
LabPMM®
an invivoscribe company
Service Catalog
invivoscribe.com

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invivoscribe.com/clinical-lab-services

LabPMM Offers Efficient and Reliable Standardized Tests that Meet the Highest Quality and Service Standards.

- **CRO Services**
- **Global Stratification and enrollment of patients in clinical trials**
- **Diagnostic testing, Research and Development**
- **Worldwide experts in precision medicine and companion diagnostics (CDx) of hematological malignancies**

The Laboratories for Personalized Molecular Medicine (LabPMM) is the Invivoscribe® global network of clinical reference labs located in the USA, Europe and Asia, which provides international access to harmonized molecular testing.

LabPMM specializes in oncology with an emphasis on leukemias and lymphomas. We offer an ever-expanding menu of flow cytometry and molecular assays to support medical diagnosis, research testing, stratification & enrollment of patients in clinical trials, optimization of treatments and development of companion diagnostics (CDx).

The comprehensive test menu is focused on biomarkers that demonstrate clinical utility, providing data and information that is clinically actionable and critical to making informed treatment decisions. Our CE-IVD assays and bioinformatics are further developed and manufactured consistently under ISO 13485 in our FDA-registered facility, making them eligible to be submitted to worldwide regulatory authorities for registration.

LabPMM is one of the only international laboratory networks that offers both flow cytometry and NGS-based MRD testing for coherent comparisons for a number of clinically significant biomarkers. Accordingly, test results generated in any of our laboratories in Europe, Asia, or the USA are internationally concordant and reproducible. The harmonized testing provided by LabPMM assists healthcare providers in offering optimized and consistent care for their patients, as the test results accurately and reproducibly stratify patients for international clinical trials, thus ensuring that patients receive optimal treatment and that drugs are approved quickly.

LabPMM Global Locations

LEARN MORE:
invivoscribe.com/company/locations

LabPMM LLC

Located in San Diego, California, USA, it holds the following accreditations and certifications: ISO 15189, CAP, and CLIA, and is licensed to provide diagnostic laboratory services in the states of California, Florida, Maryland, New York, Pennsylvania, and Rhode Island.

LabPMM GmbH

Based in Hallbergmoos (Munich), Germany. It is an ISO 15189 accredited international reference laboratory offering diagnostic services.

LabPMM 合同会社

Located near Tokyo in Kawasaki (Kanagawa), Japan. It is an ISO 15189 and JAB accredited international reference laboratory.

Invivoscribe Diagnostic Technologies (Shanghai) Co., Ltd.

Located in Shangai, China. It is the newest CAP accredited international reference lab, supporting clinical trial work in China.

Available services include: CDx *FLT3*, NGS Gene Panels, Clonality testing (B- & T-cell), MRD assays, Custom assays, and Multiparametric Flow Cytometry

LabPMM® specializes in personalized flow cytometry and molecular testing services for oncology, including leukemia and lymphoma. We are committed to providing high-quality testing in support of Personalized Molecular Medicine®.

Our diagnostic and research portfolio includes a full range of oncology services, such as single gene assays for *FLT3*, *NPM1*, clonality testing of B- and T-cells, minimal or measurable residual disease (MRD) assessments and comprehensive next-generation sequencing (NGS) gene panels for AML and other hematologic malignancies.

Rapid turnaround times are vital to ensure that the physician can make timely informed treatment decisions. Our turnaround times for individual gene tests are in the range of 1 to 3 days following sample receipt, while turnaround times for our NGS assays and gene panels are 7 to 21 days. When using LabPMM, physicians receive results faster which expedites patient care and streamlines clinical trials. The reason is simple: all of our LabPMM sites initiate tests the day of clinical sample receipt, avoiding delays caused by batching of samples for testing.

Customer support is an important aspect of our services. We provide responsive, timely support both via email and telephone. We are also bound by strict privacy laws and use only secure proven methods to communicate patient-related data and results.

How to Order a Test

Please contact your local LabPMM site to receive the necessary forms to initiate a services ordering account.

EMAIL:
inquiry@invivoscribe.com

Ordering Details

Specimen Collection and Shipment

We advise our customers to send all specimens through an overnight delivery service. Please notify your local LabPMM site of urgent samples so we know when to expect the specimens and can investigate any shipping issues if needed.

Specimens for DNA Assays

Collect blood and bone marrow specimens in sodium heparin, EDTA, or an ACD (acid citrate dextrose) tube. Specifically for *FLT3* ITD MRD and *NPM1* MRD, only samples collected in EDTA are accepted. Blood and bone marrow may be stored at 2-8 °C for up to 7 days.

Please ship blood and bone marrow at ambient temperature or with cool packs, do not freeze. Please ship previously isolated DNA at ambient temperature, with cool packs, or on dry ice, as applicable. Previously isolated DNA may be stored indefinitely at -65°C to -85°C.

Specimens for Flow Cytometry Panels

Collect blood or bone marrow specimens in sodium heparin or EDTA tubes. Blood and bone marrow may be stored at 2-8 °C for up to 7 days. Please ship blood and bone marrow at ambient temperature or with cool packs, do not freeze.

CDx *FLT3* Mutation Assay

Peripheral blood or bone marrow aspirate samples collected in sodium heparin or EDTA tubes are accepted. Preserved specimens may be stored at 2-8°C for up to 7 days. ACD specimen collection not accepted.

Accredited Menu

LabPMM, LLC (Americas)

CAP ISO 15189-accredited and CLIA-certified

CDx *FLT3*, *FLT3* ITD MRD, *NPM1*, *NPM1* MRD, NGS B-cell Clonality, NGS T-cell Clonality, B-cell MRD, MyAML, MyMRD, MFC Hematolymphoid Screening Panel, MFC AML MRD Assay, MFC CLL MRD Assay

New York State Licensed Tests

CDx *FLT3*, *NPM1*

LabPMM GMBH (EU/Middle East/Africa)

DAkkS-accredited tests to ISO 15189

CDx *FLT3*, *NPM1*, NGS B-cell Clonality, NGS T-cell Clonality

LabPMM GK (Asia/Pacific)

Licensed Clinical Lab

CDx *FLT3*

Invivoscribe Diagnostic Technologies (Shanghai) Co., Ltd.

CAP-accredited

CDx *FLT3*, NGS B-cell Clonality

Patient Consent and Confidentiality

LEARN MORE:
invivoscribe.com/clinical-lab-services

Patient Consent

» LabPMM will only process routine diagnostic samples submitted by medical institutions, whereby consent for diagnostic testing is obtained by the submitting physician.

» No data is forwarded to outside organizations without specific prior consent.

» Samples for the MyAML and MyMRD assays must have a completed patient consent form, signed by the patient and the submitting physician to confirm that the patient has understood and given consent for the testing requested.

Patient Confidentiality

» By sending samples to LabPMM for routine diagnostic testing, patients will be protected by the strict data protection laws.

» Patient samples will only be reused for quality control of the assays requested on the original requisition form.

» At LabPMM GmbH, unless prior consent is given, primary samples or DNA from patient samples is retained for 12 months for quality control purposes only. Thereafter patient samples are de-identified and destroyed.

» Our data servers are located in a facility in the USA. Data is encrypted prior to transfer and the transferred data is subject to the same safeguards as data held in Germany.

Partner with Us

Your Ideal Partner for Laboratory Services, Clinical Trial Testing, and Companion Diagnostic Development.

EMAIL:
businessdevelopment@invivoscribe.com

LabPMM (an Invivoscribe® company) is Your Partner of Choice for Diagnostic, Research, and Clinical Trial Services.

Our network of laboratories located in the USA, Europe and Asia specialize in internationally harmonized molecular testing, and flow cytometry, and collectively have CLIA and ISO 15189 certifications via CAP and DAkkS. We also offer contract research organization (CRO) services, and are a comprehensive companion diagnostics (CDx) and custom assay development partner, providing ISO 13485-compliant biomarker development, cGMP manufacturing, regulatory capability, global laboratory services and commercialization.

We offer an ever expanding menu of molecular assays, including NGS gene and MRD panels, *FLT3* and *NPM1* mutation assays, and B- and T-cell clonality and MRD assessment. Recently, LabPMM expanded its testing capabilities to include multiparametric flow cytometry. Our comprehensive test menu will now eliminate the need for partners to split primary specimens, dramatically decreasing turnaround times and allowing for coherent comparison of flow-based and NGS-based MRD test results.

State of the Art

We thrive in international cooperation and in continuous investment in the advancement of precision medicine. We work with a full range of collaborators: key opinion leaders, leading healthcare institutions, and top-tier pharmaceutical companies. We work on the premise that all those reliant on data and results from clinical testing (healthcare providers, pharmaceutical companies and most importantly, patients) will benefit from better standardization and more consistent performance of molecular diagnostic tests.

Quality

Internationally-harmonized diagnostics through our global network of laboratories. We follow full QSR design control for assay and software development. Products are manufactured under cGMP and ISO 13485.

Partnership

We support partnerships worldwide to develop, validate, and commercialize custom biomarker assays and reagents. Our global distribution network operates in more than 700 laboratories in 160 countries.

Expertise

With nearly 30 years of experience we are the foremost experts in providing molecular products and services for oncologic testing. We offer dedicated support in design and development, manufacturing, software and bioinformatics, technical support, quality assurance, and global regulatory affairs.

An Ideal CDx Partner for Drug Approvals

EMAIL:
businessdevelopment@invivoscribe.com

IVD Product Development

» Nearly 30 years of assay development experience
» Biomarker assays & software development under full ISO 13485 design controls
» Comprehensive NGS gene panels that identify actionable biomarkers
» Custom biomarker assay and CDx development

Global Regulatory, Quality and Commercial Expertise

» Experienced staff & proven Quality Management System
» Full adherence to FDA 21 CFR part 820 and ISO13485 standards
» Registered Medical Device Establishment with the US FDA, KFDA, Saudi Arabia, and the PMDA
» Multiple CDx approvals supporting various drugs: by the FDA (US) and PMDA/MHLW (Japan)
» CDx CE-marks in the EU
» 50+ CE-marked IVDs available in the EU and select ROW markets; 60 tests registered with the ARTG in Australia
» Marketing Authorization Holder (MAH) and National reimbursement for CDx in Japan
» CDx submitted for reimbursement in the US
» Supporting ongoing clinical drug trials in the US, EU, Japan, China and ROW

Clinical Testing

Global Clinical Reference Laboratory Network

» A dozen years of clinical reference lab experience
» Internationally standardized CDx and biomarker testing with labs serving the US, Europe, and Asia
» Standardized CAP/CLIA-certified Multiparametric Flow Cytometry panels for screening, trial enrollment and MRD monitoring
» Comprehensive LymphoTrack® clonality/MRD assays and CAP and CLIA-certified NGS MyGene™ panels identify clinically actionable biomarkers
» Complementary MRD assays for all biomarkers – potential for surrogate endpoints per agency inputs
» Testing services have supported hundreds of enrollment sites worldwide

Manufacturing

» FDA/CDRH-registered and ISO 13485-certified cGMP manufacturing facility based in San Diego
» Comprehensive Dx and CDx Manufacturing:
    » CDx for USA (PMA), Japan, EU, and ROW markets
    » 50+ CE-IVDs (NGS assays + bioinformatics software) IUO & RUO assays, ASRs & GPRs
» DNA / RNA controls, MRD controls & proficiency panels

Join the 75+ Pharma Companies Worldwide Working with Us

EMAIL:
businessdevelopment@invivoscribe.com

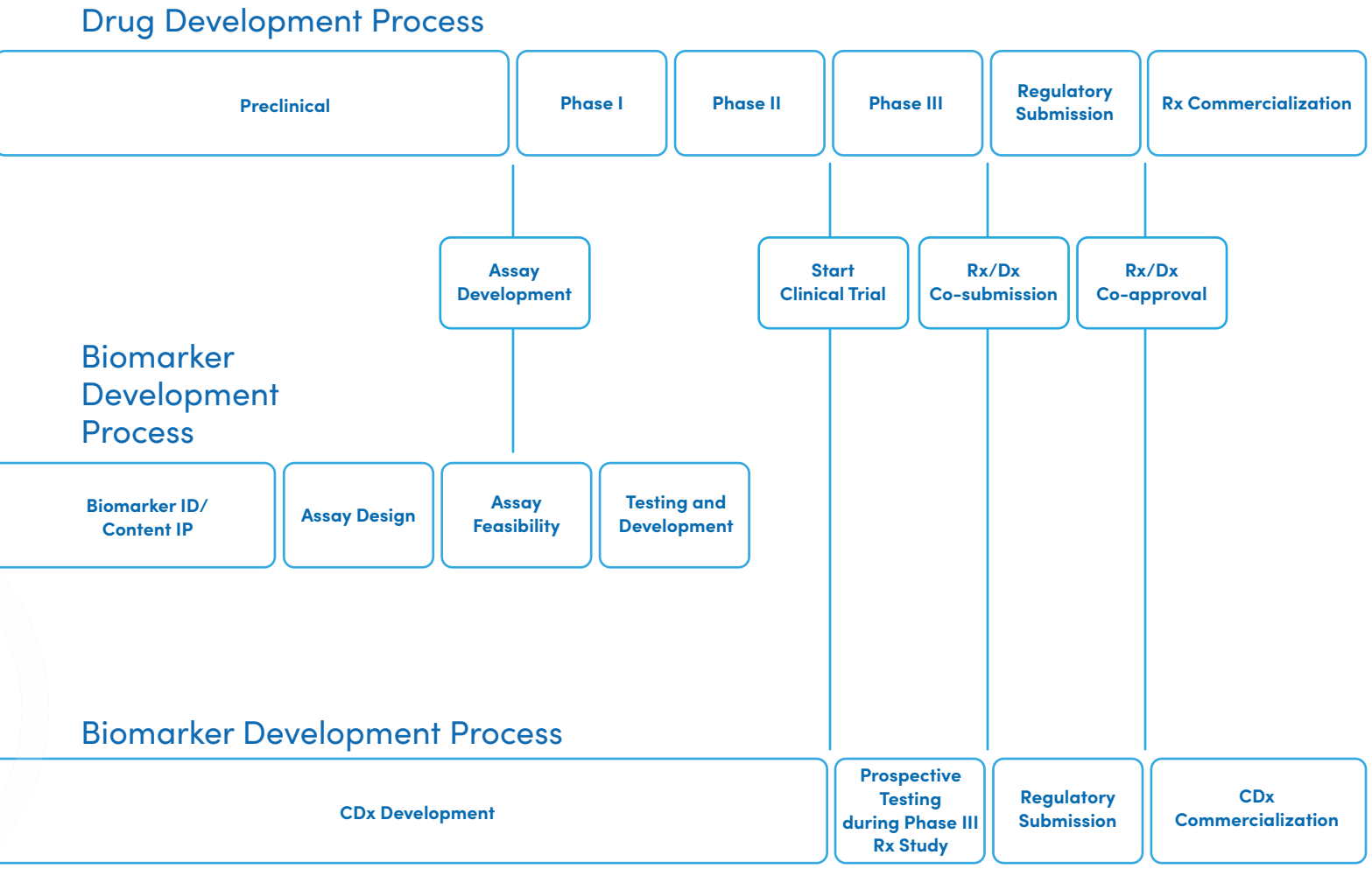
Integrated Approach to CDx Development

We provide efficient handling of all stages of CDx development, from the biomarker discovery process to commercialization, including:

» Supportive, collaborative relationship with our pharmaceutical partners

» Dedicated CDx development team with extensive expertise in program management, feasibility studies, product development, quality control, regulatory, and commercialization

» Sense of urgency and commitment to partner's success



CDx Commercialization Phasing

EMAIL:
businessdevelopment@invivoscribe.com

Planning

» Develop plan in collaboration with partner
» Share market insights and collective knowledge
» Align Rx / Dx commercial objectives
» Define commercialization strategy and country level prioritization/timing
» Determine activities requiring partner support

Pre-Launch

» Identify and nurture key opinion leaders (KOLs)
» Align CDx development studies with commercialization studies
» Voice of customer to drive product requirements and commercialization considerations
» Prepare marketing message for PMA submission

Launch

» Establish lab network
» Create physician awareness
» Activate KOL network to start commercialization studies
» Complete HEOR studies, prepare HTAs, request reimbursement coverage
» Initiate PR and marketing campaigns

Post-Launch

» Expand lab network and physician awareness after reimburement established and guidelines updated
» Continue to nurture KOLs
» Monitor and adjust activities to achieve market adoption
» Transition to maintenance campaigns

Examples of *FLT3* CDx Partnerships

Novartis

» *FLT3* CDx for RYDAPT® (midostaurin)
» Breakthrough designation in the USA
» FDA, Swissmedic and EU approval in 2017

Astellas

» *FLT3* CDx for XOSPATA® (gilteritinib fumarate)
» More than 140 international collection sites
» PMDA approval in Japan in 2018
» Reimbursement approved in Japan
» FDA approval in USA in 2018
» EU approval in 2019

Daiichi-Sankyo

» *FLT3* CDx for VANFLYTA® (quizartinib hydrochloride)
» Bridging study for multiple labs in the USA, Europe and Asia
» PMDA approval in Japan in 2019

Companion Diagnostic Testing

According to the U.S. FDA definition, a companion diagnostic is a medical device, often an *in vitro* device (IVD), which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The use of a companion diagnostic will therefore help clinicians and healthcare providers determine whether a patient is likely to benefit from the drug in question and monitor the response. In the European Union under the new IVDR, the definition of a companion diagnostic expands to require patient screening before and/or during treatment for those likely to experience benefit and/or increased risk as a result of treatment with the corresponding medicinal products.

The use of assays that have not been specifically validated for the safety and effectiveness of a drug or biological product may deliver inaccurate results that could harm the patient. For instance, a false positive result could lead to treatment with a drug without the proven benefits, exposing the patient to potential toxic side effects. Likewise, a false negative test result could withhold or delay a potentially beneficial treatment, putting the patient at risk.

Companion diagnostics help demonstrate drug efficacy and accelerate approval. They have become an important tool for improving individual patient treatment.

LabPMM embraces international harmonization and partnering. We work with key opinion leaders to standardize molecular diagnostic testing and we are also partnered with pharmaceutical companies to develop companion diagnostic tests. Our proud history of partnerships have led to outstanding work towards internationally standardized testing, exemplified by FDA and PMDA approval of the first companion diagnostic for acute myeloid leukemia.

LeukoStrat®
CDx *FLT3* Mutation Assay

United States - FDA Approved

Predictive test for the efficacy of RYDAPT® (midostaurin), XOSPATA® (gilteritinib), or VANFLYTA® (quizartinib)

Intended Use

The LeukoStrat CDx *FLT3* Mutation Assay is a PCR-based in vitro diagnostic test designed to detect internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations D835 and I836 in the *FLT3* gene in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with acute myelogenous leukemia (AML).

The LeukoStrat CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with AML for whom RYDAPT® (midostaurin) treatment is being considered.

The LeukoStrat CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with AML for whom XOSPATA® (gilteritinib) treatment is being considered.

The LeukoStrat CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with *FLT3*-ITD+ AML for whom VANFLYTA® (quizartinib) treatment is being considered.

The test is for use on the 3500xL Dx Genetic Analyzer.

- Mutations in the *FLT3* gene are the most common mutations found in AML
- Presence of a *FLT3* activation mutation in patients with AML may be prognostic and clinically actionable.
- The LeukoStrat CDx *FLT3* Mutation Assay is used as aid in the selection of AML patients for whom midostaurin, gilteritinib, or quizartinib are being considered
- NCCN, ELN and CAP Guidelines recommend *FLT3* testing to inform patient treatment decisions.
- Gilteritinib was approved by the FDA for the treatment of adult patients with relapsed/ refractory *FLT3*mut+ AML
- Midostaurin was approved by the FDA for the treatment of adult patients with newly diagnosed AML who are *FLT3* mutation positive
- Quizartinib was approved by the FDA for the treatment of adult patients with newly diagnosed *FLT3*-ITD+AML
- First-to-market, this CDx is FDA approved (PMA#P160040) as a predictive test for the efficacy of midostaurin therapy in all AML patients, regardless of cytogenetics.

Test Name

LeukoStrat® CDx *FLT3* Mutation Assay

Assay Type

Capillary Electrophoresis

Method Description

The LeukoStrat® CDx *FLT3* Mutation Assay is designed to detect ITD and TKD mutations in the *FLT3* gene. The assay is performed on DNA isolated from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with AML.

Primers targeting both in and around the juxtamembrane region for ITD testing and kinase domain of the *FLT3* gene are used to amplify DNA extracted from a patient sample.

The TKD PCR product is further digested with a restriction enzyme. The ITD PCR products and the digested TKD PCR products are analyzed on a capillary electrophoresis instrument.

FLT3 ITDs are detected by a change in the expected size of a wild type fragment. An amplicon larger than the wild type fragment indicates the presence of *FLT3* ITD. The TKD digestion pattern identifies loss of the normal gene sequences and ensures that digestion occurred.

Indications for Testing

- At initial diagnosis or relapse of AML
- As an aid in the assessment of patients with AML for whom RYDAPT® (midostaurin) treatment is being considered.
- As a tool to identify AML patients eligible for treatment with XOSPATA® (gilteritinib).
- As an aid in the assessment of patients with *FLT3*-ITD+ AML for whom VANFLYTA® (quizartinib) treatment is being considered.

Interpretation

An interpretive report will be issued, indicating whether the patient is eligible for midostaurin, gilteritinib, or quizartinib treatment

Turnaround Time

2 to 3 business days
>95% patient samples are reported within 48 hours of receipt

Specimen Requirements

Recommended Specimen Volume (Preservative)
2 mL of peripheral blood in Sodium Heparin or EDTA
0.5mL of bone marrow in Sodium Heparin or EDTA

Minimum Specimen Volume (Preservative)
1mL of peripheral blood in Sodium Heparin or EDT
0.25 mL of bone marrow in Sodium Heparin or EDTA

Shipping Conditions

2°C to 8°C up to 72 hours; do not freeze.

Specimen Stability

2°C to 8°C up to 7 days

LeukoStrat®
CDx *FLT3* Mutation Assay

CE-marked

Predictive test for the efficacy of RYDAPT® (midostaurin) and XOSPATA® (gilteritinib fumarate)

Intended Use

The LeukoStrat® CDx *FLT3* Mutation Assay is a PCR-based *in vitro* diagnostic test designed to detect internal tandem duplications (ITD) and tyrosine kinase domain (TKD) mutations D835 and I836 in the *FLT3* gene in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with acute myelogenous leukemia (AML).

In regions where midostaurin is available, the LeukoStrat® CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with AML for whom RYDAPT® (midostaurin) treatment is being considered.

In regions where gilteritinib fumarate is available, the LeukoStrat® CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with AML for whom XOSPATA® (gilteritinib fumarate) treatment is being considered.

- Mutations in the *FLT3* gene are the most common mutations found in AML
- Presence of a *FLT3* activation mutation in patients with AML may be prognostic and clinically actionable.
- NCCN, ELN and CAP Guidelines recommend *FLT3* testing to inform patient treatment decisions.
- The LeukoStrat® CDx *FLT3* Mutation Assay is used as an aid in the assessment of AML patients for whom midostaurin and/or gilteritinib fumarate treatment is being considered
- Midostaurin was approved by the Swissmedic and European Commission for the treatment of adult patients with newly diagnosed AML who are *FLT3* mutation positive
- Gilteritinib fumarate was approved by the European Commission for the treatment of relapsed/ refractory *FLT3*mut+ AML

Test Name

LeukoStrat® CDx *FLT3* Mutation Assay

Assay Type

Capillary Electrophoresis

Method Description

The LeukoStrat® CDx *FLT3* Mutation Assay is designed to detect ITD and TKD mutations in the *FLT3* gene.

The assay is performed on DNA isolated from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with AML.

Primers targeting both in and around the juxtamembrane region for ITD testing and kinase domain of the *FLT3* gene are used to amplify DNA extracted from a patient sample. The TKD PCR product is further digested with a restriction enzyme. The ITD PCR products and the digested TKD PCR products are analyzed on a capillary electrophoresis instrument.

FLT3 ITDs are detected by a change in the expected size of a wild type fragment. An amplicon larger than the wild type fragment indicates the presence of *FLT3* ITD. The TKD digestion pattern identifies loss of the normal gene sequences and ensures that digestion occurred.

Indications for Testing

- At initial diagnosis or relapse of AML
- In regions where midostaurin is available, the LeukoStrat CDx *FLT3* mutation assay is used as an aid in the assessment of AML patients for whom midostaurin treatment is being considered.
- In regions where gilteritinib fumarate is available, the LeukoStrat CDx *FLT3* mutation assay is used as an aid in the assessment of AML patients for whom gilteritinib fumarate treatment is being considered.

Interpretation

An interpretive report will be issued indicating the absence or presence of a *FLT3* mutation and its corresponding signal ratio. The report will further indicate whether the patient is eligible for a therapy with midostaurin or gilteritinib fumarate.

Turnaround Time

2 to 3 business days
>95% patient samples are reported within 48 hours of receipt

Specimen Requirements

Recommended Specimen Volume (Preservative)
2 mL of peripheral blood in Sodium Heparin or EDTA
0.5mL of bone marrow in Sodium Heparin or EDTA

Minimum Specimen Volume (Preservative)
1mL of peripheral blood in Sodium Heparin or EDT
0.25 mL of bone marrow in Sodium Heparin or EDTA

Shipping Conditions

2°C to 8°C up to 72 hours; do not freeze.

Specimen Stability

2°C to 8°C up to 7 days

LeukoStrat

リューコストラット CDX FLT3 変異検査

Japan - MHLW/PMDA Approved

Predictive test for the efficacy of Gilteritinib Fumarate and Quizartinib Hydrochloride

Intended Use

The LeukoStrat CDx *FLT3* Mutation Assay is a PCR-based, *in vitro* diagnostic test designed to detect internal tandem duplication (ITD) mutations and tyrosine kinase domain (TKD) mutations D835 and I836 in the *FLT3* gene in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with acute myelogenous leukemia.

The LeukoStrat CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with AML for whom Gilteritinib Fumarate treatment is being considered.

The LeukoStrat CDx *FLT3* Mutation Assay is used as an aid in the assessment of patients with AML for whom Quizartinib Hydrochloride treatment is being considered.

- Mutations in the *FLT3* gene are the most common mutations found in AML
- Presence of a *FLT3* activation mutation in patients with AML may be prognostic and clinically actionable.
- The LeukoStrat® CDx *FLT3* Mutation Assay is the first PMDA approved test for assessment of AML patients eligible for treatment with Gilteritinib Fumarate or Quizartinib Hydrochloride
- Gilteritinib Fumarate received manufacturing and marketing approval for the treatment of *FLT3* mutation-positive relapse or refractory AML in Japan
- Quizartinib Hydrochloride is MHLW/PMDA approved for the treatment of relapsed/ refractory *FLT3*-ITD^{+} AML

Test Name

LeukoStrat® CDx *FLT3* Mutation Assay

Assay Type

Capillary Electrophoresis

Method Description

The LeukoStrat® CDx *FLT3* Mutation Assay is designed to detect ITD and TKD mutations in the *FLT3* gene.

The assay is performed on DNA isolated from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with AML.

Primers targeting both in and around the juxtamembrane region for ITD testing and kinase domain of the *FLT3* gene are used to amplify DNA extracted from a patient sample. The TKD PCR product is further digested with a restriction enzyme. The ITD PCR products and the digested TKD PCR products are analyzed on a capillary electrophoresis instrument.

FLT3 ITDs are detected by a change in the expected size of a wild type fragment. An amplicon larger than the wild type fragment indicates the presence of *FLT3* ITD. The TKD digestion pattern identifies loss of the normal gene sequences and ensures that digestion occurred.

Indications for Testing

- At initial diagnosis or relapse of AML
- As a tool for the assessment of AML patients for whom Gilteritinib Fumarate treatment is being considered
- As a tool for the assessment of AML patients for whom Quizartinib Hydrochloride treatment is being considered

Interpretation

An interpretive report will be issued, indicating whether the patient is eligible for Gilterinib Fumarate treatment or Quizartinib Hydrochloride

Turnaround Time

2 to 3 business days
>95% patient samples are reported within 48 hours of receipt

Specimen Requirements

Recommended Specimen Volume (Preservative)
2 mL of peripheral blood in Sodium Heparin or EDTA
0.5mL of bone marrow in Sodium Heparin or EDTA

Minimum Specimen Volume (Preservative)
1mL of peripheral blood in Sodium Heparin or EDT
0.25 mL of bone marrow in Sodium Heparin or EDTA

Shipping Conditions

2°C to 8°C up to 72 hours; do not freeze.

Specimen Stability

2°C to 8°C up to 7 days

Reimbursement Points

4200 points

Molecular Diagnostic Tests

Somatic mutations play an increasingly important role in the risk stratification and management of leukemia and lymphoma patients. Traditionally, classification and risk stratification have relied on cytogenetic studies; however, molecular detection of gene mutations and gene rearrangements are now central in the classification, risk stratification, and management of lymphoproliferative diseases. Molecular testing also complements cytogenetic testing results, which helps further refine stratification and prognosis, especially within specific disease subgroups.

All of LabPMM's molecular tests conform to the Standard of Care as defined by the World Health Organization (WHO) and are recommended by members of the National Comprehensive Cancer Network, LeukemiaNet, and other world opinion leaders in hematology.

NPM1 Mutation Assay

Clinical Information

The Nucleophosmin (*NPM1*) gene is one of the most commonly mutated genes in acute myeloid leukemia (AML), occurring in about 35% of AML patients at diagnosis.[1] The vast majority of *NPM1* mutations are insertions in exon 12 occurring near the C-terminus of the protein that result in cytoplasmic localization.[2] Currently there are over 40 known *NPM1* mutations, most of which will be detected with our assay.

Clinical studies have found that *NPM1* mutations are associated with increased blast counts, higher extramedullary involvement and increased platelet counts in AML.[3] Furthermore, in the absence of a *FLT3* ITD mutation (or *FLT3* ITD with a low ratio), *NPM1* mutations are associated with a favorable prognosis.[4]

It has been suggested that the identification of mutations in both *NPM1* and *FLT3* genes allows for the stratification of the AML patients into three different prognostic groups:

- Favorable prognosis: *NPM1* mutation without *FLT3* ITD or with *FLT3* ITD^{low}
- Intermediate prognosis: *NPM1* mutation and *FLT3* ITD^{high}; *NPM1*$^{-}$ without *FLT3* ITD or with *FLT3* ITD^{low} (without adverse-risk genetic lesions)
- Poor prognosis: *NPM1* wild-type and *FLT3* ITD^{high}

It is recommended that AML patients be screened for *NPM1* mutations as an effort to assess prognosis and aid in treatment decisions. Results from *NPM1* and *FLT3* mutational screening should be available within 48 to 72 hours (at least in patients eligible for intensive chemotherapy). Utilizing both *NPM1* and *FLT3* (mutant:wild-type ratio) mutation status is the most common molecular method for stratification of the AML population.

Test Name

NPM1 mutation analysis (qualitative)

Assay Type

Capillary Electrophoresis

Method Description

Primers targeting exon 12 on the *NPM1* gene are used to amplify the patient's DNA. The size of the *NPM1* PCR product is determined by capillary electrophoresis.

LabPMM offers the only internationally harmonized assay for *NPM1* mutations and testing is performed pursuant to patents licensed from Cardiff Oncology Inc. of San Diego, CA.

Indications for Testing

- At initial diagnosis of AML
- Stratification high and low risk AML
- Recurrence of leukemia after induction therapy on patients not initially screened for *NPM1* mutations

Interpretation

An interpretive report will be issued indicating whether a *NPM1* mutation was detected

Turnaround Time

1-3 business days

Specimen Requirements

1-3 mL peripheral blood in EDTA, ACD or Heparin
0.25-1 mL bone marrow in EDTA, ACD or Heparin
250 ng of previously isolated DNA

Shipping Conditions

Ambient or Cool; do not freeze (peripheral blood or bone marrow
Ambient or frozen on dry ice (isolated DNA)

Specimen Stability

Room Temp up to 72 hours
2-8 °C up to 7 days

Clonality Tests

The unique process of genetic rearrangements in the immunoglobulin (Ig) and T-cell receptor (TCR) gene loci during B- and T-cell development and maturation generates a vast pool of genetically distinct cells.

During early lymphoid differentiation, genes encoding the Ig and TCR molecules are formed by stepwise rearrangement of variable (V), diversity (D), and joining (J) gene segments. During this V-D-J recombination process, nucleotides are deleted and randomly inserted at the joining sites, resulting in an enormous diversity of unique antigen receptors. As Ig/TCR gene rearrangements occur sequentially in the earliest stages of lymphoid differentiation, they are present in almost all immature and mature lymphoid cells.

Since lymphoma is a cancer of the lymphatic or the immune system, the vast majority of lymphomas exhibit rearrangements in Ig and/or TCR genes. Lymphoid malignancies are characterized by the reduced population diversity of these gene loci originating from the proliferative transformation of an individual lymphoid cell. The associated cellular population typically shares one or more cell-specific or "clonal" antigen-receptor gene rearrangements. The detection of these clonal cells provides the basis for clonality assessment in leukemia, lymphoma, and hematologic disease diagnosis.

Invivoscribe (LabPMM's parent company) is an industry pioneer with nearly 3 decades of experience in providing clonality test solutions. Our expertise in clonality testing assures the highest rates of detection of clonal populations as well as international standardization of results.

B-Cell Clonality Assay

Clinical Information

Lymphoid cells are different from the other somatic cells in the body as during development, the antigen receptor genes in these cells undergo somatic gene rearrangement.[1] Since leukemia and lymphomas originate from the malignant transformation of individual lymphoid cells, all leukemias and lymphomas generally share one or more cell-specific or "clonal" antigen receptor gene rearrangements. Clonality does not always imply malignancy; all results must be interpreted in the context of all of the other available diagnostic criteria. Tests that detect Ig clonal rearrangements are useful in the characterization, monitoring, and treatment of B- and T-cell malignancies.

Immunoglobulin Heavy (*IGH*)

The human *IGH* gene locus on chromosome 14 (14q32.3) includes 46-52 functional and 30 non-functional variable (V_H) gene segments, 27 functional diversity (D_H) gene segments, and 6 functional joining (J_H) gene segments spread over 1250 kilobases. During B-cell development, genes encoding the human *IGH* proteins are assembled from multiple polymorphic gene segments that undergo rearrangements and selection, generating V_H-D_H-J_H combinations that are unique in both length and sequence for each cell.[2-3]

Somatic Hypermutation (SHM)

An additional level of diversity is generated by point mutations in the variable regions, also known as SHM. Immunoglobulin variable heavy chain gene hypermutation status provides important prognostic information for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The presence of *IGH* SHM is defined as greater or equal to 2% difference from the germline V_H gene sequence, whereas less than 2% difference is considered evidence of no SHM. The status of SHM for clone(s) has clinical relevance, as there is a clear distinction in the median survival of patients with and without SHM. Hypermutation of the *IGH* variable region is strongly predictive of a good prognosis, while lack of mutation predicts a poor prognosis.[4] In addition, this assay identifies clonal rearrangements involving the V3-21 gene, which has been associated with a poor prognosis in CLL independent of SHM status. This assay has been shown to further stratify CLL patients.[5]

Immunoglobulin Kappa (*IGK*)

The human *IGK* locus on chromosome 2 (2p11.2) includes 7 variable (Vκ) region gene segments and 5 joining (Jκ) gene segments upstream of the constant (Cκ) region. The Kappa deleting element (K_{de}), approximately 24 kb downstream of the Jκ-Cκ region, can also rearrange with Vκ gene segments and the isolated recombination signal sequence in the Jκ-Cκ intronic region.[6] Specifically during B-cell development, genes encoding *IGK* molecules are assembled from multiple polymorphic gene segments that undergo rearrangements generating gene receptors unique in both length and sequence.

Test Name

B-cell Clonality Assay

Assay Type

Next-Generation Sequencing (NGS)

Method Description

Specimens received for B-cell clonality are tested for the recommended immunoglobulin gene target(s) based on clinical indications. Next-generation sequencing of the PCR products is used to identify DNA sequences specific to clonal gene rearrangements. Bioinformatics tools facilitate the identification and characterization of significant clonal rearrangements. These sequences can be used to track specific clonal populations in follow-up testing.

Indications for Testing

- Identify clonality in atypical lymphoproliferative disorders
- Support a differential diagnosis between reactive lesions and hematologic malignancies
- Assign presumptive lineage in mature monoclonal lymphoproliferative disorders
- Monitor and evaluate disease recurrence

Interpretation

An interpretive report will be issued indicating the level of clonality along with the rearrangement locus for the dominant clones and the specific sequence for the dominant clone.

Turnaround Time

12 to 14 business days

Specimen Requirements

1-3 mL of peripheral blood in EDTA , ACD or Heparin
0.25-1 mL of bone marrow in Heparin, EDTA or ACD
500 ng of previously isolated DNA

Shipping Conditions

Ambient or Cool; do not freeze (peripheral blood or bone marrow)
Ambient or frozen on dry ice (isolated DNA)

Specimen Stability

2-8 °C up to 7 days prior to testing

References

1. Tonegawa, S (1983) *Nature.* 302:575-581.
2. Trainor, KJ et al. (1990) *Blood.* 75:2220-222 2.
3. van Dongen, JJM et al. (2003) *Leukemia.* 17:2257–2317.
4. Ghia, P et al. (2007) *Leukemia.* 21:1-3.
5. Stamatopoulos, B et al. (2017) *Leukemia.* 31(4):837-845.
6. Miller, JE et al. (2013, 2nd ed.) *Springer Science & Business Media.* 2.7.13 and 30.2.7.18.

T-Cell Clonality Assay

Clinical Information

Lymphoid cells are different from the other somatic cells in the body. During development the antigen receptor genes in lymphoid cells (including gene segments within *TRG* and *TRB*), undergo somatic gene rearrangement.[1] These developmentally regulated, programmed gene rearrangements generate V_Y-J_Y combinations that are unique for each cell.[2]

Since leukemias and lymphomas originate from the malignant transformation of individual lymphoid cells, which means that all leukemias and lymphomas generally share one or more cell-specific or "clonal" antigen receptor gene rearrangements. Clonality does not always imply malignancy; all results must be interpreted in the context of all of the other available diagnostic criteria. Tests that detect *TCR* clonal rearrangements can be used to help identify T-cell and certain B-cell malignancies.

T-cell Receptor Gamma (*TRG*)

The human *TRG* locus on chromosome 7 (7q14) includes 14 variable (V_Y) genes (Group I, II, III, and IV), 5 joining (J_Y) gene segments, and 2 constant (C_Y) genes spread over 200 kilobases.[3]

During T-cell ontogeny rearrangement of the *TRG* locus occurs before rearrangement of the alpha beta loci. So, clonal rearrangements of *TRG* are often present, commonly detected, and can be tracked in T-cell malignancies involving alpha-beta T-cells. This makes *TRG* a powerful tool for both clonal and MRD analysis of T-cell and some B-cell tumors.

T-cell Receptor Beta (*TRB*)

The human *TRB* gene locus on chromosome 7 (7q34) includes 64-67 variable (Vß) gene segments (belonging to 30 subgroups), 2 diversity (Dß) gene segments, and 13 joining (Jß) gene segments, spread over 685 kilobases, making this locus far more complex than others. Nevertheless, accurate molecular analysis of the *TRB* genes is an important tool for the assessment of clonality in suspected T-cell and some B-cell proliferations, as *TRB* gene rearrangements occur not only in almost all mature T-cell malignancies, but also in about one-third of precursor B-acute lymphoblastic leukemias (B-ALL).[3]

Test Name

T-cell Clonality Assay

Assay Type

Next-Generation Sequencing (NGS)

Method Description

Specimens received for T-cell clonality are tested for the recommended T-cell receptor gene target(s) based on clinical indications. Next-generation sequencing of the PCR products is used to identify DNA sequences specific to clonal gene rearrangements. Bioinformatics tools facilitate the characterization of sequences present at greater than 2.5% of the population. These sequences can be used to track specific clonal populations in follow-up testing.

Indications for Testing

- Identify clonality in atypical lymphoproliferative disorders
- Support a differential diagnosis between reactive lesions and hematologic malignancies
- Assign presumptive lineage in mature monoclonal lymphoproliferative disorders
- Monitor and evaluate disease recurrence

Interpretation

An interpretive report will be issued indicating whether evidence of clonality was detected. The report further provides a summary of the top 5 merged sequences, including the % total reads, the rearrangement class and the sequence.

Turnaround Time

12 to 14 business days

Specimen Requirements

1-3 mL of peripheral blood in Heparin, EDTA or ACD
0.25-1 mL of bone marrow in Heparin, EDTA or ACD
500 ng of previously isolated DNA

Shipping Conditions

Ambient or Cool; do not freeze (peripheral blood or bone marrow)
Ambient or frozen on dry ice (isolated DNA)

Specimen Stability

2-8 °C up to 7 days prior to testing

References

1. Tonegawa, S. (1983) *Nature.* 302:575-581.
2. Miller, JE et al. (2013, 2nd ed.) *Springer Science & Business Media.* 302.2.7.13 and 30.2.7.18.
3. Lawnickie, LC et al. (2003) *Journal of Molecular Diagnostics.* 5:82-87.

Measurable Residual Disease Tests

Measurable also known as Minimal Residual Disease (MRD) testing has shown strong potential for the optimization of therapeutic management of lymphoproliferative diseases. Currently, MRD tests complement and leverage the information obtained at diagnosis. Due to their increased sensitivity, these measurements are most useful at time points where they are compared and contrasted with more traditional methods. An example of this is before transplant, when MRD levels have been shown to be predictive of transplantation success.

Several patient-specific PCR-based (e.g. ASO-PCR) and flow cytometric technologies have been developed by regional test centers in order to routinely assess MRD levels during the course of therapy. However, ASO-PCR requires patient- and tumor-specific primer and probe sets, making it cost prohibitive and impossible to offer as a standardized method. Flow cytometry assays are also subjective and difficult to standardize between testing centers. Even innovative multiparametric flow cytometry methods are difficult to standardize and therefore do not meet the standards required to take them through the regulatory agencies.

Next-Generation Sequencing (NGS) methods have recently been developed for the detection and monitoring of MRD. These forefront technologies use regulatory-compliant chemistries, run on regulatory-compliant instruments, and can be interpreted using regulatory compliant, and design-controlled bioinformatics software. Due to the read depth of this non-biased patient agnostic testing approach, ultra deep sequencing overcomes virtually all of the shortcomings of other MRD technologies, providing internationally harmonized MRD testing for virtually any targeted biomarker.

LabPMM's MRD tests are NGS-based assays that can be used to detect clonal gene rearrangements identified at diagnosis within the B- and T-cell antigen receptor loci. Once a specific rearrangement sequence (the clonotype) has been identified in a primary sample, bioinformatics tools allow for objective longitudinal tracking of clonal populations with a sensitivity up to 1×10^{-6}, provided sufficient DNA is tested.

LabPMM also offers *FLT3* ITD and *NPM1* MRD assays, which are used for the detection of targeted mutations. These sensitive NGS-based assays reliably detect sequences present at 5×10^{-5}.

AML – *FLT3* ITD MRD Assay

Clinical Information

Measurable residual disease (MRD) detection in patients with leukemia has proven to be useful in the clinical management of disease and can facilitate the development of new therapies. Mutations in the fms-like tyrosine kinase 3 (*FLT3*) gene are the most prevalent mutations found in acute myeloid leukemia (AML)[1] and are characterized by an aggressive phenotype with a high prevalence of relapse. Internal tandem duplication (ITD) mutations within the juxtamembrane domain are the most common mutations of *FLT3*.[2] The development of a sensitive and specific assay for *FLT3* ITD mutations represents a significant advancement in guiding treatment decisions.

LabPMM's *FLT3* ITD MRD test is an NGS-based, targeted, deep-sequencing assay that detects ITDs ranging from 3 bp to over 200 bp in size. Once a specific ITD (length and sequence) has been identified in a primary sample, it can easily be tracked in subsequent samples at a sensitivity of $5x10^{-5}$, provided sufficient DNA quantity is tested.

The treatment of AML has become a paradigm for precision medicine. This MRD assay is at least two orders of magnitude more sensitive than other commercially available *FLT3* assays. It detects the persistence of a driver mutation, *FLT3* ITD, in patients with no overt evidence of disease, allowing clinicians to identify those patients that can benefit from continuation or modification of treatment.[3]

MRD detection by Next-Generation Sequencing has demonstrated utility in predicting clinical outcomes and in generating clinically actionable results, allowing early intervention, confirmation of disease status prior to transplant, and increased confidence in remission status.

Test Name

FLT3 ITD MRD Assay

Assay Type

Next-Generation Sequencing (NGS)
CLIA-validated assay

Method Description

To track and identify previously detected *FLT3* ITD mutations in post-treatment follow-up samples, a multiplex master mix targeting the juxtamembrane domain of the *FLT3* gene is used to amplify DNA extracted from a patient sample.

Next-generation sequencing of the PCR products is used to identify DNA sequences specific to previously identified mutations detected at diagnosis. Bioinformatics tools facilitate the detection of these specific sequences present at an allelic sensitivity level of $5x10^{-5}$.

Indications for Testing

» Identify tumor-specific markers for post-treatment monitoring
» Monitor and evaluate disease recurrence

Interpretation

An interpretive report will be issued indicating whether *FLT3* ITD MRD was detected

Turnaround Time

7 to 10 business days

Specimen Requirements

1-3 mL of peripheral blood in EDTA
0.25-1 mL of bone marrow in EDTA
1 µg of previously isolated DNA

Shipping Conditions

Ambient or Cool; do not freeze (peripheral blood or bone marrow)
Ambient or frozen on dry ice (isolated DNA)

Specimen Stability

2-8 °C up to 7 days prior to testing

References

1. The Cancer Genome Atlas Research Network (2013) Genomic and Epigenomic Landscapes of Adult De Novo Acute Myeloid Leukemia. *N Engl J Med.* 368: 2059–2074.
2. Konig H. et al. (2015) Targeting *FLT3* to treat leukemia. *Expert Opin Ther Targets* 19:37-54.
3. Levis, M. J. et al (2018) A next-generation sequencing–based assay for minimal residual disease assessment in AML patients with *FLT3*-ITD mutations. *Blood Advances,* 2: 825-831.

AML – *NPM1* MRD Assay

Clinical Information

Measurable residual disease (MRD) detection in patients with leukemia is useful for the clinical management of disease, and can facilitate the development of new therapies.

Mutations in the nucleophosmin (*NPM1*) gene represent some of the most prevalent gene mutations in AML.[1] *NPM1* mutations predominantly occur in AML with normal cytogenetics and are of prognostic value, especially within the context of *FLT3* ITD mutations. Furthermore, because *NPM1* displays a homogeneous mutation pattern, this gene represents an attractive target for MRD monitoring.[2]

LabPMM's *NPM1* MRD test is a NGS-based, targeted, deep-sequencing assay that can be used to detect *NPM1* mutations that were previously identified in a primary sample. The sensitive assay reliably detects sequences present at 5 x 10^{-5}.

MRD detection by Next-Generation Sequencing has demonstrated utility in predicting clinical outcomes and in generating clinically actionable results, allowing early intervention, confirmation of disease status prior to transplant, and increased confidence in remission status.

Test Name

NPM1 MRD Assay

Assay Type

Next-Generation Sequencing (NGS)
CLIA-validated assay

Method Description

To track and identify previously detected *NPM1* mutations in post-treatment follow-up samples, a multiplex master mix targeting exon 12 on the *NPM1* gene is used to amplify DNA extracted from a patient sample. Next-generation sequencing of the PCR products is used to identify DNA sequences specific to previously identified mutations detected at diagnosis. Bioinformatics tools facilitate the detection of these specific sequences present at an allelic sensitivity level of 5x10^{-5}.

Indications for Testing

» Identify tumor-specific markers for post-treatment monitoring
» Monitor and evaluate disease recurrence

Interpretation

An interpretive report will be issued indicating whether *NPM1* ITD MRD was detected

Turnaround Time

7 to 10 business days

Specimen Requirements

1–3 mL of peripheral blood in EDTA
0.25–1 mL of bone marrow in EDTA
1 µg of previously isolated DNA

Shipping Conditions

Ambient or Cool; do not freeze (peripheral blood or bone marrow)
Ambient or frozen on dry ice (isolated DNA)

Specimen Stability

2–8 °C up to 7 days prior to testing

References

1. Falini B. et al. (2005) Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. *N Engl J Med* 352:254–266.

2. Krönke J. et al. (2011) Monitoring of minimal residual disease in *NPM1*-mutated acute myeloid leukemia: a study from the German-Austrian acute myeloid leukemia study group. *J Clin Oncol* 29:2709–2716.

B-cell MRD Assay

Clinical Information

Combinations of chemotherapy, radiation therapy and bone marrow transplantation are potentially curative for several hematologic malignancies. However, in some patients, occult tumor cells exist and are thought to increase the patient's risk of relapse.[1]
These subclinical levels of residual leukemia are termed measurable residual disease (MRD) and can be evaluated using more sensitive assays. The tracking of antigen-receptor gene rearrangements for clonality analyses and MRD monitoring can be applied to virtually all patients. During early B-cell development, the germline variable (V_H), diverse (D_H), and joining (J_H) fragments of the human immunoglobulin heavy chain (*IGH*) locus become rearranged through the random deletion or insertion of nucleotides within the junctional region, generating specific and unique sequences within each lymphocyte. Cancer cells that arise from alterations in single lymphoid precursors acquire clonal *IGH* junctional regions, which can be used as tumor-specific markers.[2,3] MRD detection by Next-Generation Sequencing has demonstrated utility in predicting clinical outcomes and in generating clinically actionable results, allowing early intervention, confirmation of disease status prior to transplant, and increased confidence in remission status.

Test Name

B-cell MRD Assay

Assay Type

Next-Generation Sequencing (NGS)
CAP/CLIA-Validated

Method Description

Clonal B-cell gene rearrangement sequences identified at diagnosis, are used to track post-treatment / follow-up samples for measurable residual disease (MRD) status. A multiplex master mix targeting the conserved framework region 1 (FR1) or framework region 3 (FR3), and the joining region is used for PCR amplification. Next generation sequencing of the PCR products is used to identify and track FR1 and/or FR3 clonal sequences that were previously identified at diagnosis. Bioinformatics tools facilitate the detection of these specific sequences present at MRD levels up to 1 x 10^{-6} with sufficient DNA input.

The assay typically requires a sample taken at diagnosis as well as the post-treatment follow-up samples. If the patient has previously been tested by LabPMM for *IGH* clonality, no diagnostic sample is needed.

Indications for Testing

» Identify tumor-specific gene rearrangement sequences for post-treatment monitoring in:
  - Multiple Myeloma
  - Chronic Lymphocytic Leukemia (CLL)
  - Mantle Cell Lymphoma (MCL)
  - Acute Lymphocytic Leukemia (ALL)

» Monitor and evaluate for refractory and relapsed disease

Interpretation

An interpretive report will be issued indicating whether *IGH* MRD was detected.

Turnaround Time

14 to 21 business days

Specimen Requirements

1-2 mL of peripheral blood in EDTA or Heparin
1-2 mL of bone marrow in EDTA or Heparin
0.5 - 20 µg of previously isolated DNA depending on level of sensitivity required

Shipping Conditions

Peripheral Blood: Ambient or Cool; do not freeze
Bone Marrow**: Ambient, cool or frozen on dry ice
Isolated DNA: Ambient or frozen on dry ice

Specimen Stability

15 to 30 °C for up to 3 days
2 to 8 °C up to 7 days
-15 to -30 °C for up to 3 months

References

1. Rezuke, WN et al. (1997) *Clinical Chemistry.* 43:1814-23.
2. Gazzola, A et al. (2014) *Therapeutic Advances in Hematology.* 5:35-47.
3. González, D et al. (2007) *Blood.* 110:3112-21.

If less than 20 µg is provided, the sensitivity of the assay may be impacted.

** Ambient bone marrow may limit the sensitivity that can be achieved.

T-cell MRD Assay

Clinical Information

Combinations of chemotherapy, radiation therapy and bone marrow transplantation are potentially curative for several hematologic malignancies. However, in some patients, occult tumor cells exist and are thought to increase the patient's risk of relapse.[1] These subclinical levels of residual leukemia are termed measurable residual disease (MRD) and can be evaluated using sensitive assays. The tracking of antigen-receptor gene rearrangements for clonality analyses and MRD monitoring can be applied to virtually all patients. During early T-cell development, the germline variable (V_γ), constant (C_γ), and joining (J_γ) fragments of the T-cell receptor gamma (*TRG*) and T-cell receptor beta loci become rearranged through the random deletion or insertion of nucleotides within the junctional region, generating specific and unique sequences within each lymphocyte. Cancer cells that arise from alterations in single lymphoid precursors acquire clonal *TRB* and/or *TRG* junctional regions which can be used as tumor-specific markers.[2,3] MRD detection by Next-Generation Sequencing has demonstrated utility in predicting clinical outcomes and in generating clinically actionable results, allowing early intervention, confirmation of disease status prior to transplant, and increased confidence in remission status.

Test Name

T-cell MRD Assay

Assay Type

Next-Generation Sequencing (NGS)
Research Use Only (RUO)

Method Description

Clonal T-cell (*TRG* or *TRB*) gene rearrangement sequences identified at diagnosis, will be used to track post-treatment / follow-up samples for measurable residual disease (MRD) status. Multiplex master mixes targeting the Vγ and the Jγ region are used for PCR amplification.

Next-generation sequencing of the PCR products is used to identify and track *TRG* and/or *TRB* clonal frequencies that were previously identified. Share clonal rearrangements detected at diagnosis. Bioinformatics tools facilitate the detection of these specific sequences present at MRD levels up to 1×10^{-6} with sufficient DNA input.
The assay typically requires a sample taken at diagnosis as well as the post-treatment follow-up samples. If the patient has previously been tested by LabPMM for clonality, no diagnostic sample is needed.

Indications for Testing

» Identify tumor-specific markers for post-treatment monitoring
» Monitor and evaluate for refractory and relapsed disease

Specimen Requirements

1-3 mL of peripheral blood in EDTA or Heparin
0.25-1 mL of bone marrow in EDTA or Heparin
0.7 - 20 µg of previously isolated DNA depending on level of sensitivity required

Shipping Conditions

Ambient or Cool; do not freeze (peripheral blood or bone marrow)
Ambient or frozen on dry ice (isolated DNA)

Specimen Stability

2 to 8 °C up to 7 days prior tot testing

References

1. Rezuke, WN et al. (1997) *Clinical Chemistry.* 43:1814-23.
2. Gazzola, A et al. (2014) *Therapeutic Advances in Hematology.* 5:35-47.
3. González, D et al. (2007) *Blood.* 110:3112-21.

* If less than 20 µg is provided, the sensitivity of the assay may be impacted.

NGS Cancer Panels

Cytogenetic identification of chromosome abnormalities has become essential for the clinical management of patients with leukemia, and it is currently used to help classify patients into risk groups. With the development of novel genomics technologies, such as Next-Generation Sequencing, numerous new mutations and gene expression signatures have been identified. These breakthroughs allow us to better understand the molecular heterogeneity of hematologic diseases and to better stratify and assess risk for cancer patients.

Using these molecular tools, it has become evident that leukemias, lymphomas, and hematologic diseases are characterized by a remarkable amount of genetic heterogeneity, with individual patients presenting distinct and almost unique combinations of chromosome changes and somatically-acquired gene mutations.

LabPMM offers comprehensive NGS gene panels for AML and other hematological malignancies. Our MyAML® cancer panel is designed to analyze and interpret sequence information in genes known or suspected to be involved in AML and other hematologic diseases. This comprehensive assay is capable of detecting single nucleotide substitutions, insertions, deletions, and gene rearrangements.

Our MyMRD® panel was designed to sensitively capture all classes of variants identified in a precisely defined set of targets that commonly drive myeloid malignancies including AML, MPN, and MDS.

Our MyAML and MyMRD cancer panels are aimed at promoting a broader understanding of patients' clinical responses and outcomes. Panels run at the time of diagnosis identify both clinically-actionable driver mutations associated with the primary tumor, as well as the subclonal architecture that may be present. Temporal specimens collected and tested during the course of treatment identify the loss or elimination of driver mutations, as well as emergence or re-emergence of new clones and new potential therapeutic targets.

MyAML®

Clinical Information

Understanding the clonal architecture of AML patients is vital for successful treatments.[1] Many different mutations, epigenetic aberrations, or downstream abnormalities can generate the same clinical treatment plan. However, these differences are responsible for the variable responses observed with therapy, which is a major feature in patients with AML.[2] Therefore, since varied somatic mutations affect patient outcomes, conventional genotyping is no longer the most suitable method for screening patients.

MyAML is a CLIA-validated assay that identifies clinically actionable, pathogenic, and potentially pathogenic mutations in 194 genes associated with AML. Using the latest version in Next-Generation Sequencing chemistry,

MyAML identifies all somatic mutations, large and small insertions/deletion, and translocations under NCCN/ELN guidelines, as well as novel somatic variants that may have prognostic significance for AML.

Screening with MyAML allows informed treatment decisions to be made once all the relevant mutations are known, both in the prevalent clones, as well as the 'secondary' or 'tertiary' clones, which could become the new prominent clones leading to refractory and relapsed disease.

List of Genes on the MyAML Panel

Structural Rearrangements: Inv(16) t(16;16) t(8;21) t(15;17) t(9;11) inv(3) t(3;3) t(6;9) t(9;22)

Genes: *CEBPA DNMT3A FLT3 IDH1 IDH2 KIT NPM1*

Other Fusions and Gene Rearrangements: *ABL1 ADGRG7 AFF1 BCR CBFB CREBBP DEK EIF4E2 ELL ETV6 GAS6 GAS7 KAT6A KAT6B KMT2A MECOM MKL1 MLLT10 MLLT1 MLLT3 MLLT4 MYH11 NSD1 NUP214 NUP98 PICALM PML RARA RBM15 RPN1 RUNX1 RUNX1T1 SEPT5 SET TFG TMEM255B*

Other Genes: *ABCC1 ACVR2B ADRBK1 AKAP13 ANKRD24 ARID2 ARID4B ASXL1 ASXL2 ASXL3 BCOR BCORL1 BRINP3 BRPF1 BUB1 CACNA1E CBL CBX5 CBX7 CDC73 CEP164 CPNE3 CSF1R CSTF2T CTCF CYLD DCLK1 DDX1 DDX23 DHX32 DIS3 DNAH9 DNMT1 DNMT3B DYRK4 EED EGFR EP300 EPHA2 EPHA3 ETV3 EZH2 FANCC GATA1 GATA2 GFI1 GLI1 HDAC2 HDAC3 HNRNPK HRAS IKZF1 JAK1 JAK2 JAK3 JMJD1C KDM2B KDM3B KDM6A KDM6B KMT2B KMT2C KRAS MAPK1 METTL3 MST1R MTA2 MTOR MXRA5 MYB MYC MYLK2 MYO3A NF1 NOTCH1 NOTCH2 NRAS NRK OBSCN PAPD5 PAX5 PDGFRA PDGFRB PDS5B PDSS2 PHF6 PKD1L2 PLRG1 POLR2A PRDM16 PRDM9 PRKCG PRPF3 PRPF40B PRPF8 PTEN PTPN11 PTPN14 PTPRT RAD21 RBBP4 RBMX RPS6KA6 SAP130 SCML2 SETBP1 SETD2 SF1 SF3A1 SF3B1 SMC1A SMC3 SMC5 SMG1 SNRNP200 SOS1 SPEN SRRM2 SRSF2 SRSF6 STAG2 STK32A STK33 STK36 SUDS3 SUMO2 SUPT5H SUZ12 TCF4 TET1 TET2 THRB TP53 TRA2B TRIO TTBK1 TYK2 TYW1 U2AF1 U2AF1L4 U2AF2 UBA3 WAC WAPAL WEE1 WNK3 WNK4 WT1 ZBTB33 ZBTB7B ZRSR2*

Test Name

MyAML - NGS Gene Panel Assay

Assay Type

Next-Generation Sequencing (NGS)
CLIA-validated assay

Method Description

Using proprietary design, the coding regions and potential genomic breakpoints within known somatic gene fusions are sequenced to an average depth of coverage of 1000x. By utilizing long read lengths, the assay accurately detects and characterizes the breakpoints of structural variants and gene fusions, often with single base-pair precision. In addition, these long reads enhance the ability to identify both the insertion site and DNA content of large internal tandem duplications. Coupling comprehensive gene coverage with enhanced depth of coverage, long read lengths, and the power of our robust annotation software and bioinformatics database, MyAML identifies the underlying somatic mutations that are present as low as 5% allelic frequency. The data and report include single base resolution of the genomic breakpoint and sequences of mutations, facilitating optimized treatment plans and longitudinal tracking of measurable residual disease.

A completed patient consent form must be submitted for each sample sent to LabPMM.

Indications for Testing

» At initial diagnosis of AML
» Stratifying risk for AML
» Monitor and evaluate for refractory and relapsed disease

Interpretation

An interpretive report will be issued indicating the SNVs, indels, inversions and translocations identified

Turnaround Time

14 to 21 business days

Specimen Requirements

3 mL of peripheral blood in Heparin, EDTA or ACD
1 mL of bone marrow in Heparin, EDTA or ACD
Cell Pellets in cell culture media or buffered solutions without fixatives
1 µg of purified, high quality genomic DNA

Shipping Conditions

Ambient or Cool; do not freeze

Specimen Stability

Room Temp up to 72 hours
2-8 °C up to 7 days

References

1. Döhner K et al. (2014) Intermediate-risk acute myeloid leukemia therapy: current and future. *Hematology Am Soc Hematol Educ Program* 1,34-43.
2. Estey EH (2014) Acute myeloid leukemia: 2014 update on risk-stratification and management. *Am J Hematol* 89:1063-1081.

MyMRD®

Clinical Information

Measurable residual disease (MRD) detection has proven to be useful in the clinical management of patients with leukemia and can facilitate the development of new therapies.

Patients with myeloid neoplasms are typically divided into different prognostic groups based upon both cytogenetics and traditional molecular profiles;[1] however, this may not reflect the heterogeneity of disease[2] that can be exploited using MRD assessment. Moreover, multiple sampling is not feasible for many patients and thus the development of a sensitive and reliable assay to detect several mutations within one sample represents a significant advancement in guiding treatment decisions.

The MyMRD is a hotspot panel that detects all classes of variants identified in a precisely defined set of targets that commonly drive myeloid malignancies including AML, MPN and MDS. It can detect SNVs, indels and translocations to the genomic base pair, yielding unparalleled precision and detection of low level mutations in patients. The MyMRD assay, detects at least one driver mutation in 90%–95% of all AMLs. This gene panel is validated to a $5x10^{-3}$ level of detection for all targeted sites.

List of Genes on the MyMRD Panel

SNV and Indel Targets in Genes (Exons) (23 genes)

ASXL1 BRAF CALR CEBPA CSF3R DNMT3A FLT3 IDH1 IDH2 JAK2 KIT KMT2A KRAS MPL MYH11 NPM1 NRAS PTPN11 RUNX1 SF3B1 SRSF2 TP53 ZRSR2

Structural Variants (Translocations and Partial Tandem Duplications in Intronic Structures)

CBFB-MYH11 KMT2A RUNX1-RUNX1T1

Test Name

MyMRD - NGS Gene Panel Assay

Assay Type

Next-Generation Sequencing (NGS)
CLIA-validated assay

Method Description

Indexed whole-genome libraries are hybridized with MyMRD probes targeting mutation hotspots in a total of 23 genes (*ASXL1 BRAF CALR CEBPA CSF3R DNMT3A FLT3 IDH1 IDH2 JAK2 KIT KRAS MPL NPM1 NRAS PTPN11 RUNX1 SF3B1 SRSF2 TP53 ZRSR2 CBFB-MYH11 KMT2A RUNX1-RUNX1T1*). In addition to targeting single nucleotide variants (SNVs) and indels in the first 21 genes, 5 structural variant breakpoints within the final 3 genes are also targeted. Coupling comprehensive gene coverage with enhanced depth of coverage, long read lengths, and the power of our robust MyInformatics® annotation software and bioinformatics database, MyMRD confidently and reproducibly detects mutations with a mutant allele frequency of $5x10^{-3}$, while some mutations, such as *FLT3* ITDs, are detected at mutation allele frequencies as low at $1x10^{-3}$.

A completed patient consent form must be submitted for each sample sent to LabPMM.

Indications for Testing

» Identify tumor-specific markers for post-treatment monitoring
» Monitor and evaluate for refractory and relapsed disease

Interpretation

An interpretive report will be issued indicating the detected pathogenic mutations and their frequencies in the interrogated sample.

Turnaround Time

14 to 21 business days

Specimen Requirements

3 mL of peripheral blood in Heparin, EDTA or ACD
1 mL of bone marrow in Heparin, EDTA or ACD
1 µg of purified, high quality genomic DNA

Shipping Conditions

Ambient or Cool; do not freeze

Specimen Stability

Room Temp up to 72 hours
2-8 °C up to 7 days

References

1. Arber, DA et al. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*, 127(20):2391-2405.
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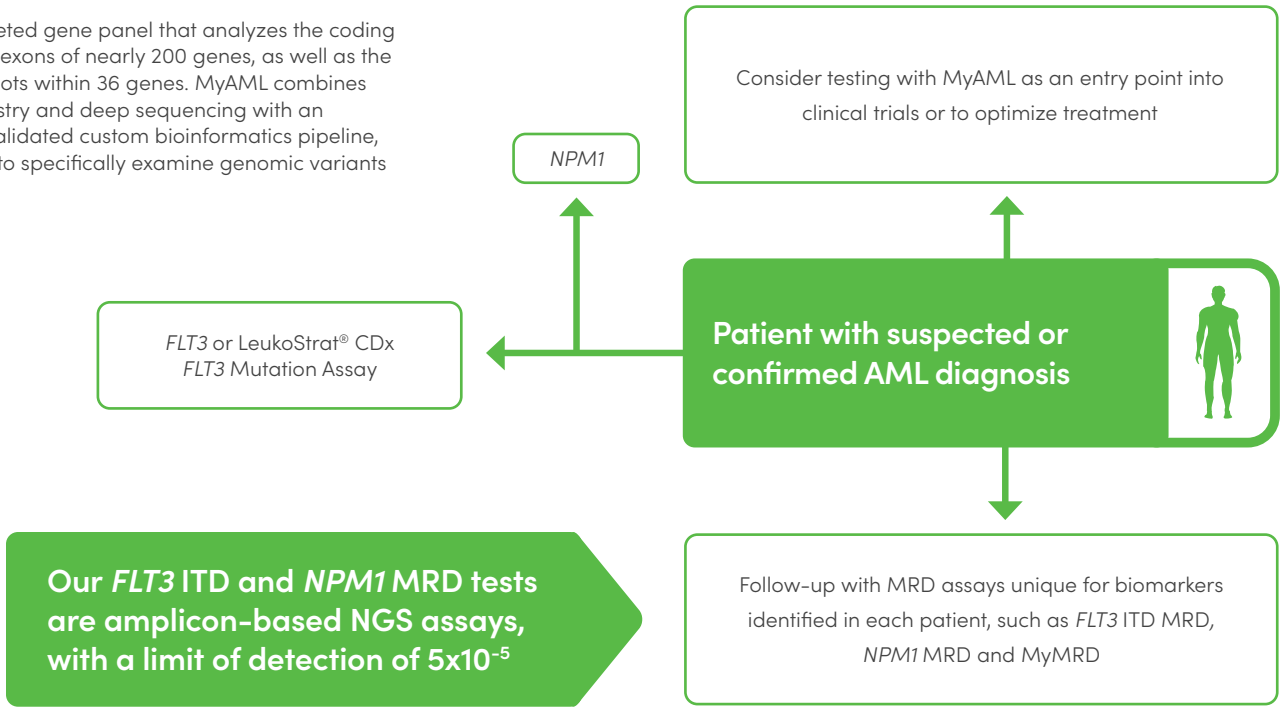
LabPMM Assay Guidelines

MyAML®

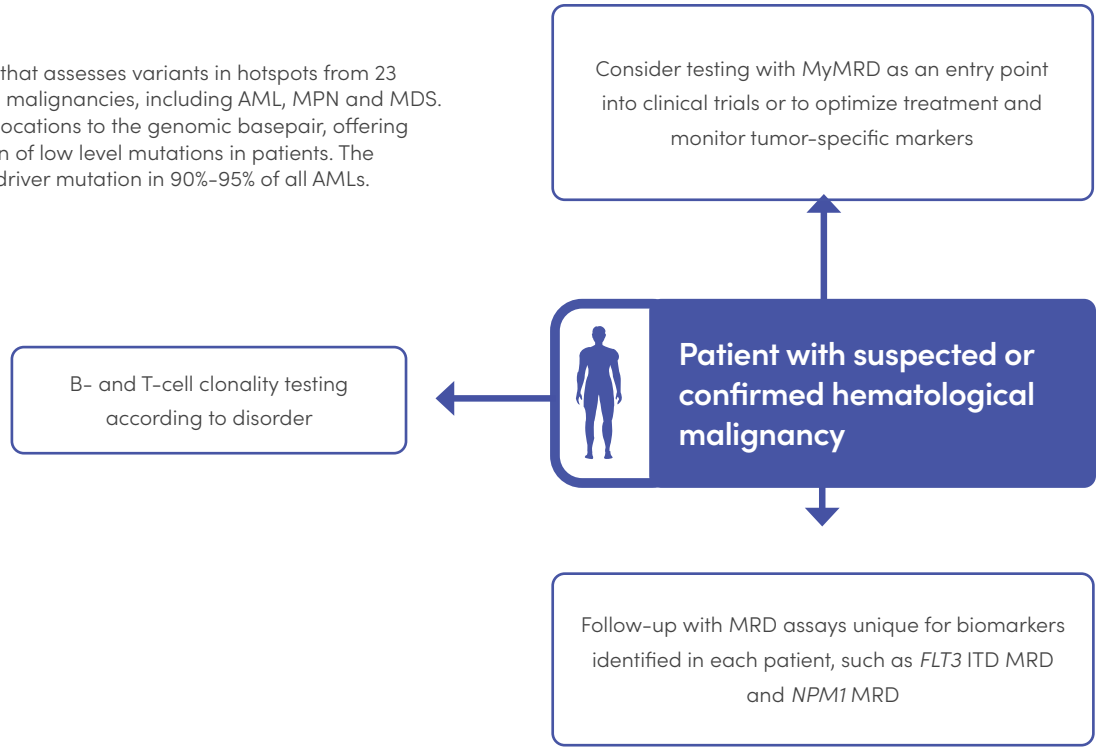
MyAML is a targeted gene panel that analyzes the coding and non-coding exons of nearly 200 genes, as well as the breakpoint hotspots within 36 genes. MyAML combines long read chemistry and deep sequencing with an optimized and validated custom bioinformatics pipeline, MyInformatics®, to specifically examine genomic variants in AML patients.



Our *FLT3* ITD and *NPM1* MRD tests are amplicon-based NGS assays, with a limit of detection of $5x10^{-5}$

MyMRD®

The MyMRD is a NGS-based panel that assesses variants in hotspots from 23 genes that commonly drive myeloid malignancies, including AML, MPN and MDS. It can detect SNVs, indels, and translocations to the genomic basepair, offering unparalleled precision and detection of low level mutations in patients. The MyMRD assay detects at least one driver mutation in 90%-95% of all AMLs.



MyAML and MyMRD are CLIA validated assays.

Multiparametric Flow Cytometry

Multiparametric Flow Cytometry (MFC) is a diverse technology platform with many clinical applications. One application of MFC is the ability to evaluate individual cells in suspension for the presence and absence of specific antigens and can be used to characterize disease in a clinical setting. The technology plays a critical role in the evaluation of peripheral blood and bone marrow samples for screening, diagnosis, prognosis and classification of many hematolymphoid neoplasia, including AML. Immunophenotyping white blood cells allows for the identification of normal and abnormal cell phenotypes which can identify normal cell populations, lymphoid neoplasia, plasma cell dyscrasia, acute leukemia and other disease of various cell lineages. MFC in the clinical setting now allows for >12 parameters to be simultaneously measured and analyzed and can provide rapid and actionable results for clinical decision making.

Another application of MFC includes measurable residual disease (MRD) testing. MRD testing by MFC can detect disease levels down below 10-4 and can provide information about remission status, outcome prediction, early identification of relapse and as a potential surrogate end point to accelerate drug testing and approvals.

Hematolymphoid Screening Panel - MFC

Clinical Information

The 10-color Hematolymphoid Screening Panel provides a comprehensive approach for evaluating bone marrow and peripheral blood samples for the presence or absence of hematolymphoid malignancies. The panel characterizes and identifies all major white blood cell lineages and identifies all major types of hematopoietic neoplasia. Biomarker selection follows the 2006 Bethesda Consensus[1] for immunophenotypic analysis of hematolymphoid neoplasia with additions chosen by our internal hematopathologist based on recent literature including the 2017 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.[2-8]

This panel not only provides evaluation and monitoring of patients with hematological malignancy but provides a wide array of applications due to its comprehensive biomarker selection.

Biomarkers in the Screening Panel

CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD20, CD23, CD33, CD34, CD38, CD45, CD56, CD57, CD64, CD71, CD117, CD123, HLA-DR, Kappa, Lambda, and *TCR* Gamma/Delta.

Test Name

Hematolymphoid Screening Panel

Assay Type

Multiparametric Flow Cytometry (10-color)
CAP/CLIA-validated

Method Description

Immunophenotyping-Lyse/Wash/Stain

Indications for Testing

» Classifying Acute Leukemia
» Diagnosing and Classifying B cell Disorders
» Evaluating T cell and NK disorders
» Evaluating Plasma Cell Dyscrasias

Interpretation

An interpretive report will indicate the presence/absence of normal and abnormal cell populations and their associated immunophenotypic profile.

Turnaround Time

24-48 hours

Specimen Requirements

2-4 mL of peripheral blood in EDTA or Sodium Heparin
2-4 mL of bone marrow in EDTA or Sodium Heparin

Shipping Conditions

Ambient or Cool; do not freeze

Specimen Stability

Specimens should be stored at 2-8°C and must be received by the lab within 48 hours after draw

References

1. BL Wood et al., *Cytometry B Clin Cytom.* 72:S14-S22 (2007).
2. FE Craig et al., *Blood.* 111(8):3941-67 (2008).
3. BL Wood. *Arch Pathol Lab Med.* 130:680-90 (2006).
4. SH Swerdlow et al., WHO Classification of Tumours, Revised 4th Edition, Volume 2 (2017)
5. CLSI H43: Clinical Flow Cytometric Analysis of Neoplastic Hematolymphoid Cells, 2nd Edition
6. JJ Van Dongen et al., *Leukemia.* 26(9):1908-75 (2012).
7. A Porwit and A Rajab. *Int. Jnl. Lab. Hem.,* 37:133-143 (2015).
8. Sheikholeslami et al., *Methods in Molecular Biology.* 378. 53-63. 10.1007/978-1-59745-323-3_4 (2007).

AML MRD Assay - MFC

Clinical Information

Measurable residual disease, also called "minimal residual disease" (MRD) refers to persistent leukemic cells in the blood or bone marrow of cancer patients during or after treatment. Undetected or untreated MRD is a main cause of cancer recurrence hence sensitive MRD tests are necessary for guiding optimal treatment programs and providing a prognostic indicator for risk stratification of treated patients.

Multi-parameter Flow Cytometry (MFC) is a widely accepted platform for assessing MRD in patients with Acute Myeloid Leukemia (AML) and can be performed within a short period of time. In our lab we utilize a comprehensive panel of antibody markers to characterize potential AML blast cells using a LAIP based different from normal (DfN) approach. This approach takes into account information from diagnosis, if available but also identifies aberrant cells that have differentiated from normal maturation without previous patient history.

Using a comprehensive selection of antibodies and a standardized panel across all testing points, MRD populations can be characterized and tracked down to 0.01% sensitivity. Utilizing up to 12 biomarkers per tube allows for the identification of more LAIPS with less sample than previously was available before.

This panel not only provides evaluation and monitoring of patients with hematological malignancy but provides a wide array of applications due to its comprehensive biomarker selection.

Biomarkers in AML MRD Assay

CD2, CD4, CD5, CD7, CD11b, CD13, CD14, CD15, CD16, CD19, CD33, CD34, CD36, CD38, CD45, CD 56, CD64, CD117, CD123, HLADR, 7AAD

Test Name

AML MRD Assay by MFC

Assay Type

Multiparametric Flow Cytometry (12-color)
CAP/CLIA-validated

Method Description

12-color Multiparametric Flow Cytometry with a 0.01% sensitivity

Indications for Testing

- Identify tumor-specific markers for post-treatment monitoring
- Clinical trial enrollment and surrogate endpoint in trials
- Monitor and evaluate for disease relapse and recurrence
- Monitor response to therapy

Interpretation

An interpretive report will indicate the presence/absence of AML cell populations, level of detection in relation to the clinical cutoff, percent and number of aberrant myeloblasts and their associated immunophenotypic profile.

Turnaround Time

24-48 hours

Specimen Requirements

2-4 mL of peripheral blood in EDTA or Sodium Heparin
2-4 mL of bone marrow in EDTA or Sodium Heparin

Shipping Conditions

Ambient or Cool; do not freeze

Specimen Stability

Specimens should be stored at 2-8°C and must be received by the lab within 48 hours after draw

References

1. Schuurhuis, Gerrit J et al. "Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party." *Blood* vol. 131,12 (2018): 1275-1291. doi:10.1182/blood-2017-09-801498NCCN
2. Wood BL. Acute Myeloid Leukemia Minimal Residual Disease Detection: The Difference from Normal Approach.Curr Protoc Cytom. 2020 Jun;93(1):e73. doi: 10.1002/cpcy.73.PMID: 32311834
3. Cloos J, Harris JR, Janssen JJWM, Kelder A, Huang F, Sijm G, Vonk M, Snel AN, Scheick JR, Scholten WJ, Carbaat-Ham J, Veldhuizen D, Hanekamp D, Oussoren-Brockhoff YJM, Kaspers GJL, Schuurhuis GJ, Sasser AK, Ossenkoppele G. Comprehensive Protocol to Sample and Process Bone Marrow for Measuring Measurable Residual Disease and Leukemic Stem Cells in Acute Myeloid Leukemia. *J Vis Exp.* 2018 Mar 5;(133):56386. doi: 10.3791/56386.PMID: 29553571
4. Short NJ, Ravandi F. How close are we to incorporating measurable residual disease into clinical practice for acute myeloid leukemia? *Haematologica.* 2019 Aug;104(8):1532-1541. doi: 10.3324/ haematol.2018.208454. Epub 2019 Jul 4. PMID: 31273094; PMCID: PMC6669140.
5. Zeijlemaker W, Kelder A, Cloos J, Schuurhuis GJ. Immunophenotypic Detection of Measurable Residual (Stem Cell) Disease Using LAIP Approach in Acute Myeloid Leukemia *Curr Protoc Cytom.* 2019 Dec;91(1):e66. doi: 10.1002/cpcy.66.PMID: 31763792 .
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CLL MRD Assay – MFC

Clinical Information

The global burden of chronic lymphocytic leukemia (CLL) has increased over the past 30 years by approximately 7%, with a higher incidence among men and adults over 65.[1,2,3] Moreover, CLL is the most prevalent type of leukemia, comprising of 25% – 30% of all leukemias in Western populations[4,5], indicating potential heredity.[6,7] While this disease has not experienced the same innovative therapeutic boon as AML, new treatment strategies have recently become available, including targeted inhibitors—which necessitate a sensitive, objective confirmation of treatment response. MRD (measurable residual disease, or often referred to as minimal residual disease) is a sensitive indicator of disease burden during and after fixed-duration treatment. MRD has been correlated with progression free survival (PFS) and overall survival (OS)[8] and is an independent prognostic indicator in patients with CLL.

Flow cytometry has long been the standard of care for management of many blood cancers including CLL[9], however, achieving MRD level sensitivity for detection of disease with limited sample requires a technique with a higher level of complexity, such as multiparametric flow cytometry (MFC). MFC is a state-of-the-art method for MRD assessment that is widely used because it is highly sensitive, fast and cost-effective.[10]

The CLL MRD Assay is an extensive 11-color MFC panel targeting CLL-specific biomarkers designed to characterize potential CLL cells with clear separation from other B-lineage cells. The design of this assay allows several key functions:

- Using a standardized panel across all time points, MRD populations can be characterized and tracked to 0.005% sensitivity
- Alignment with International Harmonized Approach[9,10,11] and ERIC protocol[9,11]
- Designed to work with Peripheral Blood and Bone Marrow specimens
- Optimize shared/limited samples by co-testing with MFC and NGS

Biomarkers in CLL MRD Assay

CD81, CD79b, CD22, CD19, CD43, CD200, CD20, CD5, CD3, CD38, CD40, 7AAD

Test Name

CLL MRD Assay by MFC

Assay Type

Multiparametric Flow Cytometry (11-color)
CAP/CLIA-validation Planned

Method Description

11-color Multiparametric Flow Cytometry with a sensitivity of 0.005% – 0.002%.

Indications for Testing

- Identify tumor-specific immunophenotypes for post-treatment monitoring and evaluation for relapse
- Stratify patient risk and streamline clinical trial enrollment
- Use as a potential surrogate endpoint in clinical trials

Interpretation

An interpretive report will indicate the presence/absence of CLL MRD in relation to the level of detection of assay and the clinical cut-off value.

Turnaround Time

24-48 hours

Specimen Requirements

2-4 mL of peripheral blood in EDTA or Sodium Heparin
2-4 mL of bone marrow in EDTA or Sodium Heparin

Shipping Conditions

Ambient or Cool; do not freeze

Specimen Stability

Specimens should be stored at 2-8°C and must be received by the lab within 48 hours after draw

References

1. Y Dong et al. *Exp Hematol Oncol* 9, 14 (2020). https://doi.org/10.1186/s40164-020-00170-6
2. WG Wierda et al. *Leukemia* 35, 3059–3072 (2021). https://doi.org/10.1038/s41375-021-01241-1
3. Y Ou et al. *Frontiers in Oncology* 12, 840616 (2022). https://doi.org/10.3389/fonc.2022.840616
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Invivoscribe's wholly-owned Laboratories for Personalized Molecular Medicine® (LabPMM) is a network of international reference laboratories that provide the medical and pharmaceutical communities with worldwide access to harmonized and standardized clinical testing services. We view internationally reproducible and concordant testing as a requirement for consistent stratification of patients for enrollment in clinical trials, and the foundation for establishing optimized treatment schedules linked to patient's individual profile.

LabPMM provides reliable patient stratification at diagnosis and monitoring, throughout the entire course of treatment in support of Personalized Molecular Medicine® and Personalized Molecular Diagnostics®.

Invivoscribe currently operates four clinical laboratories to serve partners in the USA (San Diego, CA), Europe (Munich, Germany), and Asia (Kawasaki, Japan and Shanghai, China). These laboratories use the same critical reagents and software which are developed consistently with ISO 13485 design control. Our cGMP reagents, rigorous standards for assay development & validation, and testing performed consistently under ISO 15189 requirements help ensure LabPMM generates standardized and concordant test results worldwide.

LabPMM is an international network of PersonalMed Laboratories® focused on flow cytometry and molecular oncology biomarker studies.

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