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MOLECULAR DIAGNOSTICS IN ACUTE LEUKEMIA: A PRACTICAL GUIDE TO RISK STRATIFICATION AND TARGETED TREATMENT

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ABSTRACT

The integration of molecular diagnostics into routine clinical practice has fundamentally transformed the management of acute leukemias over the past decade. Next-generation sequencing technologies have enabled comprehensive genomic profiling that refines prognostic stratification, guides selection of targeted therapies, and enables monitoring of measurable residual disease. This review synthesizes current evidence on the role of molecular diagnostics in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), focusing on clinically relevant genetic alterations including FLT3, IDH1/2, NPM1, KMT2A rearrangements, and Philadelphia chromosome-like ALL. We examine how molecular findings inform risk stratification according to European LeukemiaNet guidelines, predict response to targeted inhibitors, and identify resistance mechanisms. Additionally, we discuss practical considerations for implementing molecular testing in clinical workflows, including optimal specimen types, testing platforms, turnaround time requirements, and interpretation of results by molecular tumor boards. Finally, we explore emerging applications of liquid biopsy for disease monitoring and early detection of relapse. As the therapeutic armamentarium expands, seamless integration of molecular diagnostics into clinical decision-making is essential to deliver precision medicine and improve outcomes for patients with acute leukemia.

KEYWORDS: Acute myeloid leukemia; acute lymphoblastic leukemia; molecular diagnostics; targeted therapy; risk stratification; next-generation sequencing; FLT3 inhibitors; IDH inhibitors; measurable residual disease.

1. INTRODUCTION

Acute leukemias comprise a heterogeneous group of hematologic malignancies characterized by clonal expansion of immature hematopoietic progenitors. For decades, treatment decisions relied primarily on morphology, immunophenotyping, and conventional cytogenetics. However, the past decade has witnessed a paradigm shift toward molecularly informed precision medicine, driven by high-throughput sequencing technologies that have elucidated the genomic landscape of acute leukemias.[1,2]

The integration of molecular diagnostics into clinical practice now enables:

1. **Refined risk stratification**: Molecular alterations define prognostic subgroups that inform treatment intensity and transplant decisions.
2. **Targeted therapy selection**: Actionable mutations guide the use of molecularly targeted agents.
3. **Resistance mechanism identification**: Serial molecular profiling reveals mechanisms of acquired resistance.

4. **Measurable residual disease monitoring**: Sensitive molecular assays detect persistent disease below morphologic thresholds.

This review provides a comprehensive update on the integration of molecular diagnostics into clinical practice for acute leukemias, emphasizing practical considerations for implementation and the therapeutic implications of genomic findings.

2. Molecular Diagnostics: Platforms and Practical Considerations

2.1 Testing Platforms

The choice of molecular testing platform depends on clinical context, required turnaround time, and available resources (Table 1).

Table 1: Comparison of Molecular Testing Platforms for Acute Leukemia.

Platform	Advantages	Limitations	Clinical Applications
Conventional karyotyping	Genome-wide view, identifies novel abnormalities	Low resolution, requires viable cells, 7-14 days	Initial diagnosis, complex karyotype
FISH	Rapid (24-48 hours), targeted	Limited to preselected loci	Rapid detection of recurrent abnormalities
RT-PCR	Highly sensitive, rapid	Detects only known fusions	MRD monitoring, rapid fusion detection
Targeted NGS panels	Comprehensive, 7-10 days turnaround	Limited to panel genes	Initial workup, resistance mutation detection
Whole exome/genome sequencing	Unbiased, research applications	Cost, turnaround time, bioinformatics demands	Clinical trials, undiagnosed cases
RNA sequencing	Detects novel fusions, expression profiling	Bioinformatics expertise required	Fusion detection in Ph-like ALL

2.2 Specimen Requirements and Turnaround Time

Optimal molecular testing requires adequate specimens with sufficient tumor cellularity. Bone marrow aspirate remains the preferred specimen, though peripheral blood with adequate blast counts may suffice.[3] Key considerations include:

- **Cellularity requirements**: Most NGS platforms require 10-20% blast percentage for reliable mutation detection.
- **Turnaround time**: Results should be available within 7-10 days to inform initial treatment decisions.
- **Dual testing**: Both DNA and RNA-based testing may be required to detect fusions not identifiable by DNA sequencing alone.

2.3 Molecular Tumor Boards

The complexity of genomic data necessitates multidisciplinary interpretation. Molecular tumor boards (MTBs) integrating hematopathologists, molecular geneticists, hematologists, and clinical pharmacists facilitate:

- Distinguishing driver from passenger mutations
- Identifying targetable alterations
- Recognizing germline predispositions requiring genetic counseling
- Recommending appropriate matched therapies or clinical trials.[4]

3. Molecular Risk Stratification in Acute Myeloid Leukemia

3.1 ELN 2022 Classification

The European LeukemiaNet (ELN) 2022 guidelines integrate molecular findings with cytogenetics to define three risk categories.[5] Key molecular determinants include:

Favorable Risk

- NPM1 mutation without FLT3-ITD
- CEBPA biallelic mutations
- RUNX1::RUNX1T1, CBFB::MYH11, or KMT2A::MLLT3 fusions

Intermediate Risk

- NPM1 mutation with FLT3-ITD
- Wild-type NPM1 with FLT3-ITD
- Myelodysplasia-related gene mutations (ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2)

Adverse Risk

- TP53 mutations
- KMT2A rearrangements other than KMT2A::MLLT3
- Complex karyotype
- RUNX1, ASXL1, or BCOR mutations

3.2 NPM1 Mutations

NPM1 mutations represent the most common molecular alteration in AML (~30% of adults) and confer favorable prognosis in the absence of FLT3-ITD.[6] Key clinical implications:

- NPM1-mutated AML exhibits unique biology with HOX gene dysregulation
- FLT3-ITD co-occurrence modifies prognosis based on allelic ratio (though ELN 2022 omits allelic ratio)
- NPM1 mutations are ideal MRD targets due to stability and absence in normal hematopoiesis

- Clearance of NPM1 mutations predicts favorable outcomes

3.3 TP53 Mutations

TP53 mutations identify the most adverse risk group in AML, associated with:

- Complex karyotype and monosomal karyotype
- Therapy-related AML
- Resistance to conventional chemotherapy
- Poor outcomes even with allogeneic transplantation.[7]

Emerging therapeutic strategies include:

- APR-246 (eprenetapopt) to restore wild-type p53 function
- Magrolimab (anti-CD47) to enhance macrophage-mediated clearance
- Clinical trials combining these agents with hypomethylating agents.[8]

4. FLT3-Mutated AML: From Diagnostics to Targeted Therapy

4.1 FLT3 Mutation Types

FLT3 mutations occur in approximately 30% of AML and exist in two forms:

FLT3-ITD (internal tandem duplication): Duplications within the juxtamembrane domain (~20-25% of AML)

- Associated with leukocytosis and poorer prognosis
- Variable length and insertion site affect biology
- High allelic ratio historically conferred adverse prognosis

FLT3-TKD (tyrosine kinase domain): Point mutations at D835/I836 (~5-7% of AML)

- Less pronounced prognostic impact
- May co-occur with ITD or occur independently

4.2 FLT3 Inhibitors in Clinical Practice

Table 2: FDA-Approved FLT3 Inhibitors.

Inhibitor	Type	Activity	Approved Indications	Key Trials
Midostaurin	Type I	ITD + TKD	Newly diagnosed FLT3-mutated AML (with chemotherapy)	RATIFY.[9]
Gilteritinib	Type I	ITD + TKD	Relapsed/refractory FLT3-mutated AML	ADMIRAL.[10]
Quizartinib	Type II	ITD only	Newly diagnosed FLT3-ITD AML (with chemotherapy)	QuANTUM-First.[11]
Sorafenib	Type II	ITD only	Post-transplant maintenance for FLT3-ITD AML	SORMAIN.[12]

4.3 Resistance Mechanisms

Molecular diagnostics at relapse reveal distinct resistance mechanisms[13,14]:

On-target resistance

- Acquired FLT3-TKD mutations (particularly D835) in patients receiving type II inhibitors
- Gatekeeper mutations (F691L) conferring pan-FLT3 resistance
- Selection of clones with higher ITD allelic ratio

Off-target resistance

- Activation of alternative signaling pathways (RAS/MAPK pathway mutations in NRAS, KRAS, PTPN11)
- Emergence of clones with mutations in other genes (IDH1/2, WT1, RUNX1)
- BCR::ABL1 fusions reported after FLT3 inhibitor therapy

4.4 Clinical Implications

- Repeat molecular testing at relapse is essential to guide inhibitor selection
- Type I inhibitors preferred if TKD mutations emerge
- Combinations with venetoclax or MEK inhibitors under investigation to overcome resistance.
- Allogeneic transplantation remains important for durable disease control.

5. IDH-Mutated AML: Differentiation Therapy

5.1 IDH Mutation Biology

IDH1 (arginine 132) and IDH2 (arginine 140 or 172) mutations occur in 15-20% of AML.[15] Neomorphic enzyme activity produces 2-hydroxyglutarate (2-HG), an oncometabolite that:

- Inhibits α-ketoglutarate-dependent dioxygenases (including TET2)
- Induces DNA hypermethylation
- Blocks differentiation
- Creates BCL-2 dependence

5.2 IDH Inhibitors

Table 3: IDH Inhibitors in Clinical Practice.

Inhibitor	Target	Approved Indications	Key Trials
Ivosidenib	IDH1	R/R IDH1-mutated AML; newly diagnosed IDH1-mutated AML (ineligible for intensive chemo)	Phase 1[16]; AGILE[17]
Olutasidenib	IDH1	R/R IDH1-mutated AML	Phase 2[18]
Enasidenib	IDH2	R/R IDH2-mutated AML	Phase 1/2[19]

5.3 Resistance Mechanisms[20,21]

IDH-intrinsic mechanisms

- Second-site mutations in IDH1 or IDH2 (e.g., IDH2 Q316E, I319M at dimer interface)
- Isoform switching (emergence of IDH2 mutations during IDH1 inhibitor therapy)

IDH-extrinsic mechanisms

- Activation of RAS/MAPK pathway mutations (NRAS, KRAS, PTPN11)
- Myeloid transcription factor mutations (RUNX1, CEBPA, GATA2)
- Leukemia stem cell persistence

5.4 Combination Strategies

- IDH inhibitors with azacitidine improve response rates and survival in newly diagnosed patients.[17]
- Addition of venetoclax enhances depth of response
- Combinations with intensive chemotherapy under investigation.[22]

6. Molecular Diagnostics in Acute Lymphoblastic Leukemia

6.1 Genetic Subtypes of B-ALL

Next-generation sequencing has defined at least 23 distinct genetic subtypes of B-ALL with prognostic and therapeutic implications.[23,24]

Table 4: Clinically Relevant B-ALL Subtypes.

Subtype	Frequency	Key Genetic Features	Prognosis	Targeted Therapy Opportunities
Ph+ B-ALL	25% (adults)	BCR::ABL1 fusion	Poor (improved with TKIs)	TKIs (imatinib, dasatinib, ponatinib)
Ph-like ALL	20-30% (AYA)	CRLF2 rearrangements, JAK-STAT activating lesions, ABL-class fusions	Poor	JAK inhibitors (ruxolitinib), TKIs (dasatinib)
KMT2A-rearranged	10% (adults), 80% (infants)	KMT2A fusions (e.g., KMT2A::AF4, KMT2A::AF9)	Very poor	Menin inhibitors (revumenib, ziftomenib)
Hypodiploid B-ALL	<5%	Low hypodiploidy (31-39 chromosomes), near haploidy	Poor	BCL-2 inhibitors (venetoclax)
ETV6::RUNX1	25% (children)	t(12;21)	Favorable	Conventional chemotherapy
TCF3::PBX1	5%	t(1;19)	Intermediate	Conventional chemotherapy
DUX4-rearranged	5-10%	DUX4 fusions	Favorable	Conventional chemotherapy

6.2 Philadelphia Chromosome-Like ALL

Ph-like ALL represents a major advance in molecular classification with direct therapeutic implications[25,26]:

Key features

- Gene expression profile resembling Ph+ ALL without BCR::ABL1 fusion
- High frequency of IKZF1 deletions
- Activation of kinase signaling pathways

Targetable lesions

- **JAK-STAT pathway** (~50%): CRLF2 rearrangements, JAK2 fusions/mutations, EPOR rearrangements
- **ABL-class fusions** (~10-15%): ABL1, ABL2, PDGFRA, PDGFRB, CSF1R

- **RAS pathway** (~5-10%): KRAS, NRAS, PTPN11, NF1
- **Other kinases** (~5%): FLT3, FGFR1, NTRK3

Clinical implications
- Patients benefit from targeted therapy based on underlying fusion
- Ruxolitinib for JAK-STAT activating lesions
- Dasatinib, imatinib, or ponatinib for ABL-class fusions
- Larotrectinib for NTRK fusions
- Testing requires comprehensive fusion detection (RNA sequencing)

6.3 KMT2A-Rearranged Leukemia and Menin Inhibitors

KMT2A (formerly MLL) rearrangements define a high-risk subgroup[27,28]:
- Common in infant leukemia (80%) and therapy-related AML
- Multiple fusion partners (over 100 described)
- Menin essential for KMT2A fusion oncogenic activity

Menin inhibitors in clinical development
- Revumenib (SNDX-5613): Phase 1/2 studies show CR/CRh rates of 30% in heavily pretreated patients.[29]
- Ziftomenib (KO-539): Activity in NPM1-mutated and KMT2A-rearranged AML.[30]
- Differentiation syndrome observed as class effect
- QTc prolongation requiring monitoring

6.4 T-ALL Molecular Subtypes

T-ALL comprises distinct molecular subgroups[31,32]:
- **Early T-cell precursor (ETP) ALL**: Immature immunophenotype, stem cell-like signature, poor prognosis
- **NOTCH1/FBXW7-mutated**: Favorable prognosis in absence of RAS/PTEN mutations
- **HOXA family dysregulated**: Associated with KMT2A rearrangements or NUP214::ABL1
- **TLX1/TLX3-rearranged**: Distinct expression profiles

Targeted therapy options limited but emerging:
- Nelarabine for relapsed T-ALL
- BCL-2 inhibitors for ETP-ALL (BCL-2 dependent)
- Daratumumab (anti-CD38) under investigation

7. Measurable Residual Disease Monitoring

7.1 Role of MRD in Acute Leukemia

Measurable residual disease (MRD) represents the most powerful prognostic factor in both AML and ALL, predicting relapse and guiding treatment intensification.[33,34]

Clinical applications
- Post-induction risk stratification
- Timing of allogeneic transplantation
- Early detection of molecular relapse
- Endpoint for clinical trials

7.2 MRD Detection Methods

Table 5: Comparison of MRD Methods.

Method	Sensitivity	Advantages	Limitations	Applicability
Multiparameter flow cytometry	10^-4 to 10^-5	Widely available, applicable to most patients	Requires expertise, variable sensitivity	AML, ALL
RT-PCR for fusion transcripts	10^-5 to 10^-6	Highly sensitive, standardized	Requires known fusion (~40% of patients)	AML (NPM1, RUNX1::RUNX1T1, CBFB::MYH11), Ph+ ALL
NGS of immunoglobulin/TCR genes	10^-5 to 10^-6	Applicable to most B-ALL, standardized	Cost, turnaround time	B-ALL, T-ALL
Digital PCR for mutations	10^-4 to 10^-5	Rapid, quantitative	Limited to known mutations	AML (NPM1, IDH1/2)

7.3 MRD in AML

- **NPM1 mutations**: Ideal MRD target; persistence predicts relapse; clearance predicts favorable outcome.[35]
- **RUNX1::RUNX1T1 and CBFB::MYH11**: MRD monitoring guides preemptive therapy
- **FLT3-ITD**: Less suitable due to instability and clonal evolution
- **Multiparameter flow cytometry**: Widely applicable, standardized approaches improving

7.4 MRD in ALL

- MRD negativity at end of induction defines favorable prognosis
- Persistence of MRD triggers treatment intensification (blinatumomab, transplantation)
- NGS-based MRD superior to flow cytometry for depth of detection
- MRD-guided preemptive therapy with blinatumomab improves outcomes.[36]

7.5 Liquid Biopsy for MRD

Circulating tumor DNA (ctDNA) analysis offers non-invasive MRD monitoring[37]:

- Complementary to bone marrow assessment
- Detects extramedullary disease
- Identifies emerging resistance mutations
- Potential for earlier relapse detection

8. Emerging Molecular Targets and Therapies

8.1 Menin Inhibitors

As discussed, menin inhibitors target KMT2A-rearranged and NPM1-mutated leukemias by disrupting menin-KMT2A interaction.[38] Ongoing trials are evaluating:

- Revumenib in combination with chemotherapy (NCT05326516)
- Ziftomenib with venetoclax/azacitidine (NCT05735184)
- Optimal sequencing and resistance mechanisms

8.2 CD47-SIRPα Axis

Magrolimab (anti-CD47) enhances macrophage-mediated phagocytosis of leukemic cells[39]:

- Phase 1b results in TP53-mutated AML: CR/CRi 41.6%
- Combination with azacitidine and venetoclax under investigation
- Phase 3 trials ongoing (NCT05079230, NCT04778397)

8.3 XPO1 Inhibition

Selinexor inhibits nuclear export, reactivating tumor suppressors[40]:

- Active in relapsed/refractory AML
- Combination with chemotherapy under study
- Role in maintenance therapy explored

8.4 CAR-T Cell Therapy

CD19-directed CAR-T cells (tisagenlecleucel, brexucabtagene autoleucel) standard for relapsed/refractory B-ALL[41]:

- Complete remission rates 70-90% in children and adults
- Toxicity: cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome
- CD22-directed CAR-T cells for CD19-negative relapse

  For AML, CAR-T development challenged by target antigen heterogeneity and on-target/off-tumor toxicity:
- CD33, CD123, CLL-1 targets under investigation
- Dual-targeting strategies to prevent antigen escape

8.5 Bispecific T-Cell Engagers

Blinatumomab (CD19×CD3) standard for MRD-positive and relapsed/refractory B-ALL[42]:

- Superior to chemotherapy in randomized trials
- Now integrated into frontline therapy (NCT03914625)

For AML, CD33×CD3 (AMG330) and CD123×CD3 (vibecotamab, flotetuzumab) under investigation.[43]

9. Practical Implementation: Integrating Diagnostics into Clinical Workflow

9.1 Diagnostic Algorithm for Newly Diagnosed AML

1. **At diagnosis**
   - Bone marrow aspirate for morphology, flow cytometry, cytogenetics, FISH for recurrent abnormalities.
   - Molecular testing: NGS panel covering ELN-relevant genes (NPM1, FLT3-ITD/TKD, CEBPA, RUNX1, ASXL1, TP53, IDH1/2, KMT2A-PTD, etc.)
   - RNA sequencing if available for fusion detection.

2. **Rapid testing for actionable targets** (24-72 hours)
   - FLT3-ITD/TKD testing to identify candidates for FLT3 inhibitor therapy.
   - IDH1/2 testing for IDH inhibitor eligibility.
   - KMT2A rearrangements for clinical trial consideration.

3. **At remission**
   - MRD assessment by flow cytometry and molecular methods.
   - NPM1 mutation clearance in appropriate patients.

4. **At relapse**
   - Repeat comprehensive molecular testing to identify resistance mechanisms and new targets.

9.2 Diagnostic Algorithm for Newly Diagnosed ALL

1. **At diagnosis**
   - Bone marrow for morphology, flow cytometry, cytogenetics
   - FISH for recurrent abnormalities: BCR::ABL1, KMT2A rearrangements, ETV6::RUNX1, TCF3::PBX1
   - Molecular testing: RT-PCR for BCR::ABL1
   - RNA sequencing for Ph-like ALL classification in high-risk patients

2. **Ph-like ALL workup**
   - Screening: Low-density microarray or targeted PCR for CRLF2 expression
   - Confirmation: RNA sequencing to identify targetable fusions
   - Rapid turnaround essential to inform therapy

3. **MRD monitoring**
   - Flow cytometry at end of induction
   - NGS-based Ig/TCR tracking for sensitive detection
   - BCR::ABL1 monitoring by RT-PCR in Ph+ ALL

9.3 Challenges and Solutions

Table 6: Implementation Challenges and Solutions.

Challenge	Solution
Turnaround time for NGS	Rapid FLT3/IDH testing by PCR; batch NGS with 7-10 day result
Sample inadequacy	Peripheral blood with sufficient blasts; repeat bone marrow if needed
Variant interpretation	Molecular tumor board; public databases (ClinVar, COSMIC)
Detection of fusions	RNA sequencing complementary to DNA panels
Clonal hematopoiesis	Paired germline sequencing when indicated
Cost/reimbursement	Advocacy for coverage; centralized testing facilities

10. Future Directions

10.1 Ultra-Sensitive MRD Detection

- **Error-corrected NGS**: Detects mutations at 10^-5 sensitivity.
- **Whole genome sequencing**: Identifies patient-specific structural variants for tracking.
- **Single-cell sequencing**: Resolves clonal heterogeneity and evolution.

10.2 Dynamic Risk Stratification

- Integrating serial MRD measurements with baseline genetics.
- Adaptive treatment algorithms based on molecular response.
- Early intervention for molecular relapse before overt recurrence.

10.3 Novel Therapeutics

- **Menin inhibitors**: Expanding to additional molecular subsets.
- **CD123-targeted therapies**: ADCs (tagraxofusp), CAR-T cells.
- **MCL-1 inhibitors**: Overcoming venetoclax resistance
- **Epigenetic therapies**: HDAC inhibitors, DOT1L inhibitors.

10.4 Artificial Intelligence in Molecular Diagnostics

- Machine learning for variant classification
- Integration of genomic, transcriptomic, and clinical data
- Prediction of drug sensitivity and resistance

11. CONCLUSIONS

The integration of molecular diagnostics into clinical practice has revolutionized the management of acute leukemias. Comprehensive genomic profiling at diagnosis enables refined risk stratification and guides selection of targeted therapies that improve outcomes. Serial molecular monitoring detects persistent disease and identifies emerging resistance mechanisms, allowing timely intervention. As the therapeutic armamentarium continues to expand, seamless integration of molecular diagnostics into clinical workflows is essential to deliver precision medicine and improve outcomes for patients with acute leukemia.

Key principles for successful implementation include:

1. Rapid turnaround time for actionable targets.
2. Comprehensive testing at diagnosis and relapse.
3. Multidisciplinary interpretation through molecular tumor boards.
4. Integration of MRD monitoring into routine care.
5. Access to clinical trials for novel targeted therapies.

The future of acute leukemia management lies in dynamic, molecularly informed treatment algorithms that adapt to individual patient biology and response, ultimately moving toward curative, toxicity-sparing approaches.

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