GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS

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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Laboratory tests have been developed that detect the expression, via messenger RNA (mRNA) or protein, of many different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early-stage breast cancer. Test results may help providers and individuals decide whether to include adjuvant chemotherapy in post-surgical management.
GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS
(cont.)

Description: (cont.)

Tests include, but are not limited to:

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Index&lt;sup&gt;SM&lt;/sup&gt;</td>
<td>bioTheranostics</td>
<td>Combines molecular grade index (MGI) and the HOXB13:IL17BR (H/I) Index</td>
</tr>
<tr>
<td>EndoPredict®</td>
<td>Sividon Diagnostics</td>
<td>12-gene RT-PCR</td>
</tr>
<tr>
<td>MammaPrint®</td>
<td>Agendia</td>
<td>MammaPrint: 70-gene DNA microarray signature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BluePrint®: 80-gene subtype classifier</td>
</tr>
<tr>
<td>BluePrint®</td>
<td>(BluePrint is-intended for use with MammaPrint)</td>
<td></td>
</tr>
<tr>
<td>Oncotype DX®</td>
<td>Genomic Health</td>
<td>21-gene RT-PCR</td>
</tr>
<tr>
<td>Oncotype DX® Breast DCIS Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosigna®</td>
<td>NanoString Technologies</td>
<td>DNA microarray based on the PAM50 breast cancer intrinsic subtype classifier</td>
</tr>
</tbody>
</table>

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.

**Gene Expression:**
The translation of the information encoded in a gene into messenger RNA (mRNA) which may or may not then be translated into a protein.

**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.
GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS (cont.)

Definitions: (cont.)

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 OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS
(cont.)

Criteria: (cont.)

Primary Breast Cancer:

- The following gene expression assays to determine prognosis in primary, invasive breast cancer for an affected individual to make an informed decision whether to use adjuvant chemotherapy are considered medically necessary with documentation of ALL of the following:

1. Unilateral tumor
2. Tumor size 0.6-1cm with moderate/poor differentiation or unfavorable features OR tumor size greater than 1 cm
3. Hormone (estrogen or progesterone) receptor positive (i.e., ER-positive or PR-positive)
4. Lymph node negative (micrometastasis ≤2mm in size is considered node negative)
5. HER-2 negative (unamplified, non-amplified)
6. Will be treated with adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors)
7. Test is ordered within six months following diagnosis

Gene expression assays include:

- Breast Cancer IndexSM
- EndoPredict®
- Oncotype DX® (21-gene RT-PCR assay)
- Prosigna®

Multiple Ipsilateral Primaries (Multicentric/Multifocal):

- Gene expression assays to determine prognosis in breast cancer for an affected individual with multiple ipsilateral primaries who meets the criteria above for primary, invasive breast cancer is considered medically necessary only on a specimen from the tumor with the most aggressive histological characteristics.

- Testing on each tumor for an individual with multiple ipsilateral primaries is considered not medically necessary and not eligible for coverage.
GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS (cont.)

Criteria: (cont.)

Ductal Carcinoma In Situ:

- Use of subset of genes from the Oncotype DX® assay of genetic expression (21-gene RT-PCR assay) for predicting recurrence risk in individuals with noninvasive ductal carcinoma in situ (i.e., Oncotype DX® Breast DCIS Score) to inform treatment planning following excisional surgery is considered experimental or investigational based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  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, and
  4. Insufficient evidence to support improvement outside the investigational setting.

All Other Indications:

- Use of gene expression assays in men with breast cancer is considered experimental or investigational based upon:
  1. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  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, and
  4. Insufficient evidence to support improvement outside the investigational setting.
GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS
(cont.)

Criteria: (cont.)

All Other Indications: (cont.)

➢ Use of gene expression assays 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, and
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, and
4. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Determination of recurrence risk in individuals with breast cancer who are lymph node-positive
- Determination of recurrence risk in individuals with bilateral breast cancer
- Determination of length of treatment with tamoxifen

Gene expression assays for all other indications include, but are not limited to:

- BluePrint® (in conjunction with MammaPrint or alone)
- Breast Cancer IndexSM
- EndoPredict®
- MammaPrint® 70-gene signature
- Oncotype DX® (21-gene RT-PCR assay)
- PAM50 Breast Cancer Intrinsic Classifier
- Prosigna®
GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS (cont.)

Resources:

Literature reviewed 01/31/17. 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 01/22/13 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS (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 niliígií Blue Cross Blue Sheid’ of Arizona haada yiit’éego bina’idílíkidgo éi dodegdo Háída bií já aniyeedígií t’áadoo le’é yina’idílíkidgo beehaz’áñii hólo díí t’áá hazaad’ehí háká a’doowolgo bee ha’z’á doo baqáh niliigóó. Ata’ halne’ígiig kojí bich’é’ hodiliinh 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 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 thống dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شخص تساهم أسلسلة بخصوص العضوية الضرورية، بلغكم من دون أي تكلفة، للتحدث مع مترجم اتصل ب. 877-475-4799.
GENETIC TESTING OF TUMOR TISSUE FOR BREAST CANCER PROGNOSIS
(cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinituwan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap 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 동역사와 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 parler 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たり、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: اگر شما یا کسی که شما به آن کمک می‌کنید، سوال در مورد اطلاعاتی به نام و در باره Blue Cross Blue Shield of Arizona داشته باشید، حق دارید این را در نظر گرفتار شوید و رایگان دریافت نمایید، 877-475-4799.

Assyrian: Blue Cross Blue Shield of Arizona, 877-475-4799

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomažete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือคนที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถขอรับความช่วยเหลือและข้อมูลในภาษาของคุณได้โดยโทรศัพท์ 877-475-4799