# Bone Marrow Failure Gene Sequencing Panel

## Genes Tested:

| | | | | |
|---|---|---|---|---|
| *ABCB7* | *ACD* | *ADA2 (CECR1)* | *AK2* | *AP3B1* |
| *ATM* | *ATR* | *BLM* | *BRCA1* | *BRCA2* |
| *BRIP1* | *CD40LG* | *CLPB* | *CSF3R* | *CTC1* |
| *CXCR2* | *CXCR4* | *DKC1* | *DNAJC21* | *EFL1* |
| *EIF2AK3* | *ELANE* | *EPO* | *ERCC4* | *ERCC6L2* |
| *FANCA* | *FANCB* | *FANCC* | *FANCD2* | *FANCE* |
| *FANCF* | *FANCG* | *FANCI* | *FANCL* | *G6PC3* |
| *GATA1* | *GATA2* | *GFI1* | *HAX1* | *HYOU1* |
| *JAGN1* | *LAMTOR2* | *LIG4* | *LYST* | *MAD2L2* |
| *MPL* | *MRTFA (MKL1)* | *MYSM1* | *NAF1* | *NBN* |
| *NHEJ1* | *NHP2* | *NOP10* | *NSMCE3* | *PALB2* |
| *PARN* | *POT1* | *RAB27A* | *RAC2* | *RAD51* |
| *RAD51C* | *RBM8A* | *RFWD3* | *RMRP* | *RNF168* |
| *RPL11* | *RPL15* | *RPL18* | *RPL26* | *RPL27* |
| *RPL31* | *RPL35* | *RPL35A* | *RPL5* | *RPL9* |
| *RPS10* | *RPS15* | *RPS15A* | *RPS19* | *RPS24* |
| *RPS26* | *RPS27* | *RPS27A* | *RPS28* | *RPS29* |
| *RPS7* | *RTEL1* | *RUNX1* | *SAMD9* | *SAMD9L* |
| *SBDS* | *SLC37A4* | *SLX4* | *SMARCD2* | *SRP54* |
| *SRP72* | *STK4* | *STN1* | *TAZ* | *TCIRG1* |
| *TCN2* | *TERC* | *TERF2IP* | *TERT* | *TINF2* |
| *TP53* | *TSR2* | *UBE2T* | *USB1* | *VPS13B* |
| *VPS45* | *WAS* | *WDR1* | *WIPF1* | *WRAP53* |
| *XRCC2* | | | | |

## Description:

This panel is specifically designed to diagnose the most common genetic causes of bone marrow failure including dyskeratosis congenita, Diamond Blackfan anemia, Fanconi anemia, familial bone marrow failure, Schwachman Diamond syndrome, congenital amegakaryocytic thrombocytopenia, and inherited causes of neutropenia. Bone marrow failure syndromes may be inherited as autosomal dominant, autosomal recessive, or X- linked disorders. Malignant transformation is a significant risk for individuals with many of these disorders; thus, accurate and timely diagnosis is crucial for appropriate medical surveillance and management.

This panel also includes sequencing for somatic level variants in *CSF3R, RUNX1,* and *TP53.* Acquired variants in *CSF3R* have been reported in patients with severe congenital neutropenia (SCN), as well as in patients whose SCN has undergone progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (Germeshausen et al. 2007; Touw 2015). Acquired variants in *RUNX1* have been reported in patients with MDS/AML who have undergone progression from SCN, including in combination with previously acquired *CSF3R* variants (Skokowa et al. 2014). Acquired variants in *TP53* have been reported in patients with Shwachman-Diamond syndrome (SDS), and may be an early event predisposing SDS patients to transformation to MDS/AML (Xia et al. 2018). Variants in these 3 genes are reported if the variant allele frequency is 5% or higher.

## Test Offerings:

**Bone marrow failure syndromes 118 gene panel by NGS**

Sub-panels are available for specific conditions:

- Chromosome Breakage Disorders
- Dyskeratosis congenita and telomere disorders
- Diamond Blackfan anemia
- Fanconi anemia
- Inherited neutropenia

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## Indications:

**Bone Marrow Failure Syndromes Panel by NGS:**

- Confirmation of genetic diagnosis in a patient with a clinical diagnosis of bone marrow failure or associated syndrome
- Carrier identification or presymptomatic diagnosis in individuals with a family history of bone marrow failure of unknown genetic basis

**Gene Specific or Sub-panel Sequencing:**

- Confirmation of genetic diagnosis in a patient with bone marrow failure and in whom a specific genetic diagnosis is suspected

**Variant Specific Analysis:**

- Presymptomatic testing of at-risk siblings and parents for medical management and prior to bone marrow donation
- Carrier identification in individuals in whom specific variant(s) have been identified in the proband with bone marrow failure
- Prenatal diagnosis of an at-risk fetus, after confirmation of variant(s) in the parent(s) and by prior arrangement only.

## Specimen:

At least 3 mLs whole blood in a lavender top (EDTA) tube or saliva in an Oragene saliva kit. Please call 513-636-4474 for a free saliva collection kit.

**Note:** For post-transplant patients, we accept pre-transplant samples or post-transplant skin fibroblasts ONLY (blood, saliva, and cytobrushes are not accepted). Culturing of skin fibroblasts is done at an additional charge.

## Testing Methodology:

**Bone Marrow Failure Syndromes Panel by NGS:**
This test is performed by enrichment of the coding exons, flanking intronic and untranslated regions (5' and 3'), as well as known pathogenic variants (HGMD 2018.4) in the promoter and deep intronic regions of the genes specified above using oligonucleotide probe hybridization followed by next-generation sequencing with >50X coverage at every target base (exception: *SAMD9* and *SAMD9L* are sequenced through Sanger methodology). Regions with <50X will be filled in by Sanger sequencing.

All pathogenic and likely pathogenic variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing. The limit of detection of somatic variants in *CSF3R, RUNX1,* and *TP53* with this methodology is 5%. Somatic variants with <20% variant allele frequency may not be confirmed by Sanger sequencing. A detailed non-coding variant list is available upon request.

**Gene specific sequencing:** PCR-based sequencing of the entire coding region and intron/ exon boundaries of the specified gene and selected known pathogenic variants in the promoter and deep intronic regions.

**Variant specific analysis:** Sanger sequencing following PCR amplification of the targeted variant(s) of the specified gene.

## Test Sensitivity:

**Analytical Sensitivity:** The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Somatic variants in *TP53, RUNX1,* and *CSF3R* are expected to be identifiable when they are present at a variant allele frequency greater than 5%.

**Limitations:** Variants in the regulatory regions and non-reported variants in the untranslated regions may not be detected by this test. Large deletions/ duplications, large insertions and other complex genetic events will not be identified using sequencing methodology.

**Note:** Deletion/duplication is available for many of the genes on this panel. For further details, visit: www.cincinnatichildrens.org/deldup.

## Turn-Around Time:

- Bone Marrow Failure Syndromes Panel by NGS: 28 days
- Single Gene Sequencing: 28 days

## Results:

Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for the clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

## Genetic Conditions Commonly Associated with Bone Marrow Failure

| Gene | Inheritance | Condition |
|---|---|---|
| *ABCB7* | X linked | Sideroblastic anemia with ataxia |
| *ACD* | AR and AD | Dyskeratosis congenita |
| *ADA2 (CECR1)* | AR | Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome |
| *AK2* | AR | Reticular dysgenesis |
| *AP3B1* | AR | Hermansky Pudlak type 2 |
| *ATM* | AR | Ataxia-telangiectasia |
| *ATR* | AR | Seckel syndrome |
| *BLM* | AR | Bloom syndrome |
| *BRCA1, BRCA2 (FANCD1), BRIP1 (FANCJ), ERCC4 (FANCQ), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, MAD2L2, PALB2 (FANCN), RAD51, RAD51C (FANCO), RFWD3, SLX4 (FANCP), UBE2T, XRCC2* | AR; except:<br>*FANCB* — X linked<br>*RAD51* — AD | Fanconi anemia |
| *CD40LG* | X linked | X-linked hyper IgM syndrome |
| *CLPB* | AR | 3-methylglutaconic aciduria type VII, with cataracts, neurologic involvement and neutropenia |
| *CSF3R* | AD, AR and somatic | Severe congenital neutropenia 7 (SCN7) (germline); predisposition to myelodysplastic syndrome (somatic) |
| *CTC1* | AR | Coats plus syndrome |
| *CXCR2* | AR | Myelokathexis |
| *CXCR4* | AD | WHIM syndrome |
| *DKC1* | XR | Dyskeratosis congenita or Hoyeraal Hreidarsson syndrome |
| *DNAJC21* | AR | Familial bone marrow failure syndrome type 3 |
| *EFL1* | AR | Shwachman-Diamond syndrome |
| *EIF2AK3* | AR | Wolcott-Rallison syndrome |
| *ELANE (ELA2)* | AD | SCN1 |
| *EPO* | AR, AD | Diamond Blackfan anemia; erythrocytosis. |
| *ERCC6L2* | AR | Familial bone marrow failure syndrome type 2 |
| *G6PC3* | AR | SCN4, nonsyndromic SCN, Dursun syndrome |
| *GATA1* | X linked | GATA1-related X-linked cytopenia |
| *GATA2* | AD | GATA2 deficiency |
| *GFI1* | AD | SCN2 |
| *HAX1* | AR | SCN3, Kostmann syndrome |
| *HYOU1* | AR | Immunodeficiency and hypoglycemia |
| *JAGN1* | AR | SCN6 |
| *LAMTOR2 (ROBLD3)* | AR | p14 deficiency |
| *LIG4* | AR | LIG4 syndrome |
| *LYST* | AR | Chediak Higashi syndrome |
| *MPL* | AR | Congenital amegakaryocytic thrombocytopenia |

## Genetic Conditions Commonly Associated with Bone Marrow Failure, Cont.

| Gene | Inheritance | Condition |
|---|---|---|
| *MRTFA (MKL1)* | AR | Neutropenia with combined immune deficiency |
| *MYSM1* | AR | Familial bone marrow failure syndrome type 4 |
| *NAF1* | AD | Pulmonary fibrosis and emphysema |
| *NBN* | AR | Nijmegen breakage syndrome |
| *NHEJ1* | AR | Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation |
| *NHP2 (NOLA2)* | AR | Dyskeratosis congenita |
| *NOP10 (NOLA3)* | AR | Dyskeratosis congenita |
| *NSMCE3* | AR | Lung disease, immunodeficiency and chromosome breakage syndrome |
| *PARN* | AD and AR | Dyskeratosis congenita; Pulmonary fibrosis and/or bone marrow failure |
| *POT1* | AD | Familial chronic lymphocytic leukemia |
| *RAB27A* | AR | Griscelli syndrome type 2 |
| *RAC2* | AR | Neutrophil immunodeficiency syndrome |
| *RBM8A* | AR | Thrombocytopenia-absent radius syndrome |
| *RMRP* | AR | Cartilage-hair hypoplasia |
| *RNF168* | AR | RIDDLE syndrome |
| *RPL5, RPL9, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35, RPL35A, RPS7, RPS10, RPS15, RPS15A, RPS19, RPS24, RPS26, RPS27, RPS27A, RPS28, RPS29, TSR2* | AD; except:<br>*TSR2* — X linked | Diamond Blackfan anemia |
| *RTEL1* | AD and AR | Dyskeratosis congenita |
| *RUNX1* | AD and somatic | Familial platelet disorders (germline); acute myeloid leukemia (germline); predisposition to myelodysplastic syndrome/ acute myeloid leukemia (somatic) |
| *SAMD9* | AD | MIRAGE syndrome |
| *SAMD9L* | AD | Ataxia-pancytopenia syndrome |
| *SBDS* | AR | Shwachman Diamond syndrome (SDS) |
| *SLC37A4* | AR | Glycogen storage disease type IB |
| *SMARCD2* | AR | Specific granule deficiency 2 |
| *SRP54* | AD | Congenital neutropenia |
| *SRP72* | AD | Familial bone marrow failure syndrome type 1 |
| *STK4* | AR | STK4 deficiency |
| *STN1* | AR | Coats plus syndrome with telomere defects |
| *TAZ* | X linked | Barth syndrome |
| *TCIRG1* | AR, AD | Osteopetrosis (AR), Congenital neutropenia (AD) |
| *TCN2* | AR | Transcobalamin II deficiency |
| *TERC (hTR)* | AD | Dyskeratosis congenita |
| *TERF2IP* | AD | Familial melanoma |

## Genetic Conditions Commonly Associated with Bone Marrow Failure, Cont.

| Gene | Inheritance | Condition |
|---|---|---|
| *TERT* | AD and AR | Dyskeratosis congenita |
| *TINF2* | AD | Classic or severe DC, Revesz syndrome, Hoyeraal Hreidarrson syndrome; AD 3 |
| *TP53* | AD and somatic | Familial bone marrow failure syndrome 5 (germline); transformation to myelodysplastic syndrome/acute myeloid leukemia in patients with Schwachman Diamond syndrome (somatic) |
| *USB1* | AR | Clericuzio-type poikiloderma with neutropenia |
| *VPS13B* | AR | Cohen syndrome; congenital neutropenia with retinopathy |
| *VPS45* | AR | SCN5 |
| *WAS* | X linked | Wiskott Aldrich syndrome, X-linked |
| *WDR1* | AR | WDR1 deficiency |
| *WIPF1* | AR | Wiskott Aldrich syndrome |
| *WRAP53 (TCAB1, WDR79)* | AR | Dyskeratosis congenita, Revesz syndrome, Hoyeraal Hreidarrson syndrome |

## CPT Codes:

- **Bone Marrow Failure NGS Panel:** 81443
- **Single gene sequencing, targeted variant analysis, and deletion/duplication:** call for information.

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

## Shipping Instructions:

Please enclose **test requisition** with sample.
**All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Saturday.

## Ship to:

Laboratory of Genetics and Genomics
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

## References:


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