Test Definition: ESTUF

Endometrial Stromal Tumor, FISH, Ts

Overview

Useful For

Supporting the diagnosis of endometrial stromal tumors when used in conjunction with an anatomic pathology consultation

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
_PBCT	Probe, +2	No, (Bill Only)	No
_PADD	Probe, +1	No, (Bill Only)	No
_PB02	Probe, +2	No, (Bill Only)	No
_PB03	Probe, +3	No, (Bill Only)	No
_IL25	Interphases,	No, (Bill Only)	No
_I099	Interphases, 25-99	No, (Bill Only)	No
_I300	Interphases, >=100	No, (Bill Only)	No

Testing Algorithm

This test does not include a pathology consultation. If a pathology consultation is requested, PATHC / Pathology Consultation should be ordered and the appropriate FISH test will be ordered and performed at an additional charge.

This test includes a charge for application of the first probe set (2 FISH probes) and professional interpretation of results. Additional charges will be incurred for all reflex probes performed. Analysis charges will be incurred based on the number of cells analyzed per probe set. If no cells are available for analysis, no analysis charges will be incurred.

Unless otherwise indicated, *JAZF1* FISH testing will be performed:

-If a *JAZF1* rearrangement is not identified by FISH, reflex testing for *PHF1* and *YWHAE* rearrangement will be performed.

-If *JAZF1* FISH testing was previously performed, reflex testing for *PHF1* or *YWHAE* may be ordered separately.

-If testing was not performed at Mayo Clinic, provide a copy of the *JAZF1* FISH report.

Method Name

Fluorescence In Situ Hybridization (FISH)

NY State Available

Yes

Specimen

Specimen Type

Tissue

Shipping Instructions

Advise Express Mail or equivalent if not on courier service.

Necessary Information

A reason for referral and pathology report are required in order for testing to be performed. Send information with specimen. Acceptable pathology reports include working drafts, preliminary pathology or surgical pathology reports.

Specimen Required

Submit only 1 of the following specimens:

Specimen Type: Tissue

Preferred: Tissue block

Collection Instructions: Submit a formalin-fixed, paraffin-embedded (FFPE) tumor tissue block. Blocks prepared with alternative fixation methods may be acceptable; provide fixation method used.

Acceptable: Slides

Collection Instructions: Six consecutive, unstained, 5 micron-thick sections placed on positively charged slides, and 1 hematoxylin and eosin-stained slide.

Forms

If not ordering electronically, complete, print, and send an Oncology Test Request (T729) with the specimen.

Specimen Minimum Volume

Three consecutive, unstained, 5 micron-thick sections placed on positively charged slides and 1 hematoxylin and eosin-stained slide

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Tissue	Ambient (preferred)		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Endometrial stromal tumors (EST) arise from the uterus and include the benign endometrial stromal nodule (ESN) and infiltrative endometrial stromal sarcoma (ESS). These tumors are characterized by a translocation that fuses *JAZF1* at 7p15 to *JJAZ1* at 17q21 or a variant 6;7 translocation involving *JAZF1* and *PHF1*. Published literature

employing FISH and reverse transcriptase PCR (RT-PCR) suggests rearrangement of *JAZF1* occurs in approximately 76% of ESN and approximately 58% of ESS. *JAZF1* is not generally considered to be involved in the genetic mechanism of the high-grade undifferentiated endometrial sarcoma (UES), although rarely some cases of UES are positive for *JAZF1*, which may reflect the presence of an ESS component.

For *PHF1* disruption, a study of 94 EST demonstrated the following:

-*PHF1/JAZF1* fusion in 4 primary ESS

-*PHF1/EPC1* fusion in 2 primary ESS and 1 extrauterine ESS

-*PHF1* rearrangement without a known partner in 6 primary or metastatic ESS and 1 extrauterine ESS

JAZF1/JJAZ1, *PHF1/JAZF1* and *PHF1/EPC1* fusions were mutually exclusive in individual patients.(4) No rearrangement of *PHF1* was found in ESN, UES, or non-EST tumors in the differential diagnosis. These results indicate that *PHF1* can rearrange with both known and unknown partners in addition to *JAZF1* and is potentially specific for ESS.

In high-grade ESS, a recurrent t(10;17)(q22;p13) resulting in fusion of *YWHAE* (also called 14-3-3epsilon at 17p13.3 with either *FAM22A* or *FAM22B* was identified. In contrast, *JAZF1* rearrangements are typically observed in low-grade ESS. *JAZF1* and *YWHAE* rearrangements are mutually exclusive and have distinct gene expression profiles. *YWHAE* rearrangement is potentially specific for high-grade ESS as no *YWHAE* disruption has been reported in other uterine or nonuterine mesenchymal tumors.

The clinical utility of identifying *JAZF1* rearrangement is mainly to address the differential diagnostic dilemma that occurs when ESS are present as metastatic lesions or exhibit variant morphology. In *JAZF1*-negative EST cases, reflex genetic analysis to identify *PHF1* or *YWHAE* rearrangement increases the diagnostic sensitivity for EST. In addition, confirmation of *YWHAE* rearrangement may have prognostic implications as *YWHAE* defines a distinct, clinically more aggressive and histologically higher grade subgroup of ESS compared to those with *JAZF1* rearrangements.

Reference Values

An interpretive report will be provided.

Interpretation

A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe.

Detection of an abnormal clone likely indicates a diagnosis of an endometrial stromal tumor of various subtypes.

The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Cautions

This test is not approved by the U.S. Food and Drug Administration and is best used as an adjunct to existing clinical and pathologic information.

Fixatives other than formalin (eg, Prefer, Bouin's) may not be successful for FISH assays, however non-formalin fixed samples will not be rejected.

Paraffin-embedded tissues that have been decalcified are generally unsuccessful for FISH analysis. The pathologist reviewing the hematoxylin and eosin-stained slide may find it necessary to cancel testing.

Supportive Data

JAZF1:

FISH analysis was performed on 101 formalin fixed paraffin-embedded tissue specimens. These included 37 endometrial stromal tumors (EST) (8 endometrial stromal nodule [ESN], 20 primary or metastatic endometrial stromal sarcoma [ESS], and 9 primary or metastatic undifferentiated endometrial sarcoma [UES]), 38 histologic mimics of EST including cellular leiomyoma and 26 noncancerous control specimens. The normal controls were used to generate a normal cutoff for this assay. No rearrangements of *JAZF1* were identified in the 26 normal controls or 37 of the histologic mimics. A single histologic mimic was positive with a complex pattern. Rearrangement of *JAZF1* was identified in 17 of 37 (46%) EST specimens (3 ESN, 13 ESS, and 1 UES).

PHF1 and *YWHAE*:

FISH analysis was performed on 91 formalin fixed paraffin-embedded tissue specimens, including 20 EST (5 ESN, 7 primary or metastatic ESS, and 8 primary or metastatic UES), 35 histologic mimics of EST and 26 non-cancerous control specimens. Also included were 6 known *JAZF1*-positive cases and 4 clinical cases that were negative for *JAZF1* rearrangement. The normal controls were used to generate a normal cutoff for this assay. No rearrangements of *PHF1* or *YWHAE* were identified in the 26 normal controls or 35 of the histologic mimics. One primary UES failed to hybridize and yielded no results for either probe. Rearrangement of *PHF1* was identified in 1 of 19 (5%) of EST specimens (primary ESS) and in 1 of 6 (17%) of known *JAZF1*-positive cases (metastatic ESS). Rearrangement of *YWHAE* was identified in 2 of 19 (11%) of EST specimens (primary ESS and metastatic UES).

Clinical Reference

1. Koontz J, Soreng AL, Nucci M, et al: Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci USA 2001;98(11):6348-6353

2. Nucci R, Harburger D, Koontz J, et al: Molecular analysis of the JAZF1-JJAZ1 gene fusion by RT-PCR and fluorescence in situ hybridization in endometrial stromal neoplasms. Am J Surg Pathol 2007;31(1):65-70

3. Huang HY, Ladanyi M, Soslow RA: Molecular detection of JAZF1-JJAZ1 gene fusion in endometrial stromal neoplasms with classic and variant histology-evidence for genetic heterogeneity. Am J Surg Pathol 2004;28(2):224-232

4. Chiang S, Ali R, Melnyk N, et al: Frequency of known gene rearrangements in endometrial stromal tumors. Am J Surg Pathol 2011;35(9):1364-1372

5. Lee CH, Marino-Enriquez A, Ou W, et al: The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: A histologically high-grade and clinically aggressive tumor. Am J Surg Pathol 2012;36(5):641-653

6. Panagopoulos I, Mertens F, Griffin CA, et al: An endometrial stromal sarcoma cell line with the JAZF1/PHF1 chimera. Cancer Genet Cytogenet 2008 Sep;185(2):74-77

7. Lee CH, Ou WB, Marino-Enriquez A, et al: 14-3-3 fusion oncogenes in high-grade endometrial stromal sarcoma. Proc Natl Acad Sci U S A 2012;109(3):929-934

8. Micci F, Panagopoulos I, Bjerkehagen B, et al: Consistent rearrangement of chromosomal band 6p21 with generation of fusion genes JAZF1/PHF1 and EPC1/PHF1 in endometrial stromal sarcoma. Cancer Res 2006;66(1):107-112

9. Gebre-Medhin S, Nord KH, Moller E, et al: Recurrent rearrangement of the PHF1 gene in ossifying fibromyxoid tumors. Am J Pathol 2012;181(3):1069-1077

Performance

Method Description

The test is performed using laboratory-developed dual-color break-apart strategy probes (BAP) for *JAZF1, PHF1,* and *YWHAE.* Formalin-fixed, paraffin-embedded tissues are cut at 5 microns and mounted on positively charged glass slides. The selection of tissue and the target areas on the hematoxylin and eosin (H and E)-stained slide are performed by a pathologist. Using the H and E-stained slide as a reference, target areas are etched with a diamond-tipped etcher on the back of the unstained slide to be assayed. The probe set is hybridized to the appropriate target areas and 2 technologists each analyze 50 interphase nuclei (100 total for each probe set) with the results expressed as the percent abnormal nuclei.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Samples processed Monday through Sunday.

Results reported Monday through Friday, 8 a.m.-5 p.m.

Analytic Time

7 days

Maximum Laboratory Time

10 days

Specimen Retention Time

Slides and H&E used for analysis are retained by the laboratory in accordance to CAP and NYS requirements. Client provided paraffin blocks and extra unstained slides (if provided) will be returned after testing is complete.

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

88271x2, 88291 Ã¢â‚¬â€œ DNA probe, each (first probe set), Interpretation and report

88271x2 Ã¢â‚¬â€œ DNA probe, each; each additional probe set (if appropriate)

88271x1 Ã¢â‚¬â€œ DNA probe, each; coverage for sets containing 3 probes (if appropriate)

88271x2 Ã¢â‚¬â€œ DNA probe, each; coverage for sets containing 4 probes (if appropriate)

88271x3 Ã¢â‚¬â€œ DNA probe, each; coverage for sets containing 5 probes (if appropriate)

88274 w/modifier 52 Ã¢â‚¬â€œ Interphase in situ hybridization, <25 cells, each probe set (if appropriate)

88274 Ã¢â‚¬â€œ Interphase in situ hybridization, 25 to 99 cells, each probe set (if appropriate)

88275 Ã¢â‚¬â€œ Interphase in situ hybridization, 100 to 300 cells, each probe set (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
ESTUF	Endometrial Stromal Tumor, FISH, Ts	In Process

Result ID	Test Result Name	Result LOINC Value
52147	Result Summary	50397-9
52149	Interpretation	69965-2
54584	Result	62356-1
CG744	Reason for Referral	42349-1
52150	Specimen	31208-2
52151	Source	31208-2
52152	Tissue ID	80398-1
52153	Method	49549-9
55026	Additional Information	48767-8
53831	Disclaimer	62364-5
52154	Released By	18771-6