PRECIPIO EXPECT MORE.
203-787-1717
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MOLECULAR

Patient: John A. Doe
DOB/Gender: 10/10/44 (74 yrs) - Male
Patient ID/MRN: 123456
Date Collected: 01/02/2023

Case# P23-00323
Status: Final
Report Category:
Not Detected

Provider: Jane Smith, M.D.
Hematology Oncology Associates
Tel: 800-123-4567
Fax: 800-765-4321

DIAGNOSIS:

Bone marrow, aspirate:
HemeScreen™ AML results reveal:
- Positive for CEBPA mutations* see comments
- Negative for FLT3 mutations
- Negative for NPM1 mutations
- Positive for IDH1 mutations* see comments
- Negative for IDH2 mutations
- Negative for KIT mutation

COMMENT

- CEBPA exon 1 variant of unknown significance detected. Base change c.573C>T. Protein change p.H191=.

- IDH1 exon 4 variant of unknown significance detected. Base change c.315C>T. Protein change p.G105=.

INTERPRETATION

CEBPA (CCAAT/enhancer binding protein a) mutations can be seen in 15% ~ 19% of patients. CEBPA mutations have a favorable prognosis, when no FLT3 mutation is present; regardless of cytogenetic abnormalities.

FLT3 (fms-like tyrosine kinase) mutation is an unfavorable prognostic marker. FLT3-ITD is the most common mutation. FLT3-TKD mutations (seen in <5% of cases) when combined with NPM1 mutation has a greater overall prognosis. FLT3 inhibitors are often paired with chemotherapy for treatment.

NPM1 (Nucleophosmin 1) mutations are most common (~ 50% of cases), and are usually seen in conjunction with other AML-associated mutations. NPM1 mutations have been suggested as a monitoring tool for MRD due to its stable nature during the course of disease. NPM1 mutation has a favorable prognosis when it is the only abnormality.

IDH1 (isocitrate dehydrogenase 1) mutation is generally associated with decreased complete remission. IDH1 mutation is often paired with NPM1 mutation and normal cytogenetics. IDH1 mutation has poor prognosis, especially when paired with FLT3. When IDH1 is paired with cytogenetic abnormalities such as PML/RARA, the overall prognosis worsens. IDH1 mutation alone has a more favorable outcome.

IDH2 (isocitrate dehydrogenase 2) mutation is generally paired with normal cytogenetics and does not affect overall prognosis. IDH2 mutations are often not associated with other prognostic AML mutations, such as FLT3, CEBPA and NPM1, however can be associated with IDH1 mutation.

KIT mutation expression is found in approximately 80% of cases. KIT mutation has a poor prognosis and clinical outcome. RUNX1 cytogenetic mutation is commonly associated with KIT mutation. Treatments include chemotherapy as well as inhibitors such as Dasatinib and Radotinib.

REFERENCES:
1. Lin TL, Smith BD. Prognostically important molecular markers in cytogenetically normal acute myeloid leukemia. Am J Med Sci. 2011;341(5):404-408. doi:10.1097/MAJ.0b013e318201109d
2. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B study. J Clin Oncol. 2010;28(14):2348-2355. doi:10.1200/JCO.2009.27.3730
3. Gregory, T.K., Wald, D., Chen, Y. et al. Molecular prognostic markers for adult acute myeloid leukemia with normal cytogenetics. J Hematol Oncol 2, 23 (2009). https://doi.org/10.1186/1756-8722-2-23
4. Boddu P, Kantarjian H, Borthakur G, et al. Co-occurrence of FLT3-TKD and NPM1 mutations defines a highly favorable prognostic AML group. Blood Adv. 2017;1(19):1546-1550. Published 2017 Aug 17. doi:10.1182/bloodadvances.2017009019
5. Feng JH, Guo XP, Chen YY, Wang ZJ, Cheng YP, Tang YM. Prognostic significance of IDH1 mutations in acute myeloid leukemia: a meta-analysis. Am J Blood Res. 2012;2(4):254-264.
6. Felicitas Thol, Frederik Damm, Katharina Wagner, Gudrun Gohring, Brigitte Schlegelberger, Dieter Hoelzer, Michael Lobbert, Wolfgang Heit, Lothar Kanz, Gunter Schlimok, Aruna Raghavachar, Walter Fiedler, Hartmut Kirchner, Gerhard Heil, Michael Heuser, Jorgen Krauter, Arnold Ganser; Prognostic impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia. Blood 2010; 116 (4): 614-616. doi: https://doi.org/10.1182/blood-2010-03-272146
7. Heo SK, Noh EK, Kim JY, et al. Targeting c-KIT (CD117) by dasatinib and radotinib promotes acute myeloid leukemia cell death. Sci Rep. 2017;7(1):15278. Published 2017 Nov 10. doi:10.1038/s41598-017-15492-5

METHOD:

Melting curve analysis in combination with real-time PCR is a natural extension of continuously monitored PCR within each cycle. During high resolution DNA melting analysis (HRM or HRMA), melting curves are produced using dyes that fluoresce in the presence of double-stranded DNA (dsDNA). Using specialized instruments designed to monitor fluorescence during heating; as the temperature increases, the fluorescence decreases, producing a characteristic melting profile.

This assay can detect mutations with a minimum sensitivity of 2% depending on the wild type background in the specimen. Although molecular testing is highly accurate rarely false-positive and false-negative diagnostic errors may occur.

HRM analysis was performed using HRM v3.1 Thermo Fisher software to discriminate DNA sequences based on their composition, length, GC content, or strand complementarities.

The somatic mutations are being confirmed by Sanger sequencing bi-directional method. This assay has a sensitivity of 5~10% for detecting mutant in wild-type background. Various factors including quantity and quality of nucleic acid, sample preparation and sample age can affect assay performance.

Electronically Signed By: Frank Bauer, MD, Precipio, Inc. (01/06/2023 11:00)

CLINICAL DATA

ICD-10: C92.00, D75.9. AML. New diagnosis.

Disclaimer: The adequacy of staining is verified by the appropriate LSI controls. The reagents used for these assays are for research use only (RUO). Th performance characteristics have been initiated by Precipio, Inc., New Haven, CT. They have not been reviewed by the FDA. The FDA has deemed that such approval is unwarranted for clinical use. These assays should be viewed as experimental and/or research use only.

Patient: John A. Doe
Case #: P23-00323
Received Information: 1 green-top tube(s), 2 lavender-top tube(s)
Received: 01/02/2023 10:39
Reported: 01/06/2023 11:30