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Preauthorization is required for testing for Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Myelodysplastic Syndrome and Myeloproliferative Neoplasms.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

DESCRIPTION

In the treatment of Philadelphia chromosome (Ph)-positive leukemias various nucleic acid-based laboratory methods may be used to detect the BCR-ABL1 fusion gene for confirmation of the diagnosis; for quantifying mRNA BCR-ABL1 transcripts during and after treatment to monitor disease progression or remission; and for identification of ABL kinase domain point mutations related to drug resistance when there is inadequate response or loss of response to tyrosine kinase inhibitors (TKIs), or disease progression.

Treatment of acute myeloid leukemia (AML) is based on risk stratification, mainly patient age and tumor cytogenetics. In patients with cytogenetically normal AML, the identification of variants in several genes, including FLT3, NPM1, and CEBPA, has been proposed to allow for further segregation in the management of this heterogeneous disease.

Acute Myelomonocytic leukemia is an acute leukemia with increased immature granulocytic and monocytic cells.

Acute promyelocytic leukemia (APML, APL) is the M3 subtype of acute myelogenous leukemia (AML), a cancer of the white blood cells. APL is due to a translocation between chromosomes 15 and 17, t(15;17).

Mutations in the gene encoding Janus kinase 2 (JAK2) protein and in the myeloproliferative leukemia virus oncogene (MPL) encoding the thrombopoietin receptor have been associated with myeloproliferative neoplasms and with acute lymphoblastic leukemia (ALL) in Down syndrome patients.

Approximately 80% of individuals with Chronic Lymphocytic Leukemia exhibit chromosomal aberrations including in genes TP53 and ATM which have been proposed as instructive in management of the disease. A strong relationship has been observed between specific genetic mutations and the clinical course of the disease.

Hairy-cell leukemia (HCL), a rare leukemia, has been associated with the V600E mutation of the BRAF gene.

Classification and treatment of lymphoma may be guided by the identification of mutations which have been associated with specific lymphomas.

In multiple myeloma, clinical outcomes have been variable among patients in the same risk category who received similar therapy. Thus, more specific methods have been sought to more finely classify multiple myeloma, including microarray-based gene expression profile (GEP) analysis that shows the underlying activity of cellular biological pathways that control, for example, cell division or proliferation, apoptosis, metabolism, or

other signaling pathways. Microarray-based GEP analysis has been proposed as a means to risk-stratify patients with multiple myeloma to guide treatment decisions.

Somatic (acquired) genetic variants in JAK2, MPL, and CALR genes have been implicated as the underlying molecular genetic drivers for the pathogenesis of myeloproliferative neoplasms (MPNs). This protocol addresses the use of genetic testing of JAK2 and CALR genes for the diagnosis, prognosis, and treatment selection in patients with MPNs.

POLICY

ACUTE LYMPHOBLASTIC LEUKEMIA

BCR/ABL1 testing for messenger RNA transcript levels and size (quantitative and qualitative) prior to initiation of treatment and during therapy may be considered **medically necessary** for monitoring of Philadelphia chromosome-positive acute lymphocytic leukemia.

If BCR/ABL1 testing as above is negative, then testing for gene fusions and variants associated with Philadelphia chromosome-like acute lymphoblastic leukemia* (see Policy Guidelines) is considered **medically necessary**.

Genetic testing in acute lymphoblastic leukemia may be **medically necessary** for:

- MLL translocations and IKZF1;
- Karyotyping of G-banded metaphase chromosomes;
- KMT2A/MLL translocations.

ACUTE MYELOID LEUKEMIA

The following may be considered **medically necessary** in Acute Myeloid Leukemia (AML) in patients with normal karyotype:

- Genetic testing for FLT3 internal tandem duplication (FLT3/ITD).
- NPM1 variant testing.

Genetic testing of the following genes may be considered **medically necessary** if the leukemia has a normal karyotype and FLT3 and NPM1 gene sequences contain no pathogenic variants:

- DNMT3A
- IDH1/2
- c-KIT
- CEBPA
- AML/ETO

The following genetic testing in AML is considered **investigational**:

- Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) variants;
- Genetic testing for FLT3, CEBPA or NPM1 variants to detect minimal residual disease;
- Genetic testing for ASXL1 and RUNX1 variants.

ACUTE MYELOMONOCYTIC LEUKEMIA

Genetic testing in acute myelomonocytic leukemia for (AML/ETO t(8;21) translocation) may be considered **medically necessary**.

ACUTE PROMYELOCYTIC LEUKEMIA

Genetic testing for acute promyelocytic leukemia (APML) may be considered **medically necessary**:

- if a diagnosis of APML is suspected but cannot be established by morphological, FISH, or cytogenetic analysis
- PML/RAR alpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis.

CHRONIC MYELOGENOUS LEUKEMIA

BCR/ABL1 qualitative testing may be considered **medically necessary** for diagnosis of chronic myeloid leukemia.

BCR/ABL1 testing for messenger RNA transcript levels and length (quantitative and qualitative) may be considered **medically necessary** for monitoring of chronic myeloid leukemia treatment response and remission.

Evaluation of ABL kinase domain point variants to evaluate patients for tyrosine kinase inhibitor resistance may be considered **medically necessary** if there is inadequate initial response to treatment or any sign of loss of response; and/or when there is progression of the disease to the accelerated or blast phase.

ABL kinase domain variant testing may be considered **medically necessary** to identify T315I variant or as a panel (which includes T315I) of the most common and clinically important variants.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Chromosome deletion analysis may be considered **medically necessary** to determine prognosis by:

- Multi-gene FISH analysis to detect deletion of the LSI TP53, LSI ATM, and LSI D13S319 probe targets and gain of the D12Z3 sequence from untreated patients with B-cell CLL to dichotomize CLL (the 13q-, +12, or normal genotype group versus the 11q- or 17p-group).
- Immunoglobulin heavy chain variable region (IGHV or IgVH) gene variant status.

Genetic testing for chronic lymphocytic leukemia/small lymphocytic lymphoma may be considered **medically necessary** for:

- Flow Cytometry of blood, bone marrow or lymph node for B cell clonality, immunophenotyping, and ZAP-70 analysis.
- TP53 gene sequencing.

HAIRY CELL LEUKEMIA

Genetic testing for BRAF V600E may be considered **medically necessary** in order to confirm the diagnosis of HCL.

LYMPHOMA

Cytogenetic testing may be considered **medically necessary** in the analysis of lymphoma and is the method of choice to detect the following abnormalities that guide classification and treatment:

- T-cell clonality analysis, IGHV analysis, or targeted FISH analysis
- Follicular lymphoma/t(14;18) IgH/BCL2
- Mantle cell lymphoma/t(11;14) IgH/CCND1
- Marginal zone lymphoma/t(11;18) API/MALT1

- Burkitt lymphoma/t(8;14) IgH/CMYC most commonly or t(2;8) or t(8;22)
- Anaplastic large cell lymphoma/t(2;5) NPM/ALK

MULTIPLE MYELOMA

The following genetic testing for Multiple Myeloma may be considered **medically necessary**:

- Metaphase cytogenetics on bone marrow;
- Plasma cell FISH for t(4;14), t(14;16), 17p13 deletions, and chromosome 1 amplification;

Microarray-based gene expression profile testing is considered **investigational** in Multiple Myeloma.

MYELOYDYSPLASTIC SYNDROME

The following genetic testing in Myelodysplastic Syndrome may be considered **medically necessary**:

- Bone marrow cytogenetic by standard karyotyping;
- CMML for 5q31-33 translocation.

Analysis of TET2 may be **medically necessary** to guide the use of hypomethylating agents.

Analysis of TP53, ASXL1, ETV6, RUNX1, and EZH2 may be considered **medically necessary** to determine prognosis and need for bone marrow transplant.

Broad multi-gene panel testing in Myelodysplastic Syndrome is considered **investigational**.

MYELOFIBROSIS, ESSENTIAL THROMBOCYTHEMIA AND POLYCYTHEMIA VERA

Genetic testing may be **medically necessary** in patients with suspected myelofibrosis, or essential thrombocythemia, when the diagnosis is unclear after bone marrow morphologic and cytogenetic analysis, to establish a diagnosis in the following situations:

- If BCR-ABL testing is negative it may define a myeloproliferative disease with a distinct leukemia subtype.
- Testing for the Janus Kinase 2 (JAK2; JAK2V617F) gene variant for the initial diagnostic assessment of adults presenting with clinical, laboratory, or pathological findings suggesting classic forms of polycythemia vera (PV).
- Testing for the Janus Kinase 2 (JAK2; JAK2V617F) gene variant for the initial diagnostic assessment of BCR-ABL negative adults presenting with clinical, laboratory, or pathological findings suggesting classic forms of essential thrombocythemia (ET) or primary myelofibrosis (PMF).
- MPL gene variants in exon 10.

Testing for the Janus Kinase 2 (JAK2; JAK2V617F) gene variant is **investigational** for:

- Diagnostic assessment of myeloproliferative disorders (MPD)/myeloproliferative neoplasms (MPN) in children.
- The Quantitative assessment of JAK2V617F allele burden subsequent to qualitative detection of JAK2V617F.

POLICY GUIDELINES

*Ph-like phenotype includes gene fusions involving ABL1/2, CRLF2, CSF1R, EPOR, JAK2 or PDGFRB or gene variants involving FLT3, IL7R, SH2B3, JAK 1/2/3.

MEDICARE ADVANTAGE

In addition to or in place of the above policy statements, testing for the following genes may be considered **medically necessary** for Medicare Advantage members when the stated criteria is met:

- Testing for ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) in patients with acute lymphoblastic leukemia (ALL) and chronic myeloid leukemia (CML) to guide therapeutic decision making;
- Testing for BCR/ABL in the evaluation of individuals with chronic myelogenous leukemia or BCR-ABL positive acute lymphoblastic leukemia to evaluate treated individuals who manifest suboptimal response to initial tyrosine kinase inhibitor therapy or loss of response to tyrosine kinase inhibitor therapy;
- Testing for CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) in patients with acute myelogenous leukemia (AML) to guide therapeutic decision making;
- Testing for FLT3 in acute myeloid leukemia (AML) to guide therapeutic decision making;
- Testing for IGH@ (Immunoglobulin heavy chain locus) for acute myeloid leukemia (AML) and lymphoma, B-cell to guide therapeutic decision making;
- Testing for JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder), exon 12 sequence and exon 13 sequence in the initial work-up of BCR-ABL and JAK2 (V617F variant) negative adults with clinical, laboratory, or pathological findings suggesting polycythemia vera;
- Testing for KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) in patients who have acute myeloid leukemia (AML) to guide therapeutic decision making;
- Testing for NPM1 (nucleophosmin) in patients with acute myeloid leukemia (AML) to guide therapeutic decision making;
- Testing for PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) in PDGFRA-associated chronic eosinophilic leukemia to guide therapeutic decision making;
- Testing for PML/RARALPHA, (t(15;17)) in patients with promyelocytic leukemia;
- Testing for TRB@ (T CELL antigen receptor, BETA) for individuals with acute lymphoid leukemia and T cell prolymphocytic leukemia to guide therapeutic decision-making;
- Testing for TRG@ (T CELL antigen receptor, GAMMA) for individuals with acute lymphoid leukemia and T cell prolymphocytic leukemia to guide therapeutic decision-making;
- The IGH@ (Immunoglobulin heavy chain locus) for acute myeloid LEUKEMIA (AML) and lymphoma, B-cell to guide therapeutic decision making;
- Testing for MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) common variants (e.g., W515A, W515K, W515L, W515R) and/or exon 10 sequence in the initial work-up of BCR-ABL negative, JAK2 negative, and CALR negative adults with clinical, laboratory, or pathological findings suggesting essential thrombocythemia (ET), or primary myelofibrosis (PMF);
- Testing for JAK2 (Janus kinase 2) exon 12 sequence and exon 13 sequence in the initial work-up of BCR-ABL and JAK2 (V617F variant) negative adults with clinical, laboratory, or pathological findings suggesting polycythemia vera;
- Testing for TP53 (tumor protein 53) targeted sequence analysis of 2-5 exons and/or full gene sequence or targeted sequence analysis of > 5 exons in individuals who have Acute Myelogenous Leukemia or Myeloplasic Disease to guide therapeutic decision-making.

A targeted genomic sequential analysis panel, hematolymphoid neoplasm, DNA analysis, 5-50 genes (see policy guidelines**) will be considered **medically necessary** in the evaluation of blood or bone marrow samples in the following clinical circumstances:

AML

- Newly diagnosed patients with acute myelogenous leukemia (AML) who are undergoing induction therapy, and who are suitable candidates for post-induction transplantation or consolidation therapy at the time of testing, and meet one of the following cytogenetic criteria:
 - normal karyotype
 - core binding factor
- Previously diagnosed patients with AML, who have not responded to induction chemotherapy, or who have progressed following induction. The patient must be a candidate for transplantation at the time of the testing.
- Patients with AML, who have responded to treatment, either chemotherapy or transplantation, with evidence of relapse.

Myelodysplastic Syndromes (MDS)

- Patients with clinical signs or symptoms of myelodysplastic syndromes (MDS) or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN), in whom clinical, laboratory, and pathologic assessment are non-diagnostic.
- Newly diagnosed MDS or MDS/MPN patients either
 - stratified by the IPSS or IPSS-R as intermediate risk, or
 - in MDS with ringed sideroblasts/RARS.

Repeat Genomic Sequential Analysis Panel testing is **not medically necessary** in MDS after initial diagnosis and risk stratification.

Myeloproliferative Neoplasms (MPN)

- Diagnosis: Clinical signs or symptoms of myeloproliferative neoplasm (MPN) or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN) when
 - clinical, laboratory, and pathologic assessment are nondiagnostic; and
 - CML excluded (BCR-ABL1 negative)
- Risk Stratification: Newly diagnosed PMF not already classified as high-risk by Dynamic International Prognostic Scoring System (DIPSS) Plus
- Monitoring: Higher-risk MF (INT-1, INT-2, High-Risk) with progression on therapy.

BACKGROUND

ACUTE LYMPHOBLASTIC LEUKEMIA AND CHRONIC MYELOGENOUS LEUKEMIA

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. ALL is the most common childhood tumor, and represents 75% to 80% of acute leukemias in children. ALL represents only 20% of all leukemias in the adult population. The

median age at diagnosis is 14 years; 60% of patients are diagnosed at before 20 years of age. Current survival rates for patients with ALL have improved dramatically over the past, primarily in children, largely due to a better understanding of the molecular genetics of the disease, incorporation of risk-adapted therapy, and new targeted agents. Current treatment regimens have a cure rate among children of about 80%. Long-term prognosis among adults is poor, with cure rates of 30% to 40%. Prognosis variation is explained, in part, by different subtypes among age groups, including the BCR-ABL fusion gene, which has a poor prognosis and is much less common in childhood ALL.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal disorder of myeloid hematopoietic cells, accounting for 15% of adult leukemias. The disease occurs in chronic, accelerated, and blast phases, but is most often diagnosed in the chronic phase. If left untreated, chronic phase disease will progress within three to five years to the accelerated phase, characterized by any of several specific criteria such as 10% to 19% blasts in blood or bone marrow, basophils comprising 20% or more of the white blood cell count, or very high or very low platelet counts.¹ From the accelerated phase, the disease progresses into the final phase of blast crisis, in which the disease behaves like an acute leukemia, with rapid progression and short survival. Blast crisis is diagnosed by the presence of either more than 20% myeloblasts or lymphoblasts in the blood or bone marrow, large clusters of blasts in the bone marrow on biopsy, or development of a solid focus of leukemia outside the bone marrow.

Extensive clinical data have led to the development of congruent recommendations and guidelines developed both in North America and in Europe on the use of various types of molecular tests relevant to the diagnosis and management of CML. These tests are useful in the accelerated and blast phases of this malignancy.

Disease Genetics

Philadelphia (Ph) chromosome–positive leukemias are characterized by the expression of the oncogenic fusion protein product Bcr-Abl1, resulting from a reciprocal translocation between chromosomes 9 and 22. This abnormal fusion product characterizes CML. In ALL, with increasing age, the frequency of genetic alterations associated with favorable outcomes declines and alterations associated with poor outcomes, such as BCR-ABL1, are more common.² In ALL, the Ph chromosome is found in 3% of children and 25% to 30% of adults. Depending on the exact location of the fusion, the molecular weight of the protein can range from 185 to 210 kDa. Two clinically important variants are p190 and p210; p190 is associated with ALL, while p210 is most often seen in CML. The product of BCR-ABL1 is also a functional tyrosine kinase; the kinase domain (KD) of the Bcr-Abl protein is the same as the KD of the normal Abl protein. However, the abnormal Bcr-Abl protein is resistant to normal regulation. Instead, the enzyme is constitutively activated and drives unchecked cellular signal transduction resulting in excess cellular proliferation.

Diagnosis

Although CML is diagnosed primarily by clinical and cytogenetic methods, qualitative molecular testing is needed to confirm the presence of the BCR-ABL1 fusion gene, particularly if the Ph chromosome was not found, and to identify the type of fusion gene, because this information is necessary for subsequent quantitative testing of fusion gene messenger RNA transcripts. If the fusion gene is not confirmed, then the diagnosis of CML is called into question.

Determining the qualitative presence of the BCR-ABL1 fusion gene is not necessary to establish a diagnosis of ALL.

Treatment and Response and Minimal Residual Disease

Before initiation of therapy for CML or ALL, quantification of the BCR-ABL transcript is necessary to establish baseline levels for subsequent quantitative monitoring of response during treatment. Quantitative determination of BCR-ABL1 transcript levels during treatment allows for a very sensitive determination of the degree of

patient response to treatment. Evaluation of trial samples has consistently shown the degree of molecular response correlates with risk of progression. Also, the degree of molecular response at early time points predicts improved rates of progression-free and event-free survival. Conversely, rising BCR-ABL1 transcript levels predict treatment failure and the need to consider a change in management. Quantitative polymerase chain reaction-based methods and international standards for reporting have been recommended and adopted for treatment monitoring.

Imatinib (Gleevec®; Novartis, Basel, Switzerland), a tyrosine kinase inhibitor (TKI), was originally developed to specifically target and inactivate the Abl tyrosine kinase portion of the Bcr-Abl1 fusion protein to treat patients with CML. In patients with chronic phase CML, early imatinib study data indicated a high response rate to imatinib compared with standard therapy, and long-term follow-up has shown that continuous treatment of chronic phase CML results in “durable responses in [a] large proportion of the patients with a decreasing rate of relapse.”³ As a result, imatinib became the primary therapy for most patients with newly diagnosed chronic phase CML.

With the established poor prognosis of Ph-positive ALL, standard ALL chemotherapy alone has long been recognized as a suboptimal therapeutic option, with 60% to 80% of patients achieving a complete response, significantly lower than that achieved in Ph-negative ALL.¹²⁷ The inclusion of TKIs to frontline induction chemotherapy has improved complete response rates, exceeding 90%.¹²⁷

Treatment response is evaluated initially by hematologic response (normalization of peripheral blood counts), then by cytogenetic response (percentage of cells with Ph-positive metaphase chromosomes in a bone marrow aspirate). Complete cytogenetic response (0% Ph-positive metaphases) is expected by six to 12 months after initial treatment with the TKI imatinib.³ It is well established that most “good responders” who are considered to be in morphologic remission but relapse may still have considerable levels of leukemia cells, referred to as minimal residual disease (MRD). Among children with ALL who achieve a complete response by morphologic evaluation after induction therapy, 25% to 50% may still have detectable MRD based on sensitive assays. Current methods used for MRD detection include flow cytometry (sensitivity of MRD detection, 0.01%), or polymerase chain reaction-based analyses (Ig and Tcell receptor gene rearrangements or analysis of BCR-ABL transcripts), which are the most sensitive methods of monitoring treatment response (sensitivity, 0.001%).⁵ Most ALL patients can be tested with Ig and T-cell receptor gene arrangement analysis, whereas only Ph-positive patients can be tested with polymerase chain reaction analysis of BCR-ABL transcripts.

Treatment Resistance

Imatinib treatment does not usually completely eradicate malignant cells. Not uncommonly, malignant clones resistant to imatinib may be acquired or selected during treatment (secondary resistance), resulting in disease relapse. Also, a small fraction of chronic phase malignancies that express the fusion gene do not respond to treatment, indicating intrinsic or primary resistance. The molecular basis for resistance is explained in the following section. When the initial response to treatment is inadequate or there is a loss of response, resistance variant analysis is recommended to support a diagnosis of resistance (based on hematologic or cytogenetic relapse) and to guide the choice of alternative doses or treatments.^{3, 6}

Structural studies of the Abl-imatinib complex have resulted in the design of second-generation Abl inhibitors, including dasatinib (Sprycel®; Bristol-Myers Squibb, New York, NY) and nilotinib (Tasigna®; Novartis, Basel, Switzerland), which were initially approved by the U.S. Food and Drug Administration for treatment of patients resistant or intolerant to prior imatinib therapy. Trials of both agents in newly diagnosed chronic phase patients have shown that both are superior to imatinib for all outcomes measured after one year of treatment, including complete cytogenetic response (primary outcome), time to remission, and rates of progression to accelerated phase or blast crisis.^{4, 7} Although initial follow-up was short, early and sustained complete cytogenetic response was considered a validated marker for survival in CML. The U.S. Food and Drug Administration has approved third-generation TKIs, ponatinib and bosutinib. Ponatinib is indicated for the treatment of patients with T315I-

positive CML or Ph-positive ALL, or for whom no other TKI inhibitor is indicated. Bosutinib is indicated for Ph-positive CML with resistance or intolerance to prior therapy. For patients with increasing levels of BCR-ABL1 transcripts, there is no strong evidence to recommend specific treatment; possibilities include continuation of therapy with dasatinib or nilotinib at the same dose, or imatinib dose escalation from 400 to 800 mg daily, as tolerated, or therapy change to an alternative second-generation TKI.³

Molecular Resistance

Molecular resistance is most often explained as genomic instability associated with the creation of the abnormal BCR-ABL1 gene, usually resulting in point variants within the ABL1 gene KD that affects protein kinase-TKI binding. BCR-ABL1 single nucleotide variants (SNVs) account for 30% to 50% of secondary resistance.⁶ (Note that new BCR-ABL SNVs also occur in 80% to 90% of cases of ALL in relapse after TKI treatment and in CML blast transformation.) At least 58 different SNVs have been identified in CML patients. The degree of resistance depends on the position of the variant within the KD (i.e., active site) of the protein. Some variants are associated with moderate resistance and are responsive to higher doses of TKIs, while other variants may not be clinically significant. Two variants, designated T315I and E255K (nomenclature indicates the amino acid change and position within the protein), are consistently associated with resistance.

The presence of ABL SNVs is associated with treatment failure. A large number of variants have been detected, but extensive analysis of trial data with low-sensitivity variant detection methods has identified a small number of variants consistently associated with treatment failure with specific TKIs; guidelines recommend testing for information on these specific variants to aid in subsequent treatment decisions. The recommended method is sequencing with or without denaturing high-performance liquid chromatography screening to reduce the number of samples to be sequenced. Targeted methods that detect the variants of interest for management decisions are also acceptable if designed for low sensitivity. High-sensitivity assays are not recommended.

Unlike imatinib, fewer variants are associated with resistance to dasatinib or nilotinib.^{10, 130} For example, Guilhot et al (2007)¹³¹ and Cortes et al (2007)¹³² studied the use of dasatinib in imatinib-resistant CML patients in the accelerated phase and in blast crisis, respectively, and found that dasatinib response rates did not vary by the presence or absence of baseline tumor cell BCR-ABL1 variants. However, neither dasatinib nor nilotinib is effective against resistant clones with the T315I variant.^{7, 8} Other treatment strategies are in development for patients with drug resistance.

Other acquired cytogenetic abnormalities such as BCR-ABL gene amplification and protein overexpression have also been reported.¹² Resistance unrelated to kinase activity may result from additional oncogenic activation or loss of tumor suppressor function, and may be accompanied by additional karyotypic changes.⁶ Resistance in ALL to TKIs is less well studied. In patients with ALL receiving a TKI, a rise in the BCR-ABL level while in hematologic complete response or clinical relapse warrants variant analysis.

ACUTE MYELOID LEUKEMIA

AML is a group of diverse hematologic malignancies characterized by the clonal expansion of myeloid blasts in the bone marrow, blood, and/or other tissues. It is the most common type of leukemia in adults, and is generally associated with a poor prognosis. The American Cancer Society has estimated there will be 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017.¹²³

Diagnosis and Prognosis of AML

The most recent World Health Organization (WHO) classification (2016) reflects the increasing number of acute leukemias that can be categorized based on underlying cytogenetic abnormalities (i.e., at the level of the chromosome including chromosomal translocations or deletions) or molecular genetic abnormalities (i.e., at the level of the function of individual genes, including gene variants). These cytogenetic and molecular changes form distinct clinico-pathologic-genetic entities with diagnostic, prognostic, and therapeutic implications.³⁰ Conventional cytogenetic analysis (karyotyping) is considered to be a mandatory component in the diagnostic evalua-

tion of a patient with suspected acute leukemia, because the cytogenetic profile of the tumor is considered to be the most powerful predictor of prognosis in AML and is used to guide the current risk-adapted treatment strategies.

Molecular variants have been analyzed to subdivide AML with normal cytogenetics into prognostic subsets. In AML, three of the most frequent molecular changes with prognostic impact are variants of CEBPA, encoding a transcription factor, variants of the FLT3 gene, encoding a receptor of tyrosine kinase involved in hematopoiesis, and variant of the NPM1 gene, encoding a shuttle protein within the nucleolus. "AML with mutated NPM1 or CEBPA" were included as categories in the 2016 World Health Organization classification of acute leukemias. AML with FLT3 variants is not considered a distinct entity in the 2016 classification. The 2008 World Health Organization classification recommended determining the presence of FLT3 variants because of the prognostic significance.¹²⁴

Recent reviews (2012-2014) have highlighted the evolving classification of AML into distinct molecular subtypes.¹²⁵⁻¹²⁷

Treatment

AML has a highly heterogeneous clinical course, and treatment generally depends on the different risk stratification categories.¹²⁵ Depending on the risk-stratification category, treatment modalities may include intensive remission induction chemotherapy, hypomethylating agents, clinical trials with innovative compounds, palliative cytotoxic treatment, or supportive care only. For patients who achieve complete remission (CR) after induction treatment, possible postremission treatment options include intensive consolidation therapy, maintenance therapy, or autologous or allogeneic hematopoietic cell transplant.¹²⁵

FLT3 Variants

FMS-like tyrosine kinase (FLT3) plays a critical role in normal hematopoiesis and cellular growth in hematopoietic stem and progenitor cells. Mutations in FLT3 are one of the most frequently encountered variants in AML, and approximately 30% of AML patients harbor some form of FLT3 variant.³² FLT3 mutations are divided into two categories: (1) internal tandem duplications (FLT3-ITD) variants, which occur in or near the juxtamembrane domain of the receptor, and (2) point variants resulting in single amino acid substitutions within the activation loop of the tyrosine kinase domain (FLT3-TKD).

FLT3-ITD variants are much more common than FLT3-TKD variants, occurring in 25% of newly diagnosed adult cases of AML, versus FLT3-TKD variants, occurring in about 7% of patients. FLT3-ITD variants are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age and with normal- or intermediate-risk cytogenetics, and is associated with an increased risk of relapse and inferior OS.³²⁻³⁴ Patients with FLT3-ITD mutations have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild-type (WT; i.e., nonmutated) FLT3. Once FLT3-ITD AML relapses, the disease is rapidly fatal.

Because of the high risk of relapse, hematopoietic cell transplantations as consolidation therapy of a first remission for an FLT3-ITD AML patient is often considered. However, this treatment must be weighed against the treatment-related mortality associated with a transplant.³²

The prognostic impact of FLT3-TKD variants is less certain, and has only been studied in small numbers of patients.^{32, 41} FLT3 tyrosine kinase inhibitors are under active clinical investigation.

NPM1 Variants

The most common molecular aberration in AML is a mutation of NPM1, which is found in 46% to 64% of cytogenetically normal AML (CN-AML) and 9% to 18% of cytogenetically abnormal AML.¹²⁵ Up to 50% of AML with mutated NPM1 also carry an FLT3-ITD. Mutated NPM1 confers an independent favorable prognosis for patients with CN-AML and either the presence or absence of an FLT3-ITD. Retrospective studies of banked clinical samples suggest that an NPM1 variant may mitigate the negative prognostic effect of an FLT3-ITD variant, but possi-

bly only if the FLT3-ITD-to-WT allelic ratio is low.³² The prognostic impact in patients with an abnormal karyotype is unclear.¹²⁵

CEBPA Variants

CEBPA (CCAAT/enhancer binding protein) is a transcription-factor gene that plays a role in cell cycle regulation and cell differentiation. Variants to CEBPA are found in approximately 15% of AML patients with a normal karyotype.⁴²⁻⁴⁴ CEBPA mutations can be either biallelic (double variants) or monoallelic. Monoallelic mutations are prognostically similar to CEBPA WT and do not confer a favorable prognosis in CN-AML; double variants of CEBPA have shown a better prognosis with higher rates of CR and OS after standard induction chemotherapy.^{45, 133}

ACUTE MYELOMONOCYTIC LEUKEMIA

Acute myelomonocytic leukemia one of the more common types of acute myelogenous leukemia, characterized by both malignant monocytes and myeloblasts. A characteristic chromosomal abnormality observed in AML-M4 is inv (16). Treatment includes intensive multidrug chemotherapy and in selected cases allogeneic bone marrow transplantation. Outcome of AML is poor with an overall survival of 35-60%.

ACUTE PROMYELOCYTIC LEUKEMIA

APL is a form of AML. In APL, there is an abnormal accumulation of promyelocytes and a deficiency of mature red blood cells in the myeloid line of cells. This disease occurs in approximately one in 250,000 people in the United States and accounts for about 10% of AML diagnosis. APL usually occurs in middle-aged adults and responds favorably to treatments including retinoids, chemotherapy and, most recently, arsenicals.

A somatic mutation may occur as a translocation between chromosomes 15 and 17, t(15;17), fusing part of the PML gene with part of the RARA gene. The protein produced from this fused gene is known as PML-RAR α and produces a different effect, interfering with the normal function of both than the PML and the RAR α proteins. As a result, white blood cells (WBCs) fail to mature appropriately beyond the promyelocyte stage, growing and dividing too rapidly so that they accumulate excessively in the bone marrow and prevent normal WBCs from developing. The PML-RARA gene fusion accounts for up to 98 percent of cases of APL. Translocations involving the RARA gene and other genes have been identified in a few cases of APL.

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the Western world, accounting for approximately 30% of all leukemia diagnosis in the United States, with an incidence of 4.7 cases per 100,000. It has a tremendously variable clinical course so that survival ranges from months to years. The median age at diagnosis of CLL is approximately 70 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well differentiated morphology. In CLL, these cells accumulate in the blood, bone marrow, lymph nodes, and spleen; in SLL they are generally confined to lymph nodes. The Revised European-American/World Health Organization Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

CLL and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent, but can undergo transformation to a more aggressive form of the disease (e.g., Richter transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as a poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and treatment outcomes are comparable for both diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses, with median survivals of six to 10 years; however, the median survival of high-risk CLL or SLL may only be two years. Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease.

HAIRY CELL LEUKEMIA

Hairy Cell Leukemia (HCL) is classified as a Mature B-Cell Neoplasm, this rare disease is so named for the appearance of B-lymphocytes which have hair like projections when viewed under a microscope. Hairy cell leukemia is a chronic disease with no generally accepted staging system. It accounts for approximately 2% of leukemia diagnosis annually in the United States, about 600-800 cases. Typically women are less likely to be affected than men, and middle aged or older adults are most at risk.

Remission is often possible and most likely longstanding. Although relapse is likely remission may be achievable more than once with survival frequently for 10 years or longer after diagnosis. The etiology of HCL is unknown, although it has been recognized that BRAF V600E mutation is present in most individuals with this disease. Vemurafenib is a drug which targets the effects of BRAF mutations and has been reported to promote a positive response in HCL, including for those with relapsed or refractory disease.

LYMPHOMAS

In general, non-hodgkin's lymphoma can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages.⁹² Early stage indolent NHL (stage 1 or 2) may be effectively treated with radiation alone.⁹⁰ Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages.⁹⁰ These patients can often be retreated if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma,⁹³ and median survival with conventional chemotherapy is one year or less.

Follicular Lymphoma (FL) is the most common indolent NHL (70%-80% of cases), and often the terms indolent lymphoma and FL are used synonymously. Also included in the indolent NHL are SLL/CLL, lymphoplasmacytic lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.

Aggressive NHL has a shorter natural history; however, 30% to 60% of these patients can be cured with intensive combination chemotherapy regimens.⁹⁰ Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt lymphoma.

Mantle Cell Lymphoma (MCL) comprises approximately 65% to 68% of NHL and has been recognized within the past 15 years as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed in 1992 by Banks et al.⁹² MCL shows a strong predilection for elderly men, and most cases (70%) present with disseminated (stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately two to four years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs, often within 12 to 18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

Most peripheral t-cell lymphomas (PTCLs) are aggressive and fall into the category of PTCL, unspecified (PTCL-u) or PTCL-NOS, angioimmunoblastic or anaplastic large cell which, combined make up approximately 60% to 70% of T cell lymphomas. PTCLs are less responsive to standard chemotherapy than diffuse large B-cell lymphomas and carry a worse prognosis than aggressive B cell counterparts. Survival rates at five years with standard chemotherapy regimens range from 20% to 35%.

MULTIPLE MYELOMA

Multiple myeloma is a malignant plasma-cell dyscrasia characterized by clonal proliferation of plasma cells derived from B cells in the bone marrow.⁹⁹ It accounts for about one in every 100 cancers and 13% of hematologic cancers. The annual age-adjusted incidence is about six cases per 100,000 persons, with median age at diagnosis of about 70 years. Before the advent of current treatment protocols, most patients with multiple myeloma succumbed to their disease within five to 10 years; in the prechemotherapy era, median survival was less than one year. Among patients who present at an age younger than 60 years, 10-year overall survival with current treatment protocols now may exceed 30%.⁹⁹

Criteria for the diagnosis, staging, and response assessment of multiple myeloma have been reported by the International Myeloma Working Group and are in widespread use.^{94,102,104} The decision to treat is based on criteria set forth in the diagnosis of multiple myeloma, which includes calcium elevation; renal insufficiency; anemia; and bone disease (i.e., CRAB). Patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering myeloma do not require therapy, irrespective of any associated risk factors, except on specifically targeted protocols.

Asymptomatic (smoldering) multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS) currently require only ongoing clinical observation, because early treatment with conventional chemotherapy has shown no benefit. However, for symptomatic patients diagnosed with multiple myeloma, prompt induction therapy is indicated. Despite achievement of complete remission and apparent eradication of disease, the clinical response is transitory in all cases, and multiple myeloma is considered incurable with current approaches.

MYELOYDYSPLASTIC SYNDROMES/MYELOPROLIFERATIVE NEOPLASMS

Myelodysplastic syndromes (MDS) can occur as a primary (idiopathic) disease or can be secondary to cytotoxic therapy, ionizing radiation, or other environmental insult. Chromosomal abnormalities are seen in 40% to 60% of patients, frequently involving deletions of chromosome 5 or 7, or an extra chromosome as in trisomy 8. Most MDS diagnoses occur in individuals older than age 55 to 60 years, with an age adjusted incidence of approximately 62% among individuals older than age 70 years. Patients either succumb to disease progression to acute myeloid leukemia (AML) or to complications of pancytopenias. Patients with higher blast counts or complex cytogenetic abnormalities have a greater likelihood of progressing to AML than do other patients.

Treatment of nonprogressing MDS has involved best supportive care, including red blood cell (RBC) and platelet transfusions and antibiotics. Active therapy was given only when MDS progressed to AML or resembled AML with severe cytopenias. Given the spectrum of treatments available, the goal of therapy must be decided upfront whether it is to improve anemia; thrombocytopenia; or neutropenia, eliminate the need for RBC transfusion, achieve complete remission, or cure the disease.

Allo-HSCT is the only approach with curative potential, but its use is governed by patient age, performance status, medical comorbidities, the patient's risk preference, and severity of MDS at presentation.

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Chronic myeloproliferative neoplasms (MPN) are clonal bone marrow stem cell disorders; as a group, approximately 8400 MPN are diagnosed annually in the United States. Like MDS, MPN primarily occur in older individuals, with approximately 67% reported in patients aged 60 years and older.

MPNs are characterized by the slow but relentless expansion of a clone of cells with the potential evolution into a blast crisis similar to AML. MPN share a common stem cell-derived clonal heritage, with phenotypic diversity attributed to abnormal variations in signal transduction as the result of a spectrum of mutations that affect protein tyrosine kinases or related molecules. The unifying characteristic common to all MPN is effective clonal

myeloproliferation resulting in peripheral granulocytosis, thrombocytosis, or erythrocytosis that is devoid of dyserythropoiesis, granulocytic dysplasia, or monocytosis.

In indolent, nonprogressing cases, therapeutic approaches are based on relief of symptoms. Supportive therapy may include prevention of thromboembolic events. Hydroxyurea may be used in cases of high-risk essential thrombocytosis and polycythemia vera, and intermediate- and high-risk primary myelofibrosis.

In November 2011, FDA approved the orally administered selective Janus kinase 1 and 2 inhibitor ruxolitinib for the treatment of intermediate- or high-risk myelofibrosis.

Myeloablative allo-HSCT has been considered the only potentially curative therapy, but because most patients are of advanced age with attendant comorbidities, its use is limited to those who can tolerate the often severe treatment-related adverse effects of this procedure. However, use of reduced-intensity conditioning for allo-HSCT has extended the potential benefits of this procedure to selected individuals with these disorders.

MYELOPROLIFERATIVE NEOPLASMS

MPNs are uncommon overlapping blood diseases characterized by the production of one or more blood cell lines. The most common forms of MPNs include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myeloid leukemia (CML). A common finding in many MPNs is clonality and a central pathogenic feature is the detection of a somatic (acquired) pathogenic variant in disease-associated genes. Pathogenic variants in disease-associated genes result in constitutively activated tyrosine kinase enzyme or cell surface receptor.

The paradigm for use of molecular genetics to revolutionize patient management is CML. A unique chromosomal translocation t(9;22), the Philadelphia chromosome, leads to a unique gene rearrangement (*BCR-ABL*) creating a fusion gene that encodes for a constitutively active Bcr-abl fusion protein. These findings led to the development of targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions.

Diagnosis and monitoring of patients with Ph-negative MPNs have been challenging because many of the laboratory and clinical features of the classic forms of these diseases—PV, ET, and PMF—can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis, or myeloid fibrosis. Additionally, these entities can be difficult to distinguish on morphologic bone marrow exam, and diagnosis can be complicated by changing disease patterns: PV and ET can evolve into PMF or undergo leukemic transformation. World Health Organization criteria were published as a benchmark for diagnosis in 2002¹ and updated in 2008 and 2016.^{28,30} Applying these criteria have been challenging because they involve complex diagnostic algorithms, rely on morphologic assessment of uncertain consistency, and require tests that are not well-standardized or widely available, such as endogenous erythroid colony formation.

Molecular Genetics of Ph-Negative MPNs

JAK2 Gene

The JAK2 gene, located on chromosome 9, contains the genetic code for making the Janus kinase 2 protein, a nonreceptor tyrosine kinase. The Janus kinase 2 (JAK2) protein is part of the JAK/STAT signal transduction pathway that is important for the controlled production of blood cells from hematopoietic stem cells. Somatic (acquired) variants in the JAK2 gene are found in patients with PV ($\approx 96\%$), ET (50%), and PMF (50%).³⁵

CALR Gene

The CALR gene, located on chromosome 19, contains the genetic code for making the calreticulin protein, a multifunctional protein located in the endoplasmic reticulum, cytoplasm, and cell surface. The calreticulin protein is thought to play a role in cell growth and division and regulation of gene activity. Somatic variants in the CALR gene are associated with ET and PMF.³⁶

MPL Gene

The *MPL* gene, located on chromosome 1, contains the genetic code for making the thrombopoietin receptor, a cell surface protein that stimulates the JAK/STAT signal transduction pathway. The thrombopoietin receptor is critical for the cell growth and division of megakaryocytes, which produce platelets involved in blood clotting. Somatic variants in the *MPL* gene are associated with ET and PMF.³⁷

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The BCR/ABL1 qualitative and quantitative genotyping tests, and ABL SNV tests, are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *JAK2* testing and *MPL* mutation testing.

In May 2017, the Food and Drug Administration granted approval for midostaurin (Rydapt®, Novartis Pharmaceuticals). Rydapt® is a targeted therapy to be used in combination with chemotherapy when an FLT3 variant is detected by the LeukoStrat® CDx FLT3 Mutation Assay (Invivoscribe).

RELATED PROTOCOLS

Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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