Angiomatoid Fibrous Histiocytoma
(FUS-ATF1 in t(12;16), EWSR1-CREB1 in t(12;22), EWSR1-CREB1 in t(2;22)) (NAAT)
on Tissues (code 60159)

Notice of Assessment

June 2013
1 GENERAL INFORMATION

1.1 Requestor: CHUQ – L'Hôtel-Dieu de Québec.

1.2 Application Submitted: August 1, 2012.

1.3 Notice Issued: April 12, 2013.

Note:
This notice is based on the scientific and commercial information (submitted by the requestor[s]) and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology
Reverse-transcriptase PCR (RT-PCR) for the diagnosis of angiomatoid fibrous histiocytoma (FUS-ATF1 in t(12;16), EWSR1-CREB1 in t(2;22)) (NAAT) on tissues (code 60159).

2.2 Brief Description of the Technology
The RT-PCR technique is "sensitive, specific, rapid and inexpensive and can be used on fresh, frozen or formalin-fixed and paraffin-embedded (FFPE) tissues, as well as on cytological preparations such as fine-needle aspiration material." (Genevay et al., 2007).

The requestor describes this technique as comprising the following steps: a) RNA purification from tissues; b) messenger RNA reverse transcription into complementary DNA (using Transcriptor by Roche Diagnostics); c) real-time PCR (six PCRs). Identification by gel electrophoresis is sometimes required.

2.3 Company or Developer: In-house technique.

2.4 Licence(s): Not applicable.

2.5 Patent, If Any: Not applicable.

2.6 Approval Status (Health Canada, FDA): Unlicensed kits.

2.7 Weighted Value: 324.0.

3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patients
Patients who have received a diagnosis of angiomatoid fibrous histiocytoma through conventional histology, to confirm the diagnosis or differential diagnosis of other soft tissue sarcomas.

3.2 Targeted Disease(s)
Angiomatoid fibrous histiocytoma, first described by Enzinger in 1979, is a rare soft-tissue tumour of low or intermediate malignancy (metastases are rare) (Fletcher et al., 2002) that usually occurs in children and young adults. It manifests as nodular subcutaneous growths (Kniffin, 2008) typically located in the extremities and rarely found on the trunk, head, or neck. Clinically, angiomatoid
fibrous histiocytoma can be mistaken for a hematoma or a hemangioma. Differential diagnoses are based on histopathology and immunohistochemical studies. However, the disease is rare (accounting for 0.3% of all soft tissue tumours) and the typical histological features are relatively unknown to pathologists, which can lead to an erroneous diagnosis of malignant disease. This is most likely due to the typical dense lymphocytic infiltrate surrounding the tumour, suggestive of a tumour metastasis to a lymph node (Sparreboom et al., 2012). Interpreting IHC results can be complex, since there are no specific markers for this disease (Sparreboom et al., 2012).

Molecular biology is thus a very useful diagnostic tool. The disease is characterized by three translocations: t(12;16) (q13;p11), t(12;22) (q13;q12) and t(2;22) (q33;q12) (information provided by the requestor; also see comments by Vicente-Duenas and Sanchez-Garcia, 2006). These translocations lead to the formation of FUS-ATF1, EWSR1-ATF1 and EWSR1-CREB1 chimeric or fusion genes (Genevay et al., 2007). “One of the genes most susceptible to... translocation... is represented by Ewing sarcoma breakpoint region 1 (EWSR1)” (Cantile et al., 2013). The fusion with transcription factors (ATF1 and CREB1) occurs in various soft tissue tumours.

Although angiomatoid fibrous histiocytoma and clear cell sarcoma of soft tissue have the same translocation, the two tumours have very different clinical presentations and anatomic-pathological features. The EWS gene involved in Ewing sarcoma is a translocation partner in several sarcomas. The detection of fusion transcripts provides information on the identity of the two translocation partners. The majority (90%) of tumours in the Ewing family of tumours have a t(11;22)(q24;q12) translocation, which results in the expression of a EWSR1-FL1 chimeric protein. However, for the remaining 10%, other translocations have been observed, such as t(2 :22)(q33;q12) with the formation of EWSR1-FEV (Lazar et al., 2006).

3.3 Number of Patients Targeted
Ten cases are anticipated over the next three years at the CHUQ's l'Hôpital-Dieu de Québec.

3.4 Medical Specialties Involved (and Other Professions, If Any)
Anatomic pathology and hematology-oncology

3.5 Testing Procedure
The test is performed on formalin-fixed and paraffin-embedded (FFPE) tissue.

4 TECHNOLOGICAL BACKGROUND

4.1 Nature of the Diagnostic Technology: Complementary, contributes to the diagnosis.

4.2 Brief Description of the Current Technological Context
Detection of the three translocations to help establish a diagnosis of angiomatoid fibrous histiocytoma; if this analysis is not performed, the diagnosis is made using conventional histology.

Other molecular techniques are available to detect the EWSR1 gene and its chimeric transcripts: FISH, quantitative PCR, and sequencing. Few studies have analyzed these techniques in relation to the diagnosis of angiomatoid fibrous histiocytoma. The selection of technique depends mainly on the pathologist's and laboratory's level of expertise (Cantile et al., 2013).

4.3 Brief Description of the Advantages Cited for the New Technology
Contributes to the confirmation of the diagnosis, as the tumour is often confused with lymphatic metastasis or a malignant tumour. An accurate diagnosis enables the treatment—a wide surgical
resection—to be properly targeted. It helps avoid overtreatment, when the tumour is misdiagnosed as a more aggressive lesion, and undertreatment, as histiocytoma presents a risk of recurrence and metastasis (Thway, 2008).

4.4 **Cost of Technology and Options:** Not assessed.

5 **EVIDENCE**

5.1 **Clinical Relevance**

5.1.1 **Other Tests Replaced:** No.

5.1.2 **Diagnostic, Prognostic, and Therapeutic Value**

Documentary research did not identify any studies linking the molecular diagnosis of the disease to mortality, morbidity, and quality of life. The requestor specifies that, in the case of a histopathological diagnosis of suspected angiomatoid fibrous histiocytoma, a molecular test will provide a definite diagnosis. A negative molecular test will not rule it out.\(^9\)

**Treatment Modifications Based on Test Results**

Molecular analysis contributes to establishing the complex diagnosis of the disease and allows appropriate treatment to be selected. Prognosis is generally good following wide surgical excision, with low potential of local recurrence and metastasis (Sparreboom et al., 2012). Molecular analysis plays an invaluable role in cases of atypical angiomatoid fibrous histiocytoma involving, for example, the mediastinum, retroperitoneum, lungs, vulva, etc. (Chen et al., 2011).

However, recent publications (Boland and Folpe, 2013; Cantile et al., 2013; Thway and Fisher, 2012) indicate that the genes and translocations sought are not specific to histiocytomas, and that other malignant sarcomatous tumours may present the same characteristics.

The genomic abnormalities identified in certain sarcomas provide very useful diagnostic markers (Genevay et al., 2007).

5.2 **Clinical Validity**

Documentary research did not identify any studies on the clinical validity of RT-PCR for angiomatoid fibrous histiocytoma. However, translocations typically associated with this disease are not necessarily exclusive to it. For example, an EWSR1-ATF1 fusion can be found in clear cell sarcoma, angiomatoid fibrous histiocytoma, and other tumours such as soft tissue myoepithelioma (STM). Therefore, all results must be considered in the final interpretation, including clinical, histopathological, and immunohistochemical results, and any molecular genetic findings (Boland and Folpe, 2013; Chetaille and Laibe, 2012).

5.3 **Analytical (or Technical) Validity**

A literature review did not reveal any studies that analyzed the technical validity of RT-PCR in the case of angiomatoid fibrous histiocytoma.

5.4 **Recommendations for Listing in Other Jurisdictions**

The National Comprehensive Cancer Network's (NCCN's) 2012 clinical practice guidelines on soft tissue sarcomas include a section on complementary diagnostic techniques for sarcomas. NCCN

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\(^9\) Electronic communication with Dr. Sébastien Labonté from the CHU de Québec (March 21, 2013).
emphasizes that histological analyses are the gold standard for the diagnosis of sarcomas. However, several complementary techniques are available, including IHC, cytogenetics, electron microscopy, and molecular genetic testing, which uses FISH or PCR. These tests must be carried out by a pathologist with experience in the diagnosis of sarcomas and the use of molecular genetic techniques. The guidelines indicate that these techniques are complex, that none is completely sensitive or specific, and that the results must be interpreted in a clinical and histopathological context (NCCN, 2012).

6 ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

6.1 Impact on Material and Human Resources: Not assessed.

6.2 Economic Consequences of Introduction Into Quebec’s Health Care and Social Services System: Not assessed.

6.3 Main Organizational, Ethical, and Other (Social, Legal, Political) Issues: Not assessed.
### 7 INESSS NOTICE IN BRIEF

**Angiomatoid Fibrous Histiocytoma** (*FUS-ATF1* in t(12;16), *EWSR1-CREB1* in t(12;22), *EWSR1-CREB1* in t(2;22)) (NAAT) on Tissues (Code 60159)

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<tr>
<th>Status of the Diagnostic Technology:</th>
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<tr>
<td>☒ Established</td>
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<td>☐ Innovative</td>
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<tr>
<td>☐ Experimental (for research purposes only)</td>
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<tr>
<td>☐ Replacement for technology: _________________, which becomes obsolete</td>
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**INESSS Recommendation:**

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<td><em>This diagnostic technology is established, but technical and clinical validity data for the specific diagnosis of angiomatoid fibrous histiocytoma, a very rare tumour, have not been identified. Molecular confirmation helps establish the diagnosis by providing a higher degree of certainty to the clinical and histopathological diagnosis. A follow-up of the results of this test is recommended.</em></td>
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<td>☐ Remove test from the Index</td>
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<td>☐ Reassess test</td>
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**Additional Recommendation:**

| ☐ Draw connection with listing of drugs, if companion test |
| ☐ Production of an optimal use guide |
| ☐ Production of indicators, when monitoring is required |
REFERENCES


