Eosinophilia Panel by FISH

Indications for Ordering

- Diagnose and classify specific eosinophilic myeloid neoplasms
  - AML with inv(16) or t(16;16)
- Myeloid neoplasms with eosinophilia and abnormalities of PDGFR, PDGFRB, or FGFR1
- Provide prognostic and predictive information for acute or chronic leukemia with eosinophilia
- Monitor therapeutic response

Test Description

- Performed on cultured bone marrow (BM)
  - Peripheral blood may be used
- Multiple fluorescence in situ hybridization (FISH) probes target specific genes
  - FGFR1 translocations
  - FIP1L1-PDGFR region rearrangements
  - PDGFRB translocations
  - CBFB/MYH11 translocation
- Probes can be run as a panel or individually

Tests to Consider

Primary test

Eosinophilia Panel by FISH 2002378
- Diagnosis, prognosis, and monitoring for newly diagnosed acute or chronic leukemia with eosinophilia

Related tests

Chromosome Analysis, Bone Marrow 2002292
- Diagnosis, prognosis, and monitoring of eosinophilic leukemia

Chromosome Analysis, Bone Marrow with Reflex to Genomic Microarray 2007130
- Diagnosis, prognosis, and monitoring of eosinophilic disorders
- If chromosome analysis is “normal” or “no growth,” then genomic microarray testing will be added

Cytogenomic SNP Microarray – Oncology 2006325
- Preferred test for fresh specimens at time of diagnosis for detecting prognostically important genomic abnormalities in leukemias/lymphomas and solid tumors involving
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
  - Monitor disease progression and response to therapy

Chromosome FISH, Interphase 2002298

- Specific FISH probes must be requested and include
  - PDGFR
  - PDGFRB
  - +8
  - Monosomy 7 or 7q deletion
  - 13q deletion
  - 5q deletion
  - 20q deletion

Myeloproliferative Disorders Panel by FISH 2002360

- Detect specific recurrent genomic aberrations in suspected MPNs
  - BCR/ABL
  - PDGFR
  - PDGFRB
  - FGFR1

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 201117

- Assess for single gene mutations, including substitutions and insertions and deletions that may have diagnostic, prognostic, and/or therapeutic significance

Disease Overview

Consensus criteria

- 2008 WHO classification of eosinophilic myeloid disorders
  - Myeloid and lymphoid neoplasms with PDGFR rearrangement
  - Myeloid neoplasms with PDGFRB rearrangement
  - Myeloid and lymphoid neoplasms with FGFR1 abnormalities
  - Chronic eosinophilic leukemia, not otherwise specified (CEL, NOS)
  - Idiopathic hypereosinophilic syndrome (HES)
  - Idiopathic hypereosinophilia

Incidence/prevalence

- PDGFR/B- and FGFR1-related disorders are not well characterized
- inv16; t(16;16)
- 5-8% of AMLs
  - Predominantly in childhood

Diagnostic criteria

See Table 1

Genetics

See Table 2

Test Interpretation

Analytic sensitivity/specificity – >95%
Results
- Normal – no evidence of rearrangement
- Abnormal – rearrangement detected
  - Diagnostic of a clonal hematopoietic neoplasm
    - Prognosis – favorable in children and adults
    - Response to high dose cytarabine- and anthracycline-based chemotherapy – yes
    - Remission rate – 92%
    - 10-year survival – 55%
  - Prognosis of a clonal hematopoietic neoplasm
    - inv(16); t(16;16)
  - Response to tyrosine kinase inhibitors (TKIs) such as imatinib – yes
    - FGFR1-rearranged
    - Prognosis – poor
    - Response to TKIs such as imatinib – currently unclear
    - Response to chemotherapy protocols developed for acute leukemias – no

Limitations
- Detects only rearrangements targeted by the probes
- PDGFRB gene on 5q33 and FGFR1 gene on 8p11 have multiple translocation partners
  - Translocation partners are not identified by this test

### Table 1

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>Features</th>
<th>Laboratory</th>
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</table>
| AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFMYH11 | • Presents as AML  
• Myeloid sarcomas may be present at initial diagnosis or relapse | • Morphology – acute myelomonocytic leukemia with increased eosinophils containing immature eosinophilic granules in the BM  
• Peripheral eosinophilia is unusual  
• Diagnosis of AML even if blasts <20%  
• Genetics  
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22) found in most cases  
    - inv(16)(p13.1q22) is found in vast majority  
    - FISH or PCR may be necessary to document this genetic alteration  
  - Secondary cytogenetic abnormalities – +22, +8, del(7q)  
  - KIT mutations may be present |
| Myeloid and lymphoid neoplasms with PDGFRB rearrangement | • Most frequently presents as CEL, but may present as AML, T-lymphoblastic lymphoma, or both  
  - Acute transformation can follow CEL presentation  
  - Organ infiltration by eosinophils  
    - Heart  
    - Lungs  
    - CNS  
    - GI tract  
  - Splenomegaly in majority of patients  
  - Pronounced male predominance | • Morphology – peripheral blood and BM eosinophilia (markedly elevated)  
• Typically <20% blasts in peripheral blood and BM  
• Increased BM mast cells common  
• Genetics  
  - Absence of BCR-ABL1 fusion gene  
  - Most commonly associated with FIP1L1-PDGFRB fusion  
  - FISH or PCR is usually necessary to document this genetic alteration  
    - Cytogenetic studies are normal  
  - Other fusion genes have rarely been identified |
| Myeloid and lymphoid neoplasms with PDGFRB rearrangement | • Presents with features of chronic myelomonocytic leukemia (usually with eosinophilia)  
• Splenomegaly in majority of patients  
• Male predominance, but much less marked than PDGFRB-associated neoplasms | Morphology – peripheral leukocytosis  
• Hypercellular BM with typically <20% blasts  
• Increased BM mast cells common  
• Genetics  
  - Most common translocation-t(5;12)(q31-33;p13) resulting in formation of ETV6-PDGFRB |
| Myeloid and lymphoid neoplasms with FGFR1 abnormalities | • Often presents with peripheral eosinophilia in the context of lymphadenopathy and lymphoblastic leukemia/lymphoma  
• Slight male predominance | Morphology  
• AML, ALL, CEL (usually associated with peripheral blood or BM eosinophilia)  
• Genetics  
  - Presence of t(8;13)(p11;q12) or a variant translocation at the 8p11 breakpoint leading to FGFR1 rearrangement  
  - Secondary cytogenetic abnormalities – trisomy 21 most often observed |
Table 2

<table>
<thead>
<tr>
<th>Gene</th>
<th>Structure/Function</th>
<th>Mutations</th>
<th>WHO Disease Association</th>
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</table>
| **CBFB-MYH11** | • CBFB  
  o 16q22  
  o Core binding transcription factor  
  • MYH11  
  o 16p13.1  
  o Codes for smooth muscle myosin heavy chain | • inv(16)(p13.1q22) or (t16;16)(p13.1;q22)  
  • Inversion results in fusion of CBFB on 16q22 to MYH11 on 16p13.1 | AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); previously FAB M4Eo |
| **PDGFR** | • Maps to 4q12  
  • Cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family  
  • Results in a constitutively active tyrosine kinase oncoprotein | • FIP1L1-PDGFRα rearrangement is a karyotypically occult 800-kb interstitial deletion (ie, CHIC2 deletion) | Myeloid and lymphoid neoplasms with PDGFRα rearrangement |
| **PDGFRB** | • Maps to 5q31-33  
  • Cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family  
  • Results in a constitutively active tyrosine kinase oncoprotein | • 20 fusion partners reported  
  • Most common translocation – t(5;12)(q31-33;p13); ETV6-PDGFRB | Myeloid and lymphoid neoplasms with PDGFRB rearrangement |
| **FGFR1** | • Maps to 8p11  
  • Cell surface tyrosine kinase  
  • Translocations result in constitutive activation of FGFR1 with the fusion of the FGFR1 C-terminal catalytic domain with unrelated proteins | • >10 fusion partners identified  
  • Most common translocation – t(8;13)(p11;q12); ZNF198-FGFR1 mutation | Myeloid and lymphoid neoplasms with FGFR1 abnormalities |