ABL1
Testing is recommended in CML with poor initial response to imatinib, relapse, or progression to accelerated/blast phase. Presence and identity of mutation may direct management to alternative drugs or stem cell transplant.

ASXL1
ASXL1 is an epigenetic regulator of gene expression. Mutations are detected in approximately 14% of MDS, 11% of AML, 45% of CMML, 30% of PMF, and 4% of PV/ET. Mutations are generally associated with aggressive disease and poor outcome in these conditions.

ATRX
The ATRX gene encodes a protein involved in chromatin remodeling and telomere biology. Mutations in ATRX have been reported in various types of hematological and solid tumor cancers such as MDS and other myeloid disorders. Testing for ATRX mutations in patients with myeloid disorders may be useful in determining the severity of the disease.

BCOR
BCOR mutations are detected in about 4% of MDS patients. Mutations in BCOR are associated with poor prognosis and tend to appear after mutations in genes involved in epigenetic regulation. BCOR analysis can be useful in risk stratification.

BCORL1
BCORL1 is a tumor suppressor gene and mutations in this gene can potentially inactivate its tumor suppression capabilities. BCORL1 mutations are present in about 1% of MDS and 6% of AML cases.

BRAF
BRAF mutations have been reported in acute myeloid leukemia and chronic myelomonocytic leukemia. The presence of these mutations in therapy-related AML has been associated with shorter overall survival. BRAF mutations have also been detected in de novo AML. Screening for BRAF mutations can help identify patients that may respond to targeted therapies such as tyrosine kinase inhibitors.

CALR
CALR mutation analysis aids diagnostic confirmation of Philadelphia-chromosome negative and JAK2/MPL-mutation negative MPN. CALR mutations are mutually exclusive with JAK2 and MPL mutations, and are detected in peripheral blood in the majority (~70-85%) of essential thrombocythemia (ET) and primary myelofibrosis (PMF) cases that are JAK2- and MPL-mutation negative. CALR mutations are not reported in polycythemia vera (PV) and can distinguish ET and PMF from PV. The presence of a CALR mutation is also associated with a better clinical course than JAK2 mutations.

CBL
Activating mutations in Casitas B-Lineage lymphoma (CBL) gene are detected in 33% atypical chronic myeloid leukemia (aCML), 5% for myelofibrosis (MF) and chronic myelomonocytic leukemia (CMML), 11% juvenile myelomonocytic leukemia (JMML), and 10% of myelodysplastic syndrome (MDS). Mutations in CBL are common in myeloproliferative neoplasms (MPNs) and patients with these mutations exhibit shorter overall survival and progression-free survival. Mutation analysis of CBL can provide prognostic details in regards to aggressiveness of MDS and its risk of transformation to AML. CBL-mutated patients may also benefit from therapeutic tyrosine kinase inhibitors.

CBLB
May act as a negative regulator for cell signaling pathways. CBLB mutations may play a role in the progression of CML into more aggressive forms of the disease. Testing for these mutations may identify patients who would benefit from tyrosine kinase inhibitors.

CBLC
May act as a negative regulator for cell signaling pathways. CBLC mutations may play a role in the progression of CML into more aggressive forms of the disease. Testing for these mutations may identify patients who would benefit from tyrosine kinase inhibitors.

CDKN2A
CDKN2A is involved in tumor suppression and mutations in this gene have been reported in various myeloid disorders. These inactivating mutations can lead to tumor progression and screening for CDKN2A status can be useful in the diagnostic and prognostic assessment of a patient’s myeloid disorder.
CEBPA

CEBPA mutations are detected in 7-15% of AML patients. Double mutations are associated with good prognosis in patients with intermediate risk and normal cytogenetics who do not have FLT3-ITD mutations. CEBPA mutations have been associated with poor prognosis and shorter overall survival in patients with MPNs.

CSF3R

CSF3R mutations are newly-identified genetic markers detected in 59% of chronic neutrophilic leukemia (CNL) or atypical chronic myeloid leukemia (aCML) that are useful for diagnosis and classification of these disorders. Identification of specific mutations may suggest the class of kinase inhibitors to which the tumor will be sensitive.

CUX1

CUX1 mutations are inactivating mutations that promote tumorigenesis and have been described in various myeloid disorders. Patients with CUX1 mutations have been shown to have poor survival.

DNMT3A

DNMT3A mutations are found in 20-25% of acute myeloid leukemia and are associated with poor outcome. Codon R882 is a mutation hot-spot with more than 60% of DNMT3A mutations occurring there. DNMT3A mutations are also found in other myeloid neoplasms and T-cell lymphoma.

ETV6

DNA sequence mutations in ETV6 are detected in acute lymphoblastic leukemia (ALL) and approximately 3% of MDS. ETV6 mutations have been shown to be independent predictors of poor prognosis in MDS. ETV6 translocations (implicated in leukemias, MDS, and sarcoma) are best detected by FISH in a separate analysis.

EZH2

Somatic EZH2 mutations are detected in ~9% of CMML and ~6% of MDS, and are independent predictors of poor overall survival in MDS. EZH2 inhibitor therapy is an active area of clinical research.

FBXW7

FBXW7 mutations are found in T-cell acute lymphoblastic leukemia, pediatric diseases and various myeloid malignancies. These mutations are involved in mediating the activation of the NOTCH pathway and cause resistance to gamma-secretase inhibitors.

FLT3

FLT3 mutations are frequently associated with leukocytosis. The presence of FLT3 mutations in patients with AML implies aggressive disease and is recommended by published guidelines for testing. Testing for FLT3 and NPM1 in AML patients with intermediate-risk cytogenetic abnormalities can classify these patients to favorable, intermediate-I or intermediate-II; depending on the specific combination of findings. In addition, FLT3 mutations have also been identified in patients with other myeloid malignancies, which can possibly play a role in pathogenesis.

GATA1

Patients with Down Syndrome and GATA1 mutations in transient abnormal myeloproliferative disorder are more likely to progress to myeloid leukemias. GATA1 mutations have also been identified in various myeloid disorders. Testing for GATA1 mutations may be useful as a clinical indicator.

GATA2

Patients with GATA2 mutations are more likely to progress from MDS to AML. Testing for GATA2 mutations may be useful as a clinical indicator.

GNAS

Guanine nucleotide-binding protein/alpha-subunit (GNAS) gene is mutated, over-expressed and/or amplified in a number of myeloid disorders and solid tumors. Testing for GNAS mutations can aid in targeted drug therapy decisions.

HRAS

HRAS is highly homologous with KRAS and NRAS; all are members of the most frequently mutated family of oncogenes. RAS mutations are found in a wide variety of solid tumor cancers and myeloid malignancies. Screening for HRAS mutations can be useful in determining sensitivity to tyrosine kinase inhibitors.

IDH1/IDH2

IDH1 or IDH2 mutations are detected in approximately 15-20% of acute myeloid leukemia (AML). Patients with AML and IDH1/IDH2 mutations are likely to have aggressive disease.

IKZF1

IKZF1 mutations are common in acute lymphoblastic leukemias and other myeloid disorders. Patients with these mutations have been associated with poor outcome.

JAK2 V617F

The JAK2 V617F mutation is present in approximately 90% of polycythemia vera (PV) cases and approximately 40% of primary myelofibrosis (PMF) or essential thrombocythemia (ET). Mutation analysis helps differentiate reactive conditions from myeloproliferative neoplasms (MPNs).

JAK2 Exon 12+14

While the majority of polycythemia vera (PV) patients carry the V617F mutation (~90%), most of those who are negative carry one of over 40 additional JAK2 mutations in exons 12-15. Mutation analysis helps differentiate reactive conditions from malignant erythrocytosis.
JAK3 mutations are associated with pathogenesis and poor clinical outcome in patients with leukemias. Testing for JAK3 mutations can provide useful prognostic information.

Somatic mutations in KDM6A have been identified in a number of cancers such as myeloid leukemias. Mutations in KDM6A lead to a shortened nonfunctional lysine-specific demethylase 6A enzyme that can’t function properly as a tumor suppressor, which ultimately contributes to the development of cancer. Testing for KDM6A mutations can be useful in identifying patients who will respond to targeted therapy treatment.

KIT mutations have been reported in AML and testing is recommended by published guidelines particularly for core binding factor leukemias. The presence of the mutation has been used as an independent predictor for poor outcome since it adversely affects survival. Screening for KIT mutations may help identify patients with a more adverse outcome and are likely to benefit from receptor tyrosine kinase inhibitors.

Mutations in the KRAS oncogene are frequently found in human cancers such as AML and other myeloid disorders. KRAS is a component of the tyrosine kinase signaling pathway mediated through ERBB, insulin-like growth factor, and MET receptors, among others. KRAS mutations lead to the constitutive activation of the cell signaling pathway. Testing for KRAS mutations can be useful in determining a patients sensitivity to tyrosine kinase inhibitors.

Partial tandem duplications in the gene MLL are detected in approximately 8% of patients with cytogenetically normal AML. MLL-PTD is a gain of function mutation that has been associated with reduced overall survival in AML. Testing for MLL mutations can provide useful clinical data.

MPL mutations are detected in up to 5% of patients with JAK2-negative myeloproliferative neoplasms. Mutation analysis helps differentiate reactive conditions from MPNs.

MYD88 mutation is the most common genetic abnormality in the activated B-cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL), detected in 40% of cases. Mutations are rare in the germinal center B-cell-like (GCB) subtype, so mutation analysis can be useful to differentiate between the ABC and GCB subtypes. MYD88 mutations have also been detected in patients with myelodysplastic syndromes.

NOTCH1 mutations have been detected in various myeloid disorders such as AML. Testing for NOTCH1 mutations can help identify patients that may show sensitivity towards NOTCH inhibitors.

Mutations in exon 12 of the nucleophosmin (NPM) gene are the genetic lesions that are most specifically and frequently associated with normal karyotype in adult and pediatric AML. The NPM1 mutation can serve as predictor of favorable prognosis in AML with normal karyotype, and as a marker for monitoring of minimal residual disease.

NRAS is highly homologous with KRAS; both are members of the most frequently mutated family of oncogenes. NRAS mutations are frequent in patients with MDS. Testing for NRAS mutations can help identify patients who will be resistant to tyrosine kinase inhibitors.

Platelet-derived growth factor receptor alpha (PDGFRα) gene is a member of the subfamily of type III receptor tyrosine kinases and has been detected in patients with MPN and other myeloid disorders. Testing for PDGFRα mutations in patients with myeloid malignancies may help identify patients that may respond to tyrosine kinase inhibitors.

PHF6 is a tumor suppressor gene. Mutations in PHF6 are involved in the pathogenesis of AML and other hematological diseases. Testing for PHF6 mutations can be useful in providing clinical data that can aid in the development of therapy strategies.

PTEN mutations have been detected in myeloid neoplasms such as MDS. Testing for PTEN mutations can be useful in the prognostic assessment as well as provide information for developing targeted drug therapies against the PI3K/AKT pathway.

Somatic mutations are detected in 34% of juvenile myelomonocytic leukemia (JMML) and 3-4% of AML, ALL, and MDS/CMML. Mutations in JMML patients are associated with worse prognosis.

RAD21 is involved in the cohesin complex and mutations in RAD21 can affect cohesin function, which may lead to myeloid leukemogenesis. Testing for RAD21 mutations may be useful in providing clinical information that may aid in the development of therapy strategies.
RUNX1 mutations are reported in AML, treatment-related MDS, and in blast crisis CML. In AML patients with intermediate-risk cytogenetics, RUNX1 mutations are associated with poor prognosis including shortened overall survival and event-free survival.

Mutation analysis of the SETBP1 gene in conjunction with other genes is useful for confirming diagnosis, predicting clinical behavior, and determining prognosis in myeloid disorders. SETBP1 mutations have been reported in approximately 24% of atypical chronic myeloid leukemia (aCML), up to 17% of secondary acute myeloid leukemia (sAML), 15% of chronic myelomonocytic leukemia (CMMML), and up to 5% of myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukemia (JMML) cases. Mutations are associated with reduced survival and leukemic transformation.

SETBP1 mutations occur in 10-15% of CLL patients and serve as independent predictors of shortened time to treatment and poorer overall survival in CLL. Mutations are also detected in approximately 28% of MDS and 19% of myelodysplastic/myeloproliferative neoplasms. In MDS/MPN, most mutations were found in the myelodysplastic syndrome refractory anemia with ring sideroblasts (RARS).

SMC1A mutations occur in about 2% of AML patients. SMC1A is involved in the cohesin complex and mutations in SMC1A can affect cohesin function, which may lead to myeloid leukemogenesis. Testing for SMC1A mutations may be useful in providing clinical information that may aid in the development of therapy strategies.

SMC3 mutations occur in about 2% of AML patients. SMC3 is involved in the cohesin complex and mutations in SMC3 can affect cohesin function, which may lead to myeloid leukemogenesis. Testing for SMC3 mutations may be useful in providing clinical information that may aid in the development of therapy strategies.

SRSF2 is a component of the RNA splicing complex, the spliceosome. Mutations are frequent in myeloid disorders including 12% MDS, 44% CMML, and 17% primary myelofibrosis (PMF), and are associated with poorer prognosis in these patients. Testing is useful for establishing diagnosis by distinguishing myeloid neoplasms from reactive processes and for assessing prognosis.

STAG2 mutations occur in about 3% of AML patients and have been shown to occur in other myeloid disorders as well. STAG2 is involved in the cohesin complex and mutations in STAG2 can affect cohesin function, which may lead to myeloid leukemogenesis.

TET2 functions in DNA methylation and plays a role in epigenetic regulation of gene expression. Mutations are detected in myeloid cancers including 19% of MDS, 12% of MPN, 16% of AML, and 22% of CMML, and are associated with poor overall survival in intermediate-risk AML.

TP53 mutations are detected in a variety of cancers and are generally associated with a poor prognosis. Testing for TP53 mutations can be useful in the prognostic assessment of patients with myeloid disorders.

U2AF1 is a component of the RNA splicing complex, the spliceosome. Mutations are detected in myeloid disorders including 6% MDS, 4% AML, and 11% CMML. In MDS, mutations indicate risk for reduced overall survival and shorter time to AML transformation. Testing is useful for establishing diagnosis by distinguishing myeloid neoplasms from reactive processes and for assessing prognosis.

WT1 mutations occur in approximately 12% of acute myeloid leukemia (AML) cases and are associated with poor outcome in cytogenetically normal AML.

ZRSR2 is a component of the RNA splicing complex, the spliceosome. Mutations are detected in 8% of MDS and 4% of CMML. Mutations in MDS have been associated with shorter overall survival and an increased rate of transformation to AML. Testing is useful for establishing diagnosis by distinguishing myeloid neoplasms from a reactive process and for assessing prognosis.