature, or arise from inherited bone marrow failure syndromes (IBMFS), such as Fanconi anemia, dyskeratosis congenita/telomerase biology disorders, Diamond-Blackfan anemia, and severe congenital neutropenia [1, 4]. Within the past decade, nearly a dozen adult-onset hereditary myeloid malignancies syndromes have been defined. Although the majority of patients with classic IBMFS are diagnosed in childhood, some patients have no or only subtle extra hematopoietic manifestations and may present in adulthood with aplastic anemia, MDS or AL [2, 5]. Recently, World Health Organization (WHO), the National Comprehensive Cancer Network (NCCN) Guidelines on Myelodysplastic Syndromes (version 2.2017) and European LeukemiaNet (ELN) have all included germline predisposition to myeloid malignancies as a new entity [6-8]. The presence of the specific underlying genetic defect or predisposition syndrome should be evaluated as part of the myeloid malignancy workup. The genes that are involved in both hereditary breast cancer/other cancers and hereditary myeloid malignancies are included in the panel.

Our Hereditary Myeloid Malignancy and Inherited Bone Marrow Failure Panel include sequence and deletion/duplication analysis of the 80 genes listed below, and deletion/duplication only of the genes listed below in bold.

Hereditary Myeloid Malignancy and Inherited Bone Marrow Failure Genes							
Familial MDS/AL	**Dyskeratosis Congenita**	**Fanconi Anemia**		**Diamond-Blackfan Anemia**	**Severe Congenital Neutropenia**	**Other**	
ANKRD26	ACD	BRCA1 (FANCS)	RAD51 (FANCR)	GATA1	CSF3R	ALAS2	RBM8A
CEBPA	CTC1	BRCA2 (FANCD1)	RAD51C (FANCO)	RPL5	CXCR4	ATM	SBDS
DDX41	DKC1	BRIP1 (FANCJ)	UBE2T (FANCT)	RPL11	ELANE (ELA2)	BLM (RECQL3)	SBF2
ETV6	NAF1	ERCC4 (FANCQ)	SLX4 (FANCP)	RPL15	G6PC3	CBL	
GATA2	NHP2	FANCA		RPL35A	GFI1	CHEK2 (CHK2)	
IKZF1	NOP10 (NOLA3)	FANCB		RPL26	HAX1	DNAJC21	
PAX5	PARN	FANCC		RPS7	VPS45	MLH1	
RUNX1	POT1	FANCD2		RPS10	WAS	MPL	
SAMD9	RTEL1	FANCE		RPS19		MSH2	
SAMD9L	TERC	FANCF		RPS24		MSH6	
SRP72	TERT	FANCG		RPS26		NBN (NBS1)	
TP53	TINF2	FANCI				NF1	
ATG2B	USB1 (C16orf57)	FANCL				PMS2	
GSKIP	WRAP53 (TCAB1)	PALB2 (FANCN)				PTPN11	

Familial Myelodysplastic Syndrome/Acute Leukemia Panel (Pure familial MDS/AL)

Pure familial MDS/AL is characterized by multiple cases of MDS and/or AL without bone marrow failure or other phenotypic features in one family. It is due to inheritance of a single abnormal copy of a gene encoding a

transcription factor that is critical for hematopoiesis [1]. Mutation carriers can have additional findings in addition to the clinical features than MDS/AL, but these may be subtle or absent [1].

Gene	Clinical Features and Molecular Pathology
ANKRD26	Mutations in the 5'UTR and protein coding regions of *ANKRD26* were reported to cause an autosomal-dominant form of inherited thrombocytopenia, THC2. It has been reported that among 105 people with confirmed or suspected *ANKRD26* mutations, 10 developed hematologic malignancies, including seven with acute leukemias. The overall incidence of development of hematologic malignancies was 240 out of 100,000, and of acute leukemia was 167 out of 100,000, both elevated over expected levels [9-11].
ATG2B/ GSKIP	Germline duplication of *ATG2B* and *GSKIP* predisposes to familial myeloid malignancies, including myeloproliferative neoplasms, frequently progressing to leukemia [12].
CEBPA	Mutations in the *CEBPA* gene are associated with familial acute myeloid leukemia (AML). Typically the first mutation present in the germline within the 5' end of the gene, and a second 3' mutation is acquired within the leukemia. Though germline 3' *CEBPA* mutations have also been identified. *CEBPA* mutations confer a relatively favorable prognosis. Patients found to have biallelic *CEBPA* mutations within their leukemic cells should be tested for germline mutations [13].
GATA2	Germline mutations in *GATA2* have been described in association with familial MDS/AML, as well as with several heterogeneous clinical syndromes, including Emberger syndrome and the MonoMAC syndrome which show an overall increased risk of developing MDS/AML [13, 14]. Although the incidence of MDS/AL appears very high, there is incomplete penetrance, with some individuals living into late adulthood without developing malignancy or demonstrating hematologic or infectious abnormalities [1]. Zhang *et al* (2014) identified germline mutations in *GATA2* in 5 out of 71 subjects with idiopathic bone marrow failure or myelodysplastic syndrome [15]. These patients did not have additional features associated with other *GATA2* disorders, Emberger syndrome and MonoMac.
DDX41	Recurrent mutations in the DEAD/H-box RNA helicase gene *DDX41* have been reported in patients with familial and acquired myelodsyplasia and acute myeloid leukemia [16].
ETV6	Germline mutations in *ETV6* are associated with thrombocytopenia, red cell macrocytosis and predisposition to hematological malignancies [17-19].
IKZF1	A germline *IKZF1* mutation can cause an autosomal dominant form of common variable immunodeficiency that is associated with a striking decrease in B-cell numbers, and is a predisposition to B-cell precursor acute lymphoblastic leukemia, pancytopenia and autoimmune diseases [20, 21].
PAX5	*PAX5* is a member of the PAX family of transcription factors and is required for normal B cell development. Germline mutations in *PAX5* are associated with susceptibility to B cell precursor acute lymphoblastic leukemia (B-ALL) [22, 23].
RUNX1	Germline mutations of *RUNX1* can cause familial platelet disorder with propensity to myeloid malignancy (FPD/AML). The clinical presentation is highly variable, but typically includes a lifelong mild to moderate bleeding tendency due to quantitative and/or functional platelet defects. The incidence of MDS/AL in individuals with germline *RUNX1* mutations is over 40% [4, 24]. Patients may present with MDS/AL at any age, with a median age of onset of 33 years and a range of 6 – 76 years [1]. Different FPD/AL families have varying risks of progressing to myeloid malignancy due to different mutations [13].
SAMD9	Mutations in *SAMD9* cause a multisystem disorder including myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy. Patients carrying a *SAMD9* mutation can develop MDS that was accompanied by loss of the chromosome 7 [25, 26].
SAMD9L	Mutations in *SAMD9L* cause ataxia-pancytopenia syndrome which is characterized by cerebellar ataxia, variable hematologic cytopenias, and predisposition to marrow failure, myelodysplastic syndrome and myeloid leukemia, sometimes associated with monosomy 7. Hematopoietic revertant mosaicism has been reported and was associated with milder disease [27, 28].
SRP72	*SRP72* encodes one of six protein subunits of the signal recognition particle (SRP), part of the cellular apparatus responsible for nascent protein processing and trafficking. To date, only a small number of families have been identified with *SRP72* mutations and aplastic anemia/MDS [13].
TP53	Li-Fraumeni syndrome, caused by an inherited germline mutation in the *TP53* tumor suppressor genes, presents with an increased risk of nearly all malignancies, including leukemias [4, 29].

Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a highly heterogeneous disorder characterized by abnormal skin pigmentation, nail dystrophy and oral leukoplakia (mucosal keratosis appearing as white patches in the oral cavity) [30]. This classic triad of findings is present in 80-90% of affected individuals [31]. Bone marrow failure is present in approximately 85% of cases [31]. Other disease manifestations can include epiphora (excessive tear production), intellectual disability, pulmonary fibrosis, abnormal pulmonary vasculature, tooth loss or decay, premature hair loss or greying, liver disease, osteoporosis, and deafness [31]. Dyskeratosis congenita is commonly associated with shortened telomeres [31]. Anticipation may be observed in affected families, and is thought to be due to the inheritance of shortened telomeres from an affected parent [31]. DC can be inherited in either an autosomal dominant, autosomal recessive or X-linked manner, depending on the causative gene.

Gene	Clinical Features

ACD	Guo Y *et al.* (2014) reported germline mutations of *ACD*, the gene encoding telomere protein TPP1 in Inherited bone marrow failure [32]. A pathogenic variant in *ACD* has also been described in a family with chronic lymphocytic leukemia [33]. Hoyeraal-Hreidarsson syndrome can also be caused by a germline mutation in *ACD* [34].
CTC1	Keller *et al.* (2012) identified compound heterozygous mutations in *CTC1* in a patient with DC [35]. The *CTC1* gene is also associated with Coats syndrome, which is characterized by bilateral exudative retinopathy, intracranial calcifications and cysts, premature hair greying, osteoporosis and anemia [36].
DKC1	Mutations in the X-linked *DKC1* gene are the most common cause of DC [37]. Age of onset and severity of symptoms is highly variable, but affected males typically present in the first decade of life, and typically die in their twenties due to complications from bone marrow failure [37]. Many mutations occur *de novo*. Female heterozygous carriers are typically asymptomatic [37].
NAF1	Mutations in *NAF1* have been described in patients with short telomere length, pulmonary fibrosis, low telomerase RNA levels, and extrapulmonary manifestations including myelodysplastic syndrome and liver disease [38].
NOP10 (NOLA3)	A homozygous mutation in *NOP10* was identified in 3 individuals with DC in a consanguineous family [39]. All three individuals had the mucocutaneous features of DC, one individual also developed bone marrow failure [39].
NHP2	Biallelic mutations in *NHP2* have been described in two patients with DC [40].
PARN	Biallelic mutations in *PARN* have been reported to be associated with severe aplastic anemia and marked hypomyelination [41, 42]. Monoallelic mutations of *PARN* can cause developmental/mental illness [41].
POT1	Germline heterozygous pathogenic variants in *POT1* have been recently reported in thyroid cancer, breast cancer, renal cell carcinoma, colorectal cancer and familial chronic lymphocytic leukemia [33, 43]. A *POT1* mutation has been recently reported implicating defective telomere end fill-in and telomere truncations in Coats plus [44].
RTEL1	Both dominant and recessive mutations in the *RTEL1* gene have been associated with Hoyeraal Hreidarsson syndrome, a clinically severe variant of DC with cerebellar hypoplasia, severe immunodeficiency, enteropathy, and intrauterine growth retardation [45]. Anticipation has been described in one family where two affected males inherited a heterozygous mutation from a clinically unaffected female with short telomeres [45]. Heterozygous mutations in *RTEL1* have been reported in patients with bone marrow failure and myelodysplastic syndromes [46, 47].
TERC	Heterozygous mutations in the *TERC* gene account for approximately 4% of all cases of DC [37]. Anticipation has been observed in families with *TERC*-associated DC, with increased disease severity and earlier age of onset seen with successive affected generations [37]. *TERC* mutations cause autosomal dominant dyskeratosis congenita which often presents later in life without classic mucocutaneous symptoms. *TERC* mutations are associated with anticipation, with progressively shorter telomeres passed down through generations [48]. Members of earlier generations often demonstrate mild disease, whereas those of younger generations experience more severe disease manifestations, such as aplastic anemia or MDS/AML [13, 49-51]
TERT	Heterozygous mutations in *TERT* have been associated with DC or aplastic anemia [37]. Penetrance of these mutations appears to be reduced, with some individuals being asymptomatic [37]. Variable expressivity has also been described, with some individuals being mildly affected [37]. Heterozygous mutations in the *TERT* gene are associated with autosomal dominant dyskeratosis congenita. Penetrance of these mutations appears to be reduced, with some individuals being asymptomatic [37]. Variable expressivity has also been described, with some individuals being mildly affected [37]. More severe disease manifestations may include aplastic anemia or MDS/AML [13, 49-51].
TINF2	Dominant mutations in *TINF2* have been described in patients with DC [52]. Both inherited and *de novo* mutations have also been described [52, 53].
USB1 (C16orf57)	Walne *et al.* (2010) identified homozygous mutations in the *USB1* (*C16orf57)* gene in 6 out of 132 families with dyskeratosis congenita (DC) [54]. DC has previously been associated with short telomeres, however patients with *USB1* mutations and DC were found to have normal length telomeres [54]. Mutations in the *USB1* gene have also been described in individuals with poikiloderma with neutropenia (PN), which is characterized by poikilodermatous rash (patchy skin discoloration), noncyclical neutropenia, small stature, pachyonychia, and pulmonary disease [55].
WRAP53 (TCAB1)	Biallelic mutations in *TCAB1* have been described in individuals with classical DC from two different families [56].

Fanconi Anemia

Fanconi anemia (FA) is a chromosomal instability disorder associated congenital anomalies, progressive bone marrow failure, and cancer predisposition [57]. The most commonly described anomalies include thumb and radial bone abnormalities, short stature and skin hyperpigmentation [57]. Some patients lack these characteristic physical features and first present with bone marrow failure or cancer [58]. Associated cancers include AML, MDS, and solid tumors of the head, neck, skin, gastrointestinal tract and genital tract [57]. The majority of cases of FA are inherited in an autosomal recessive manner. Mutations in the *FANCB* gene are inherited in an X-linked manner.

Gene	Clinical Features
BRCA1 (FANCS)	Recently, two cases of individuals harboring biallelic deleterious *BRCA1* mutations were reported [59, 60]. Detailed phenotypic and cellular characterization of one patient provided lines of evidence supporting the hypothesis that biallelic BRCA1 mutations cause a new Fanconi anemia subtype associated with increased breast and ovarian cancer susceptibility [59].
BRCA2 (FANCD1)	Homozygous or compound heterozygous mutations in *BRCA2* are associated with FA complementation group D1. *BRCA2* mutations are associated with early-onset leukemia and solid tumors, and a high rate of spontaneous chromosome aberration compared to other types of FA [61, 62]. Heterozygous mutations in *BRCA2* are associated with hereditary breast and ovarian cancer [63].
BRIP1 (FANCJ)	FA complementation group J is associated with biallelic mutations in the *BRIP1* gene [64]. There is some evidence that heterozygous BRIP1 mutations may be associated with increased breast cancer susceptibility [65].
ERCC4 (FANCQ)	FA complementation group Q is associated with biallelic *ERCC4* mutations [66]. *ERCC4* mutations can also be associated with xeroderma pigmentosa [67].
FANCA	Biallelic *FANCA* mutations are associated with FA complementation group A [68]. Patients with mutations associated with no FANCA protein production may have earlier onset anemia and higher risk of leukemia, compared with patients with production of an abnormal FANCA protein [68].
FANCB	Mutations in the X-linked *FANCB* are associated with FA complementation group B. Affected patients typically have multiple malformations, including a ventriculomegaly or hydrocephalus, bilateral radial defects, vertebral defects, and renal agenesis [69]. An estimated 50% of affected males do not survive the perinatal period; heterozygous females are typically unaffected and exhibit skewed X-inactivation [69].
FANCC	FA complementation group C is associated with biallelic mutations in *FANCC*. A founder mutation in *FANCC* exists in the Ashkenazi Jewish population, and has a carrier frequency of 1 in 100 [70].
FANCD2	Biallelic mutations in *FANCD2* are associated with FA complementation group D2, and account for approximately 3-6% of all cases of FA [71]. Patients with *FANCD2* mutations frequently have congenital malformations, and have earlier onset hematological manifestations compared FA cases overall [71].
FANCE	Homozygous mutations in *FANCE* have previously been identified in 2 Turkish patients and 1 Bangladeshi patient with FA complementation group E [72].
FANCF	FA complementation group F is caused by homozygous or compound heterozygous mutations in the *FANCF* gene [73].
FANCG	Biallelic *FANCG* mutations are associated with FA complementation group G. FANCG mutations are typically associated with more severe cytopenia and a higher risk of leukemia than is observed with cases of FA in general [68].
FANCI	FA complementation group I is caused by homozygous or compound heterozygous mutations in the *FANCI* gene [74].
FANCL	A patient with FA complementation group L and compound heterozygous mutations in *FANCL* has previously been described [75].
PALB2 (FANCN)	FA complementation group N has been associated with compound heterozygous mutations in *PALB2*. Heterozygous mutations in *PALB2* have been associated with increased susceptibility to breast cancer [76].
RAD51 (FANCR)	Wang *et al.,* 2015, identified a *de novo* heterozygous mutation in *RAD51* in a patient with a FA-like phenotype [77].
RAD51C (FANCO)	A homozygous mutation in *RAD51C* has previously been described in a family with FA complementation group O [78]. Heterozygous mutations in this gene have been associated with breast cancer predisposition [79].
UBE2T (FANCT)	Two unrelated individuals were reported with biallelic *UBE2T* missense mutations that rendered the UBE2T protein unable to interact with FANCL and caused Fanconi anemia [80].
SLX4 (FANCP)	FA complementation group P has been associated with either homozygous or compound heterozygous mutations in the *SLX4* gene [81].

Severe Congenital Neutropenia (SCN)

Severe congenital neutropenia (SCN) is characterized by severe neutropenia at birth [82]. Bone marrow exhibits arrest of neutrophil maturation at the promyelocyte or myelocyte stage of development [82]. By age 6 months, 90% of patients with SCN develop bacterial infections such as skin or deep tissue abscesses, oral ulcers and pneumonia [82]. Despite improvements in therapy there remains a 12% risk of death due to sepsis by age 15 years [82]. Patients with SCN also have an increased risk of AML and MDS, with a hazard rate of 2% per year [82]. SCN can be inherited in either an autosomal dominant, autosomal recessive or X-linked manner, depending on the causative gene.

Gene	Clinical Features
CSF3R	Biallelic loss-of-function mutations in *CSF3R* have been described in patients with SCN [83]. Plo *et al.* (2009) identified a heterozygous activating mutation in *CSF3R* in a family with dominantly inherited chronic neutropenia [84]. One affected family member also developed MDS.
CXCR4	Heterozygous mutations in the *CXCR4* gene WHIM syndrome is an immunodeficiency disease characterized by neutropenia, hypogammaglobulinemia, and extensive human papillomavirus (HPV) infection [85, 86].

ELANE (ELA2)	Heterozygous mutations in the *ELANE* gene are responsible for the majority of cases of SCN [87]. *ELANE* can also be associated with cyclic neutropenia [87]. To clear phenotype-genotype correlations exist, and there is significant overlap between predicted severity of the mutation and the clinical phenotype [87].
G6PC3	Biallelic mutations in *G6PC3* have been associated with SCN type 4 [88]. Patients with *G6PC3* deficiency commonly present with congenital anomalies including cardiac anomalies, urogenital malformations and venous angietasia [88]. Alangari *et al.* (2013) described a consanguineous family where affected individuals presented with either SCN or cyclic neutropenia [88].
GFI1	Dominant-negative mutations in *GFI1* have been associated with SCN [89]. *GFI1* mutations have also been identified in patients with nonimmune chronic idiopathic neutropenia of adults [90].
HAX1	Biallelic mutations in *HAX1* account for 15% of cases of SCN [89]. A proportion of patients with *HAX1*-associated SCN also develop neurological disease such as cognitive impairment, developmental delay, and epilepsy [89].
VPS45	Stepensky *et al.* (2013) identified homozygous mutations in *VPS45* in patients with SCN [91]. Affected individuals developed neutropenia, thrombasthenia, myelofibrosis and progressive bone marrow failure [91].
WAS	Activating mutations in the X-linked *WAS* gene are associated with SCN and lmyphopenia [89]. Loss of function mutations in *WAS* have been associated with Wiskott-Aldrich syndrome, associated with immunodeficiency, eczema, microthromobocytopenia, and susceptibility to malignant lymphoma [89].

Diamond-Blackfan Anemia (DBA)

Diamond-Blackfan anemia (DBA) is an inherited red blood cell aplasia disorder associated with reduced or absent erythroid precursors in bone marrow, macrocytic anemia and reticulocytopenia [82]. Approximately 30% of cases have growth retardation and 50% have congenital anomalies, which may include thumb anomalies, congenital heart defects and midline facial defects such as cleft palate and hypertelorism [82]. Patients have an increased risk of malignancies, including AML, MDS, and solid tumors such as osteogenic sarcoma [82]. The cumulative incidence of solid tumors or leukemia is 22% by age 46 [92]. DBA is a genetically heterogeneous condition, with the currently known genes accounting for 50-70% of cases [82]. All the DBA genes included on this panel are inherited in an autosomal dominant manner. An estimated 55-60% of cases are caused by *de novo* mutations; DBA has variable expressivity and penetrance is incomplete.

Gene	Clinical Features
GATA1	Patients with inherited thrombocytopenia in a concurrent hemolytic anemia should raise the suspicion of thrombocytopenia caused by *GATA1* mutations or sitosterolemia [93]. Recent exome sequencing has identified a novel splice site mutation in *GATA1* in two siblings with DBA [94].
RPL5	DBA type 6, caused by heterozygous mutations in *RPL5*, is typically associated with multiple physical anomalies, including craniofacial, thumb and cardiac anomalies [95].
RPL11	Heterozygous mutations in *RPL11* are associated with DBA type 7. In terms of observed congenital malformations, mutations in *RPL11* are predominantly associated with isolated thumb defects [95].
RPL15	Deletions of *RPL15* have been identified in patients with Diamond-Blackfan anemia recently [96, 97].
RPL35A	Mutations in *RPL35A* have been identified in both familial and sporadic cases of DBA type 5. In one familial case, some individuals were found to have subclinical DBA with macrocytic anemia [98].
RPL26	Gazda HT *et al.* (2012) identified a frameshift mutation in p53 regulator *RPL26* that is associated with multiple physical abnormalities and a specific pre-ribosomal RNA processing defect in diamond-blackfan anemia[99].
RPS7	*RPS7* has been associated with DBA type 8 [100]. At least one individual with no associated physical anomalies has been described [95].
RPS10	*RPS10* mutations are associated with DBA type 6, and are estimated to account for 2.6% of all DBA cases [101].
RPS19	Mutations in the *RPS19* gene account for an estimated 24% of all DBA cases overall [102].
RPS24	*RPS24* mutations are associated with DBA type 3, and account for an estimated 2% of DBA cases [103]. Both sporadic and familial mutations have been described [103].
RPS26	Mutations in *RPS26* are associated with DBA type 10, and account for an estimated 6.4% of DBA cases overall. Based on available data from a limited number of cases, physical malformations appear to be rare in patients with *RPS26* mutations [101].

Other Genetic Causes of Bone Marrow Failure

Gene	Clinical Features
ALAS2	The most common form is X-linked sideroblastic anemia, due to loss-of-function mutations in the erythroid-specific δ-aminolevulinate synthase (ALAS2), which is the first enzyme of the heme biosynthesis pathway in erythroid cells [104]. ALAS2 gain-of-function mutations lead to the increased erythroid protoporphyrin accumulation causing X-linked protoporphyria [105].
ATM	Approximately 10% of patients with ataxia telangiectasia due to biallelic *ATM* mutations develop cancer, mostly of the lymphoid malignancies including Hodgkin's lymphoma, non-Hodgkin's lymphoma, and several forms of leukemia [106, 107]. AML has also been reported in patients with AT [108, 109].

BLM (RECQL3)	Mutations in the gene encoding DNA helicase RecQ protein-like-3 (BLM) cause Bloom syndrome. A 13%-25% lifetime risk of MDS/AML has been reported in patients with Bloom syndrome [24, 29].
CBL	Germline mutations of the CBL gene are associated with CBL syndrome with predisposition to juvenile myelomonocytic leukemia [110].
CHEK2 (CHK2)	Li-Fraumeni syndrome, which can be caused by an inherited germline mutation in the *CHEK2* tumor suppressor gene, presents with an increased risk of nearly all malignancies, including leukemias [4, 29].
DNAJC21	Biallelic mutations in *DNAJC21* cause Shwachman-Diamond syndrome and bone marrow failure prone to hematological malignancies [111, 112].
MLH1 MSH2 MSH6 PMS2	Heterozygous mutations in *MLH1, MSH2*, *MSH6* and *PMS2* are associated with hereditary nonpolyposis colon cancer (HNPCC), which is associated with an increased risk of certain cancers, particularly colon and ovarian cancers. Homozygous or compound heterozygous mutations in these genes lead to a mismatch repair deficiency that can result in a mutator phenotype characterized by early onset gastrointestinal tumors, leukemia and/or lymphoma and features of neurofibromatosis type 1. These features can be summarized with the acronym CoLoN' (Colon tumors or/and Leukemia/Lymphoma or/and Neurofibromatosis features [113-115].
MPL	Biallelic mutations in the *MPL* gene have been associated with congenital amegakaryocytic thrombocytopenia (CAMT), which typically presents with thrombocytopenia during infancy, but can also present as bone marrow failure without a specific history of thrombocytopenia [57].
NBN (NBS1)	Biallelic mutations in the *NBS1* gene are responsible for the Nijmegen breakage syndrome which display an elevated risk to lymphoblastic leukemia [114].
NF1	*NF1* microdeletions are associated with a more severe neurofibromatosis 1 (NF1) phenotype and increased risk for developing malignant tumors, including leukemias (especially juvenile myelomonocytic leukemia, with a risk of progression toward AML) [116, 117].
PTPN11	*PTPN11* mutations are the most common cause of Noonan syndrome, and cause 90% of LEOPARD syndrome cases [118]. Patients with Noonan syndrome and LEOPARD syndrome have a predisposition for leukemia and certain solid tumors [119-121]. Noonan syndrome and a pathogenic *PTPN11* mutation represents a 3.5 times increased risk of developing a cancer compared with the general population [118].
RBM8A	The *RBM8A* gene is associated with thrombocytopenia-absent radius (TAR) syndrome, a rare autosomal recessive disorder [122]. Affected individuals have severe thrombocytopenia at birth, and bilateral radial hypoplasia or aplasia, with preservation of thumbs [122]. The majority of patients with TAR are heterozygous for a 200kb deletion at 1q21.1 which encompasses the *RBM8A* gene. In patients who carry the 200kb deletion, the remaining *RBM8A* allele is typically hypomorphic due the presence of 1 of 2 known low frequency SNPs, either in the 5' UTR or in the first intron.
SBDS	Homozygous or compound heterozygous mutations in *SBDS* are associated with Shwachman-Diamond syndrome, which is characterized by short stature, exocrine pancreatic insufficiency, and bone marrow dysfunction [123]. Hematologic findings can include intermittent neutropenia, anemia, increased fetal hemoglobin levels, thrombocytopenia and aplastic anemia [123]. There is an increased risk of malignant transformation, including a risk of AML [123]. Heterozygous mutations in SBDS have been associated with aplastic anemia [124].
SBF2	A homozygous mutation in the *SBF2* gene has been described in a family with congenital thrombocytopenia and mucocutaneous bleeding [125]. Homozygous mutations in *SBF2* have also been associated with Charcot-Marie-Tooth disease type 4B2 [126].

Testing Options

Hereditary Myeloid Malignancy and Inherited Bone Marrow Failure Panel (sequencing and deletion/duplication analysis of 80 genes, an deletion/duplication analysis only of two additional genes)

Sample specifications:	2 T-25 flasks of cultured skin fibroblasts, or DNA extracted from fibroblasts. NOTE: Peripheral blood samples are not accepted for patients with a history of MDS/leukemia.
Cost:	$4,000
CPT codes:	81406, 81407
Turn-around time:	4-6 weeks

Note: We do not bill insurance directly for this specific test

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All novel

and/or potentially pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Results:

Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire panel. All abnormal results are reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Churpek, J.E., 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): p. 28-35.
2. Bannon, S.A. and C.D. DiNardo, *Hereditary Predispositions to Myelodysplastic Syndrome.* Int J Mol Sci, 2016. **17**(6).
3. Babushok, D.V., M. Bessler, and T.S. Olson, *Genetic predisposition to myelodysplastic syndrome and acute myeloid leukemia in children and young adults.* Leuk Lymphoma, 2016. **57**(3): p. 520-36.
4. Owen, C., M. Barnett, and J. Fitzgibbon, *Familial myelodysplasia and acute myeloid leukaemia--a review.* Br J Haematol, 2008. **140**(2): p. 123-32.
5. Babushok, D.V. and M. Bessler, *Genetic predisposition syndromes: when should they be considered in the work-up of MDS?* Best Pract Res Clin Haematol, 2015. **28**(1): p. 55-68.
6. Arber, D.A., et al., *The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia.* Blood, 2016. **127**(20): p. 2391-405.
7. Greenberg, P.L., et al., *Myelodysplastic Syndromes, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology.* J Natl Compr Canc Netw, 2017. **15**(1): p. 60-87.
8. Dohner, H., et al., *Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel.* Blood, 2017. **129**(4): p. 424-447.
9. Pippucci, T., et al., *Mutations in the 5' UTR of ANKRD26, the ankirin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia, THC2.* Am J Hum Genet, 2011. **88**(1): p. 115-20.
10. Noris, P., et al., *Mutations in ANKRD26 are responsible for a frequent form of inherited thrombocytopenia: analysis of 78 patients from 21 families.* Blood, 2011. **117**(24): p. 6673-80.
11. Al Daama, S.A., et al., *A missense mutation in ANKRD26 segregates with thrombocytopenia*, in *Blood*2013: United States. p. 461-2.
12. Saliba, J., et al., *Germline duplication of ATG2B and GSKIP predisposes to familial myeloid malignancies.* Nat Genet, 2015. **47**(10): p. 1131-40.
13. Nickels, E.M., et al., *Recognizing familial myeloid leukemia in adults.* Ther Adv Hematol, 2013. **4**(4): p. 254-69.
14. Ishida, H., et al., *GATA-2 anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia.* Eur J Pediatr, 2012. **171**(8): p. 1273-6.
15. Zhang, M.Y., et al., *Genomic analysis of bone marrow failure and myelodysplastic syndromes reveals phenotypic and diagnostic complexity.* Haematologica, 2014.
16. Polprasert, C., et al., *Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms.* Cancer Cell, 2015. **27**(5): p. 658-70.
17. Noetzli, L., et al., *Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia.* Nat Genet, 2015. **47**(5): p. 535-8.

18. Zhang, M.Y., et al., *Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy.* Nat Genet, 2015. **47**(2): p. 180-5.
19. Topka, S., et al., *Germline ETV6 Mutations Confer Susceptibility to Acute Lymphoblastic Leukemia and Thrombocytopenia.* PLoS Genet, 2015. **11**(6): p. e1005262.
20. Kuehn, H.S., et al., *Loss of B Cells in Patients with Heterozygous Mutations in IKAROS.* N Engl J Med, 2016. **374**(11): p. 1032-43.
21. Hoshino, A., et al., *Abnormal hematopoiesis and autoimmunity in human subjects with germline IKZF1 mutations.* J Allergy Clin Immunol, 2016.
22. Shah, S., et al., *A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia.* Nature Genetics, 2013. **45**: p. 1226-1231.
23. Hyde, R.K. and P.P. Liu, *Germline PAX5 mutations and B cell leukemia.* Nature Genetics, 2013. **45**: p. 1104-1105.
24. Liew, E. and C. Owen, *Familial myelodysplastic syndromes: a review of the literature.* Haematologica, 2011. **96**(10): p. 1536-42.
25. Narumi, S., et al., *SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7.* Nat Genet, 2016. **48**(7): p. 792-7.
26. Schwartz, J.R., et al., *Germline SAMD9 mutation in siblings with monosomy 7 and myelodysplastic syndrome.* Leukemia, 2017.
27. Chen, D.H., et al., *Ataxia-Pancytopenia Syndrome Is Caused by Missense Mutations in SAMD9L.* Am J Hum Genet, 2016. **98**(6): p. 1146-58.
28. Tesi, B., et al., *Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms.* Blood, 2017. **129**(16): p. 2266-2279.
29. Churpek, J.E. and K. Onel, *Heritability of hematologic malignancies: from pedigrees to genomics.* Hematol Oncol Clin North Am, 2010. **24**(5): p. 939-72.
30. Sakaguchi, H., K. Nakanishi, and S. Kojima, *Inherited bone marrow failure syndromes in 2012.* Int J Hematol, 2013. **97**(1): p. 20-9.
31. Kirwan, M. and I. Dokal, *Dyskeratosis congenita, stem cells and telomeres.* Biochim Biophys Acta, 2009. **1792**(4): p. 371-9.
32. Guo, Y., et al., *Inherited bone marrow failure associated with germline mutation of ACD, the gene encoding telomere protein TPP1.* Blood, 2014. **124**(18): p. 2767-74.
33. Speedy, H.E., et al., *Germline mutations in shelterin complex genes are associated with familial chronic lymphocytic leukemia.* Blood, 2016.
34. Kocak, H., et al., *Hoyeraal-Hreidarsson syndrome caused by a germline mutation in the TEL patch of the telomere protein TPP1.* Genes Dev, 2014. **28**(19): p. 2090-102.
35. Keller, R.B., et al., *CTC1 Mutations in a patient with dyskeratosis congenita.* Pediatr Blood Cancer, 2012. **59**(2): p. 311-4.
36. Armanios, M., *An emerging role for the conserved telomere component 1 (CTC1) in human genetic disease.* Pediatr Blood Cancer, 2012. **59**(2): p. 209-10.
37. Mason, P.J. and M. Bessler, *The genetics of dyskeratosis congenita.* Cancer Genet, 2011. **204**(12): p. 635-45.
38. Stanley, S.E., et al., *Loss-of-function mutations in the RNA biogenesis factor NAF1 predispose to pulmonary fibrosis-emphysema.* Sci Transl Med, 2016. **8**(351): p. 351ra107.
39. Walne, A.J., et al., *Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10.* Hum Mol Genet, 2007. **16**(13): p. 1619-29.
40. Vulliamy, T., et al., *Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita.* Proc Natl Acad Sci U S A, 2008. **105**(23): p. 8073-8.
41. Dhanraj, S., et al., *Bone marrow failure and developmental delay caused by mutations in poly(A)-specific ribonuclease (PARN).* J Med Genet, 2015. **52**(11): p. 738-48.

42. Bertuch, A.A., *The Molecular Genetics of the Telomere Biology Disorders.* RNA Biol, 2015: p. 0.
43. Wilson, T.L., et al., *A new POT1 germline mutation-expanding the spectrum of POT1-associated cancers.* Fam Cancer, 2017.
44. Takai, H., et al., *A POT1 mutation implicates defective telomere end fill-in and telomere truncations in Coats plus.* Genes Dev, 2016. **30**(7): p. 812-26.
45. Ballew, B.J., et al., *Germline mutations of regulator of telomere elongation helicase 1, RTEL1, in Dyskeratosis congenita.* Hum Genet, 2013. **132**(4): p. 473-80.
46. Cardoso, S.R., et al., *Myelodysplasia and liver disease extend the spectrum of RTEL1 related telomeropathies.* Haematologica, 2017.
47. Keel, S.B., et al., *Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients.* Haematologica, 2016. **101**(11): p. 1343-1350.
48. Vulliamy, T., et al., *Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC.* Nat Genet, 2004. **36**(5): p. 447-9.
49. Armanios, M., *Telomerase and idiopathic pulmonary fibrosis.* Mutat Res, 2012. **730**(1-2): p. 52-8.
50. Parry, E.M., et al., *Syndrome complex of bone marrow failure and pulmonary fibrosis predicts germline defects in telomerase.* Blood, 2011. **117**(21): p. 5607-11.
51. Vulliamy, T.J., et al., *Mutations in the reverse transcriptase component of telomerase (TERT) in patients with bone marrow failure.* Blood Cells Mol Dis, 2005. **34**(3): p. 257-63.
52. Savage, S.A., et al., *TINF2, a component of the shelterin telomere protection complex, is mutated in dyskeratosis congenita.* Am J Hum Genet, 2008. **82**(2): p. 501-9.
53. Tsangaris, E., et al., *Ataxia and pancytopenia caused by a mutation in TINF2.* Hum Genet, 2008. **124**(5): p. 507-13.
54. Walne, A.J., et al., *Mutations in C16orf57 and normal-length telomeres unify a subset of patients with dyskeratosis congenita, poikiloderma with neutropenia and Rothmund-Thomson syndrome.* Hum Mol Genet, 2010. **19**(22): p. 4453-61.
55. Wang, L.L., et al., *Absence of RECQL4 mutations in poikiloderma with neutropenia in Navajo and non-Navajo patients.* Am J Med Genet A, 2003. **118A**(3): p. 299-301.
56. Zhong, F., et al., *Disruption of telomerase trafficking by TCAB1 mutation causes dyskeratosis congenita.* Genes Dev, 2011. **25**(1): p. 11-6.
57. Khincha, P.P. and S.A. Savage, *Genomic characterization of the inherited bone marrow failure syndromes.* Semin Hematol, 2013. **50**(4): p. 333-47.
58. Chirnomas, S.D. and G.M. Kupfer, *The inherited bone marrow failure syndromes.* Pediatr Clin North Am, 2013. **60**(6): p. 1291-310.
59. Sawyer, S.L., et al., *Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype.* Cancer Discov, 2015. **5**(2): p. 135-42.
60. Domchek, S.M., et al., *Biallelic deleterious BRCA1 mutations in a woman with early-onset ovarian cancer.* Cancer Discov, 2013. **3**(4): p. 399-405.
61. Hirsch, B., et al., *Association of biallelic BRCA2/FANCD1 mutations with spontaneous chromosomal instability and solid tumors of childhood.* Blood, 2004. **103**(7): p. 2554-9.
62. Wagner, J.E., et al., *Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia.* Blood, 2004. **103**(8): p. 3226-9.
63. Martin, A.M., et al., *Germline mutations in BRCA1 and BRCA2 in breast-ovarian families from a breast cancer risk evaluation clinic.* J Clin Oncol, 2001. **19**(8): p. 2247-53.
64. Levitus, M., et al., *The DNA helicase BRIP1 is defective in Fanconi anemia complementation group J.* Nat Genet, 2005. **37**(9): p. 934-5.

65. Seal, S., et al., *Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles.* Nat Genet, 2006. **38**(11): p. 1239-41.
66. Bogliolo, M., et al., *Mutations in ERCC4, encoding the DNA-repair endonuclease XPF, cause Fanconi anemia.* Am J Hum Genet, 2013. **92**(5): p. 800-6.
67. Cleaver, J.E., et al., *A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy.* Hum Mutat, 1999. **14**(1): p. 9-22.
68. Faivre, L., et al., *Association of complementation group and mutation type with clinical outcome in fanconi anemia. European Fanconi Anemia Research Group.* Blood, 2000. **96**(13): p. 4064-70.
69. McCauley, J., et al., *X-linked VACTERL with hydrocephalus syndrome: further delineation of the phenotype caused by FANCB mutations.* Am J Med Genet A, 2011. **155A**(10): p. 2370-80.
70. Kutler, D.I. and A.D. Auerbach, *Fanconi anemia in Ashkenazi Jews.* Fam Cancer, 2004. **3**(3-4): p. 241-8.
71. Kalb, R., et al., *Hypomorphic mutations in the gene encoding a key Fanconi anemia protein, FANCD2, sustain a significant group of FA-D2 patients with severe phenotype.* Am J Hum Genet, 2007. **80**(5): p. 895-910.
72. de Winter, J.P., et al., *Isolation of a cDNA representing the Fanconi anemia complementation group E gene.* Am J Hum Genet, 2000. **67**(5): p. 1306-8.
73. de Winter, J.P., et al., *The Fanconi anaemia gene FANCF encodes a novel protein with homology to ROM.* Nat Genet, 2000. **24**(1): p. 15-6.
74. Dorsman, J.C., et al., *Identification of the Fanconi anemia complementation group I gene, FANCI.* Cell Oncol, 2007. **29**(3): p. 211-8.
75. Ali, A.M., et al., *Identification and characterization of mutations in FANCL gene: a second case of Fanconi anemia belonging to FA-L complementation group.* Hum Mutat, 2009. **30**(7): p. E761-70.
76. Poumpouridou, N. and C. Kroupis, *Hereditary breast cancer: beyond BRCA genetic analysis; PALB2 emerges.* Clin Chem Lab Med, 2012. **50**(3): p. 423-34.
77. Wang, A.T., et al., *A Dominant Mutation in Human RAD51 Reveals Its Function in DNA Interstrand Crosslink Repair Independent of Homologous Recombination.* Mol Cell, 2015. **59**(3): p. 478-90.
78. Vaz, F., et al., *Mutation of the RAD51C gene in a Fanconi anemia-like disorder.* Nat Genet, 2010. **42**(5): p. 406-9.
79. Golmard, L., et al., *Germline mutation in the RAD51B gene confers predisposition to breast cancer.* BMC Cancer, 2013. **13**: p. 484.
80. Hira, A., et al., *Mutations in the gene encoding the E2 conjugating enzyme UBE2T cause Fanconi anemia.* Am J Hum Genet, 2015. **96**(6): p. 1001-7.
81. Stoepker, C., et al., *SLX4, a coordinator of structure-specific endonucleases, is mutated in a new Fanconi anemia subtype.* Nat Genet, 2011. **43**(2): p. 138-41.
82. Wilson, D.B., et al., *Inherited bone marrow failure syndromes in adolescents and young adults.* Ann Med, 2014: p. 1-11.
83. Triot, A., et al., *Inherited biallelic CSF3R mutations in severe congenital neutropenia.* Blood, 2014.
84. Plo, I., et al., *An activating mutation in the CSF3R gene induces a hereditary chronic neutrophilia.* J Exp Med, 2009. **206**(8): p. 1701-7.
85. Hernandez, P.A., et al., *Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease.* Nat Genet, 2003. **34**(1): p. 70-4.
86. Balabanian, K., et al., *WHIM syndromes with different genetic anomalies are accounted for by impaired CXCR4 desensitization to CXCL12.* Blood, 2005. **105**(6): p. 2449-57.

87. Germeshausen, M., et al., *The spectrum of ELANE mutations and their implications in severe congenital and cyclic neutropenia.* Hum Mutat, 2013. **34**(6): p. 905-14.
88. Alangari, A.A., et al., *A novel homozygous mutation in G6PC3 presenting as cyclic neutropenia and severe congenital neutropenia in the same family.* J Clin Immunol, 2013. **33**(8): p. 1403-6.
89. Boztug, K. and C. Klein, *Genetics and pathophysiology of severe congenital neutropenia syndromes unrelated to neutrophil elastase.* Hematol Oncol Clin North Am, 2013. **27**(1): p. 43-60, vii.
90. Person, R.E., et al., *Mutations in proto-oncogene GFI1 cause human neutropenia and target ELA2.* Nat Genet, 2003. **34**(3): p. 308-12.
91. Stepensky, P., et al., *The Thr224Asn mutation in the VPS45 gene is associated with the congenital neutropenia and primary myelofibrosis of infancy.* Blood, 2013. **121**(25): p. 5078-87.
92. Vlachos, A., et al., *Incidence of neoplasia in Diamond Blackfan anemia: a report from the Diamond Blackfan Anemia Registry.* Blood, 2012. **119**(16): p. 3815-9.
93. Pecci, A., *Diagnosis and treatment of inherited thrombocytopenias.* Clin Genet, 2016. **89**(2): p. 141-53.
94. Sankaran, V.G., et al., *Exome sequencing identifies GATA1 mutations resulting in Diamond-Blackfan anemia.* J Clin Invest, 2012. **122**(7): p. 2439-43.
95. Gazda, H.T., et al., *Ribosomal protein L5 and L11 mutations are associated with cleft palate and abnormal thumbs in Diamond-Blackfan anemia patients.* Am J Hum Genet, 2008. **83**(6): p. 769-80.
96. Landowski, M., et al., *Novel deletion of RPL15 identified by array-comparative genomic hybridization in Diamond-Blackfan anemia.* Hum Genet, 2013. **132**(11): p. 1265-74.
97. Farrar, J.E., et al., *Exploiting pre-rRNA processing in Diamond Blackfan anemia gene discovery and diagnosis.* Am J Hematol, 2014. **89**(10): p. 985-91.
98. Farrar, J.E., et al., *Abnormalities of the large ribosomal subunit protein, Rpl35a, in Diamond-Blackfan anemia.* Blood, 2008. **112**(5): p. 1582-92.
99. Gazda, H.T., et al., *Frameshift mutation in p53 regulator RPL26 is associated with multiple physical abnormalities and a specific pre-ribosomal RNA processing defect in diamond-blackfan anemia.* Hum Mutat, 2012. **33**(7): p. 1037-44.
100. Gerrard, G., et al., *Target enrichment and high-throughput sequencing of 80 ribosomal protein genes to identify mutations associated with Diamond-Blackfan anaemia.* Br J Haematol, 2013. **162**(4): p. 530-6.
101. Doherty, L., et al., *Ribosomal protein genes RPS10 and RPS26 are commonly mutated in Diamond-Blackfan anemia.* Am J Hum Genet, 2010. **86**(2): p. 222-8.
102. Willig, T.N., et al., *Mutations in ribosomal protein S19 gene and diamond blackfan anemia: wide variations in phenotypic expression.* Blood, 1999. **94**(12): p. 4294-306.
103. Gazda, H.T., et al., *Ribosomal protein S24 gene is mutated in Diamond-Blackfan anemia.* Am J Hum Genet, 2006. **79**(6): p. 1110-8.
104. Fujiwara, T. and H. Harigae, *Pathophysiology and genetic mutations in congenital sideroblastic anemia.* Pediatr Int, 2013. **55**(6): p. 675-9.
105. Bishop, D.F., et al., *Molecular expression and characterization of erythroid-specific 5-aminolevulinate synthase gain-of-function mutations causing X-linked protoporphyria.* Mol Med, 2013. **19**: p. 18-25.
106. Boultwood, J., *Ataxia telangiectasia gene mutations in leukaemia and lymphoma.* J Clin Pathol, 2001. **54**(7): p. 512-6.
107. Taylor, A.M., et al., *Leukemia and lymphoma in ataxia telangiectasia.* Blood, 1996. **87**(2): p. 423-38.
108. *Acute myeloid leukemia in a patient with ataxia-telangiectasia: a case report and review of the literature.* 2001. **15**(10).

109. Lin, C.-H., et al., *Child With Ataxia Telangiectasia Developing Acute Myeloid Leukemia.* 2010.
110. Perez, B., et al., *Germline mutations of the CBL gene define a new genetic syndrome with predisposition to juvenile myelomonocytic leukaemia.* J Med Genet, 2010. **47**(10): p. 686-91.
111. Dhanraj, S., et al., *Biallelic mutations in DNAJC21 cause Shwachman-Diamond syndrome.* Blood, 2017. **129**(11): p. 1557-1562.
112. Tummala, H., et al., *DNAJC21 Mutations Link a Cancer-Prone Bone Marrow Failure Syndrome to Corruption in 60S Ribosome Subunit Maturation.* Am J Hum Genet, 2016. **99**(1): p. 115-24.
113. Ricciardone, M.D., et al., *Human MLH1 deficiency predisposes to hematological malignancy and neurofibromatosis type 1.* Cancer Res, 1999. **59**(2): p. 290-3.
114. Stieglitz, E. and M.L. Loh, *Genetic predispositions to childhood leukemia.* Ther Adv Hematol, 2013. **4**(4): p. 270-90.
115. Bandipalliam, P., *Syndrome of early onset colon cancers, hematologic malignancies & features of neurofibromatosis in HNPCC families with homozygous mismatch repair gene mutations.* Fam Cancer, 2005. **4**(4): p. 323-33.
116. Jenne, D.E., et al., *A common set of at least 11 functional genes is lost in the majority of NF1 patients with gross deletions.* Genomics, 2000. **66**(1): p. 93-7.
117. Jenne, D.E., et al., *Molecular characterization and gene content of breakpoint boundaries in patients with neurofibromatosis type 1 with 17q11.2 microdeletions.* Am J Hum Genet, 2001. **69**(3): p. 516-27.
118. Pandit, B., et al., *Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy.* Nat Genet, 2007. **39**(8): p. 1007-12.
119. Laux, D., C. Kratz, and A. Sauerbrey, *Common acute lymphoblastic leukemia in a girl with genetically confirmed LEOPARD syndrome.* J Pediatr Hematol Oncol, 2008. **30**(8): p. 602-4.
120. Ucar, C., et al., *Acute myelomonocytic leukemia in a boy with LEOPARD syndrome (PTPN11 gene mutation positive).* J Pediatr Hematol Oncol, 2006. **28**(3): p. 123-5.
121. Jongmans, M.C., et al., *Cancer risk in patients with Noonan syndrome carrying a PTPN11 mutation.* Eur J Hum Genet, 2011. **19**(8): p. 870-4.
122. Yassaee, V.R., et al., *A new approach for molecular diagnosis of TAR syndrome.* Clin Biochem, 2014.
123. Kuijpers, T.W., et al., *Hematologic abnormalities in Shwachman Diamond syndrome: lack of genotype-phenotype relationship.* Blood, 2005. **106**(1): p. 356-61.
124. Calado, R.T., et al., *Mutations in the SBDS gene in acquired aplastic anemia.* Blood, 2007. **110**(4): p. 1141-6.
125. Abuzenadah, A.M., et al., *Identification of a novel SBF2 missense mutation associated with a rare case of thrombocytopenia using whole-exome sequencing.* J Thromb Thrombolysis, 2013. **36**(4): p. 501-6.
126. Conforti, F.L., et al., *A new SBF2 mutation in a family with recessive demyelinating Charcot-Marie-Tooth (CMT4B2).* Neurology, 2004. **63**(7): p. 1327-8.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu. You can also contact us at 773-834-0555 or ucgslabs@genetics.uchicago.edu

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS' NEEDS