GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Medical Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Medical Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Medical Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Medical Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Description:

Most thyroid cancers originate from thyroid follicular cells and include well-differentiated papillary thyroid carcinoma (PTC) and follicular carcinoma. Various genetic variants have been discovered in thyroid cancer. The four gene variants that are the most common and carry the highest impact on tumor diagnosis and prognosis are BRAF and RAS single nucleotide variants (SNVs) and RET/PTC and PAX8/PPARγ rearrangements. Testing for genetic variants and rearrangements uses cells from a thyroid lesion taken with a fine needle aspiration (FNA) biopsy.

TERT promoter variants occur with varying frequency in different thyroid cancer subtypes. Overall, TERT C228T or C250T variants have been reported in approximately 15% of thyroid cancers, with higher rates in the undifferentiated and anaplastic subtypes compared with the well-differentiated subtypes.

Genetic Variant Detection and Rearrangement Testing:

Single nucleotide variants (SNVs) in specific genes, including BRAF, RAS and RET and evaluation for rearrangements associated with thyroid cancers can be accomplished by gene sequencing and next-generation sequencing (NGS) panels. Thyroid Cancer Mutation Panel (Quest Diagnostics) includes BRAF and RAS variant analysis and testing for RET/PTC and PAX8/PPARγ rearrangements.

The ThyroSeq® v.2 Next Generation Sequencing panel (CBLPath) includes sequencing of more than 60 genes.

The ThyGenX™ Thyroid Oncogene Panel (formerly miRInform® Thyroid; Interpace Diagnostics) is another NGS sequencing panel that sequences 8 genes and identifies specific gene variants and translocations associated with thyroid cancer. ThyGenX is intended to be used in conjunction with the ThyraMIR™ microRNA expression test when the initial ThyGenX test is negative.

Gene Expression Profiling:

Genetic alterations associated with thyroid cancer can be assessed through the use of gene expression profiling, which refers to analysis of the expression (activity) of many genes simultaneously. Several gene expression profiling tests have been developed to biologically stratify tissue from thyroid nodules.

The Afirma® Gene Expression Classifier (GEC) analyzes the expression of 142 different genes to determine patterns associated with benign findings on surgical biopsy.

The ThyraMIR (Interpace Diagnostics) is a micro-RNA expression-based classifier intended for use in thyroid nodules with indeterminate cytology on FNA following a negative result from the ThyGenX Thyroid Oncogene Panel.
GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Description: (cont.)

Algorithmic Testing:
Algorithmic testing involves the use of two or more tests in a prespecified sequence, with a subsequent test automatically obtained depending on the results of the earlier test.

Algorithmic Testing Using Afirma GEC With Afirma MTC and Afirma BRAF:
Veracyte offers 2 “malignancy classifiers” that use mRNA expression-based classification to evaluate for BRAF variants (Afirma BRAF) or variants associated with medullary thyroid carcinoma (Afirma MTC).

Afirma MTC and Afirma BRAF Testing Algorithms:

<table>
<thead>
<tr>
<th>Test #1</th>
<th>Test #1 Result</th>
<th>Reflex to Test #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid nodule on fine needle aspirate</td>
<td>“Intermediate”</td>
<td>Afirma MTC</td>
</tr>
<tr>
<td>Afirma GEC</td>
<td>“Malignant” or “Suspicious”</td>
<td>Afirma MTC</td>
</tr>
<tr>
<td>Afirma GEC</td>
<td>“Suspicious”</td>
<td>Afirma BRAF</td>
</tr>
</tbody>
</table>

Algorithmic Testing Using ThyGenX and ThyraMIR:
The testing strategy for combined ThyGenX and ThyraMIR testing is first to predict malignancy. A positive result on ThyGenX would “rule in” individuals for surgical resection. The specific testing results from a ThyGenX positive test would be used to inform preoperative planning when positive. For a ThyGenX negative result, the reflex testing involves the ThyraMIR microRNA expression test to “rule out” for a surgical biopsy procedure given the high negative predictive value of the second test. Individuals with a negative result from the ThyraMIR test would be followed with active surveillance and avoid a surgical biopsy.

Summary of Molecular Tests for Indeterminate Thyroid Cytopathology Fine Needle Aspirates:

<table>
<thead>
<tr>
<th>Test</th>
<th>Methodology</th>
<th>Analyte(s)</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afirma GEC</td>
<td>mRNA gene expression</td>
<td>167 genes</td>
<td>Benign/suspicious</td>
</tr>
<tr>
<td>Afirma BRAF</td>
<td>mRNA gene expression</td>
<td>1 gene</td>
<td>Negative/positive</td>
</tr>
<tr>
<td>Afirma MTC</td>
<td>mRNA gene expression</td>
<td></td>
<td>Negative/positive</td>
</tr>
<tr>
<td>ThyroSeq v2</td>
<td>Next generation sequencing</td>
<td>60+ genes</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>ThyGenX</td>
<td>Next generation sequencing</td>
<td>8 genes</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>TERT single-gene test</td>
<td></td>
<td>1 gene</td>
<td>Specific gene variants</td>
</tr>
<tr>
<td>miRInform (predicate test to ThyGenX and not commercially available)</td>
<td>Multiplex PCR by sequence specific probes</td>
<td>14 DNA variants, 3 RNA fusions</td>
<td>Specific gene variant/translocation</td>
</tr>
<tr>
<td>ThyraMIR</td>
<td>microRNA expression</td>
<td>10 micro RNAs</td>
<td>Negative/positive</td>
</tr>
<tr>
<td>RosettaGX Reveal</td>
<td>microRNA expression</td>
<td>24 micro RNAs</td>
<td>Benign Suspicious for malignancy High risk for medullary carcinoma</td>
</tr>
</tbody>
</table>
GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Definitions:

Genetic Testing:
Analysis of DNA, RNA, chromosomes, proteins and certain metabolites in order to detect alterations related to an inherited disorder.

Gene:
A hereditary unit consisting of segments of DNA that occupies a specific location on chromosomes. Genes undergo mutation when their DNA sequence changes.

Genetic Counseling:
Instruction that provides interpretation of genetic tests and information about courses of action that are available for the care of an individual with a genetic disorder or for future family planning.

Affected Individual:
An individual displaying signs or symptoms characteristic of a suspected or specific inherited disorder.

Unaffected Individual:
An individual who displays no signs or symptoms characteristic of a suspected or specific inherited disorder.

Screening:
Genetic screening is the testing of an individual with no symptoms for a specific inherited disorder to determine if the individual carries an abnormal gene. Screening can be used to predict risk or potential risk for the individual or their offspring.

Criteria:

➢ Genetic testing and/or counseling of an unaffected individual, regardless of risk factors is considered screening and not eligible for coverage.

➢ Genetic testing and/or counseling of an affected individual to confirm a disease when confirmation of the diagnosis would not impact the care and/or management is considered not medically necessary and not eligible for coverage.
GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Criteria: (cont.)

- Genetic testing and/or counseling using the Afirma Gene Expression Classifier or ThyroSeq v2 in fine-needle aspirates of the thyroid is considered medically necessary with documentation of ALL of the following:

  1. Fine needle aspirate samples from thyroid nodule(s) have indeterminate cytology as indicated by ONE or more of the following:
     - Bethesda diagnostic category III (atypia/follicular lesion of undetermined significance [AUS])
     - Bethesda diagnostic category IV (follicular (Hurthle cell) neoplasm (FN) or suspicious for a follicular neoplasm (SFN))
     - Follicular lesion of undetermined significance (FLUS)

  2. Thyroid nodule >1cm
  3. With or without clinical suspicion of malignancy based on provider judgment and ultrasonography
  4. No compressive manifestations

- Genetic testing and/or counseling for molecular marker testing or for gene variant analysis in fine needle aspirates of thyroid nodules with indeterminate or suspicious findings to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery is considered medically necessary with documentation of ALL of the following:

  1. ANY of the following:
     - Bethesda diagnostic category III (atypia/follicular lesion of undetermined significance)
     - Bethesda diagnostic category IV (follicular neoplasm/suspicion for a follicular neoplasm)
     - Bethesda diagnostic category V (suspicious for malignancy)

  2. ANY of the following tests:
     - ThyroSeq v2
     - ThyraMIR microRNA/ThyGenX
     - Afirma BRAF after Afirma Gene Expression Classifier
     - Afirma MTC after Afirma Gene Expression Classifier
GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Criteria: (cont.)

- Genetic testing with gene expression classifiers, genetic variant analysis and molecular marker testing in fine-needle aspirates of the thyroid for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes,
  2. Insufficient evidence to support improvement of the net health outcome, and
  3. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives.

These tests include, but are not limited to:

- RosettaGX Reveal
- Single-gene TERT testing

Resources:

Literature reviewed 07/31/18. We do not include marketing materials, poster boards and non-published literature in our review.

The BCBS Association Medical Policy Reference Manual (MPRM) policy is included in our guideline review. References cited in the MPRM policy are not duplicated on this guideline.

Resources prior to 05/22/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


GENETIC TESTING IN FINE NEEDLE ASPRATES OF THE THYROID (cont.)

Resources: (cont.)


MEDICAL COVERAGE GUIDELINES

GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda e información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah nilíngígíí Blue Cross Blue Shield of Arizona haada yit’éégo bina’idiłkídgo éí doodago Háída bii já aniyléeéíígíí táado lo’éé yina’idiłkídgo beehaz’áanii hólo díí t’áá hazaak’ehíí háhá a’doowolgo bee ház’a doo baą́ą ilíngióó. Ata’ halne’igíí kojį’ bíchį’ hodílíníí 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有关於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thể thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thông dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساعدك أسئلة بخصوص خصوصيات Blue Cross Blue Shield of Arizona، فلنكن الحك في الحصول على المساعدة والمعلومات. للتحدث مع مررجم اتصل ب 877-475-4799.
GENETIC TESTING IN FINE NEEDLE ASPIRATES OF THE THYROID (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutuuan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may kapatid na ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makuhsap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 통역사와 얘기하기 위해서는 877-475-4799로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Pour parle à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizonaについてご質問がございましたら、ご希望の言語でサポートを受けて、情報を入手したりすることができます。料金はかかりません。通訳とお話される場合、877-475-4799までお電話ください。

Farsi: 
آگر شما هم یا کسی که شما به او کمک می‌کنید، سوال ندارید و اطلاعاتی به زبان خود را به طور رایگان دریافت نمایید 877-475-4799.

Assyrian: 
Blue Cross Blue Shield of Arizona ؛ دانشگاه چین، دانشگاه چین، دانشگاه چین، دانشگاه چین.

Serbo-Croatian: Ukoliko vi ili neko kome vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da bešplatan dobiti pomoć i informacije na vašem jeziku. Da biste razgovarali sa prevodocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่คุ้นเคยกับภาษาไทยของคุณไม่สามารถพบ Blue Cross Blue Shield of Arizona ตามคำแนะนำที่อยู่ในภาษา ของคุณได้ โปรดโทรร้องความใน 877-475-4799.