Eosinophilia Panel by FISH

Indications for Ordering

- Diagnose and classify myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1*
- Provide prognostic and therapeutic information for these entities
- Monitor therapeutic response

Test Description

- Performed on bone marrow (BM) or peripheral blood
- Panel of fluorescence in situ hybridization (FISH) probes targeting specific rearrangements
  - *FIP1L1-PDGFRA* fusion
  - *PDGFRB* rearrangement
  - *FGFR1* rearrangement

Tests to Consider

Primary Test

Eosinophilia Panel by FISH 2002378

- Use for diagnosis, prognosis, and monitoring of newly diagnosed myeloid and lymphoid neoplasms with eosinophilia

Related Tests

Chromosome Analysis, Bone Marrow 2002292

- Use for the diagnosis, prognosis, and monitoring of myeloid and lymphoid neoplasms with eosinophilia
- Assess rearrangement partners for FISH-positive cases with cytogenetically visible translocations

Chromosome FISH, Interphase 2002298

- Test for individual probe ordering
- Specific FISH probes must be indicated
- Probes may include
  - *PDGFRA*
  - *PDGFRB*
  - *FGFR1*
  - *JAK2*
  - *CBFB*

Myeloproliferative Disorders Panel by FISH 2002360

- Detect specific recurrent genomic aberrations in suspected myeloproliferative neoplasms
  - *BCR/ABL1*
  - *PDGFRA*
  - *PDGFRB*
  - *FGFR1*

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117

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

Disease Overview

Consensus Criteria

- 2016 WHO classification of myeloid and lymphoid neoplasms with eosinophilia
  - Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
  - Myeloid and lymphoid neoplasms with *PDGFRB* rearrangement
  - Myeloid and lymphoid neoplasms with *FGFR1* rearrangement
  - Chronic eosinophilic leukemia-not otherwise specified (CEL-NOS)
  - Myeloid and lymphoid neoplasms with *PCM1-JAK2* (provisional entity)

Incidence/Prevalence

- The incidence and prevalence of hypereosinophilic syndromes has not been characterized; incidence rate from 2001–2005 was ~0.036 per 100,000 individuals
- Eosinophilias with recurrent genetic abnormalities comprise the minority of cases, with *FIP1L1-PDGFRA* fusion being the most common abnormality in this subgroup (Shomali, 2019)

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
  - *PDGFRA and PDGFRB*
    - Prognosis: improving with use of tyrosine kinase inhibitors (TKIs)
    - Response to TKIs such as imatinib: yes

- *FGFR1*-rearranged
  - Prognosis: poor
  - Response to TKIs such as ponatinib and other small molecule inhibitors: under investigation

Limitations

- FISH detects only rearrangements targeted by the probes
- *PDGFRB* gene on 5q33 and *FGFR1* gene on 8p11 have multiple rearrangement partners
  - Rearrangement partners are not identified by this test

Reference

Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. Am J Hematol. 2019;94(10):1149-1167.

Table 1

WHO Classification	Features	Laboratory
Myeloid and lymphoid neoplasms with *PDGFRA* 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 ○ Central nervous system ○ Gastrointestinal tract • Splenomegaly in majority of patients • Pronounced male predominance (17:1), median age of onset late 40s	• Morphology ○ Peripheral blood and BM eosinophilia (markedly elevated) ○ Typically <20% blasts in peripheral blood and BM ○ Increased BM mast cells common • Genetics ○ Typically due to *FIP1L1-PDGFRA* fusion due to cytogenetically cryptic interstitial deletion of *CHIC2* in 4q12 ▪ FISH or RT-PCR is necessary to document this genetic alteration; cytogenetic studies are normal
Myeloid and lymphoid neoplasms with *PDGFRB* rearrangement	• Presents with features of chronic myelomonocytic leukemia (usually with eosinophilia) • Splenomegaly in majority of patients • Male predominance (2:1), median age of onset late 40s	• Morphology ○ Peripheral leukocytosis ○ Hypercellular BM with typically <20% blasts ○ Increased BM mast cells common • Genetics ○ Rearrangement involving 5q31-33 (*PDGFRB*) ○ Most common translocation- t(5;12)(q31-33;p13), resulting in *ETV6-PDGFRB* fusion ▪ Due to variant breakpoints in 5q31-q33, consider molecular confirmation by RT-PCR to confirm *ETV6-PDGFRB* fusion to guide imatinib therapy
Myeloid and lymphoid neoplasms with *FGFR1* rearrangement	• Often presents with peripheral eosinophilia in the context of lymphadenopathy and lymphoblastic leukemia/lymphoma • Slight male predominance (1.5:1), median age of onset 32y	• Morphology ○ CEL (usually associated with peripheral blood or BM eosinophilia) AML, T-cell lymphoblastic leukemia/lymphoma, or (least often) B-lymphoblastic leukemia/lymphoma or mixed-phenotype AL • Genetics ○ Rearrangement involving 8p11.2 (*FGFR1)* ○ Most common translocation- t(8;13)(p11.2;q12.1), resulting in *ZMYM2-FGFR1* fusion

Table 2

Gene	Structure/Function	Mutations	WHO Disease Association
PDGFRA	• 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-PDGFRA* rearrangement is a cytogenetically cryptic: 800 kb interstitial deletion (i.e., *CHIC2* deletion) within 4q12 • Other *PDGFRA* fusion genes have rarely been identified such as t(1;4)(q44;q12) and t(4;10)(q12;p11.1-11.2)	Myeloid and lymphoid neoplasms with *PDGFRA* rearrangement
PDGFRB	• Maps to 5q32 • Cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family • Results in a constitutively active tyrosine kinase oncoprotein	• >30 fusion partners reported • Most common rearrangement: t(5;12)(q32;p13) resulting in *ETV6-PDGFRB* fusion	Myeloid and lymphoid neoplasms with *PDGFRB* rearrangement
FGFR1	• Maps to 8p11.2 • Cell surface tyrosine kinase • Rearrangement results in constitutive activation of *FGFR1* with the fusion of the *FGFR1* C-terminal catalytic domain with unrelated proteins	• >10 fusion partners identified • Most common rearrangement: t(8;13)(p11.2;q12.1) resulting in *ZMYM2-FGFR1* fusion	Myeloid and lymphoid neoplasms with *FGFR1* rearrangement