CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT

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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CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (cont.)

Description:

Normal and tumor cells release small fragments of DNA into the blood. Circulating tumor DNA (ctDNA) originates directly from the tumor or from circulating tumor cells (CTCs). CTCs are tumor cells that shed from tumors and enter the bloodstream. Genetic testing of ctDNA and CTCs in peripheral blood, also referred to as liquid biopsy, has been investigated as a noninvasive alternative to tissue biopsy for therapeutic decision making and clinical prognosis in individuals with cancer.

Genetic testing of ctDNA can be targeted at specific genes or at commonly found, acquired, somatic variants ("hotspots") that occur in specific cancers, which can impact therapy decisions (e.g., EGFR and ALK in non-small cell lung cancer (NSCLC)).

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.

➢ Cobas EGFR Mutation Test v2 for the analysis of small deletions in exon 19 and point mutation variant in exon 21 (L858R) in the EGFR gene is considered medically necessary”.

➢ The use of ctDNA and/or CTCs for all other indications not previously listed or if above criteria not met is considered experimental/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:

• Analysis of small deletions in exon 19 and point mutation variant in exon 21 (L858R) for individuals with advanced NSCLC of squamous cell type
• Analysis of EGFR T790M resistance variant for NSCLC targeted therapy with osimertinib
• Analysis for presence of all other cancers except NCSLC
• Analysis of other EGFR sensitizing variants within exons 18 to 24 using ctDNA for applications related to NSCLC
CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (cont.)

Resources:

Literature reviewed 06/26/18. 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 06/14/16 may be requested from the BCBSAZ Medical Policy and Technology Research Department.


CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (cont.)

Resources: (cont.)

Liquid biopsy tests, include, but are not limited to:

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Test Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocpt Liquid Biopsy (Biocpt, Inc.)</td>
<td>Targets variants found in lung and breast cancers. The test uses a proprietary real-time quantitative PCR and using Sanger sequencing, sequences the amplified product to confirm variants.</td>
</tr>
<tr>
<td>CancerIntercept® (Pathway Genomics)</td>
<td>A 96-gene panel designed to detect variants in 9 driver genes involved primarily in breast, ovarian, lung and colorectal cancers, as well as melanoma.</td>
</tr>
<tr>
<td>CellSearch® System (Janssen Diagnostics, formerly Veridex)</td>
<td>FDA-approved for monitoring metastatic breast, colorectal and prostate disease and CTCs.</td>
</tr>
<tr>
<td>CellMax-LBx Liquid Biopsy (CellMax Life)</td>
<td>Uses a blood sample to profile 73 genes from circulating tumor DNA (ctDNA), to identify and assess actionable genomic alterations.</td>
</tr>
<tr>
<td>CellMax-CRC Colorectal Cancer Early Detection Test (CellMax Life)</td>
<td>Uses a blood sample to locate circulating tumor cells, screening for colorectal cancer at earlier stages.</td>
</tr>
<tr>
<td>CellMax-PanCa Monitoring Test (CellMax Life)</td>
<td>Uses a blood sample to locate circulating tumor cells.</td>
</tr>
<tr>
<td>CellMax-Prostate Cancer Test</td>
<td>Uses a blood sample to assess the probability of a positive prostate biopsy for individuals with interderminate PSA levels.</td>
</tr>
<tr>
<td>Circulogene Liquid Biopsy (Circulogene Theranostics)</td>
<td>Uses a finger stick blood sample and NGS to monitor known tumor variants in 50 cancer-associated genes for targeted therapy.</td>
</tr>
<tr>
<td>ClearID®Solid Tumor Panel (Cynvenio)</td>
<td>Uses a blood sample to analyze both circulating tumor cells and cell-free DNA alongside the individuals healthy DNA (germline) to determine a clear distinction between tumor and germline.</td>
</tr>
<tr>
<td>ClearID® HER2 Expression Liquid Biopsy (Cynvenio)</td>
<td>Uses a blood test to monitor for the presence of Her-expressing cells. In addition to breast cancer, HER2 has been shown to be overexpressed in several other malignancies including gastric and lung cancers.</td>
</tr>
<tr>
<td>Cobas® EGFR Mutation Test v2 (Roche Molecular Systems)</td>
<td>A real-time PCR test FDA-approved as a companion diagnostic aid for selecting individuals with NSCLC who have EGFR exon 19 deletions and L858R substitution variants for targeted therapy with Tarceva® (erlotinib).</td>
</tr>
<tr>
<td>DEPArray™ HER2 (PacificDX)</td>
<td>Uses droplet digital PCR to analyze cell-free DNA and RNA to identify specific driver variants for which targeted therapy is available for NSCLC.</td>
</tr>
<tr>
<td>FoundationAct® (Foundation Medicine)</td>
<td>Liquid biopsy assay for solid tumors, such as non-small cell lung cancer, breast, colon and prostate.</td>
</tr>
<tr>
<td>GeneStrat® (Biodesix)</td>
<td>Uses droplet digital PCR to analyze cell-free DNA and RNA to identify specific driver variants for which targeted therapy is available for NSCLC.</td>
</tr>
</tbody>
</table>

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CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (cont.)

Resources: (cont.)

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<table>
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</tr>
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<tr>
<td>Guardant360® (Guardant Health)</td>
<td>Uses NGS to identify variants in 73 genes associated with several different cancers.</td>
</tr>
<tr>
<td>PlasmaSELECT™ (Personal Genome Diagnostics)</td>
<td>Targeted panel of 64 cancer genes. Analyses for sequence mutations, rearrangement or microsatellite instability can be performed together or separately.</td>
</tr>
<tr>
<td>OncoBEAM™ (Sysmex Inostics)</td>
<td>Tests allow for molecular genetic analysis of cell-free tumor DNA from blood.</td>
</tr>
<tr>
<td>Oncotype SEQ™ (Genomic Health)</td>
<td>Uses next-generation sequencing (NGS) to identify actionable genomic alterations for late-stage lung, breast, colon, melanoma, ovarian, and gastrointestinal cancers.</td>
</tr>
<tr>
<td>Velox™ (IVDiagnostics)</td>
<td>Monitors circulating tumor cells in the body. It is used for patients with metastatic (advanced stage) cancers: breast, lung, Ovarian, prostate, colorectal, kidney, melanoma, leukemia and pancreatic.</td>
</tr>
</tbody>
</table>
CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (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 nílnígíí Blue Cross Blue Shield of Arizona haada yít’éego bina’id’ilkidgo éí doodago Háída bíí aníiyeedígíí t’áádoó le’é yina’id’ilkidgo beehaz’áánii hóló díí t’áá hazaadk’éhí háká a’doowolgo bee haza’á doó báq̲h̲ ilínígóó. Atá’ halne’ilígíí kójí bíchí’í hadilínih 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關入插項目的名稱 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 thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một tháng dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعدك قضية بخصوص Blue Cross Blue Shield of Arizona الضرورية بلغتك من دون أي تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.
CIRCULATING TUMOR DNA AND CIRCULATING TUMOR CELLS FOR CANCER MANAGEMENT (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyon tinutuwan, ay may mga katarungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuhang tulog at impormasyon sa iyon wika ng walang gastos. Upang makuasa 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 그림도 다음과 정보를 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 그렇게 해서 귀하의 문제에 대해 877-475-4799를 전화해주시기 바랍니다.

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 او کمک می‌کنید، سوال در مورد اطلاعات به زبان خرد را به شماره رایگان دریافت نمایید 877-475-4799.

Assyrian: Blue Cross Blue Shield of Arizona بە دەستبەردەوەیە بۆ کەسەکەیان یەکەلەیەکان دەکاتە، نێوەیەکان دەکاتە، 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: หากคุณหรือผู้ที่ได้รับการช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizonaคุณสามารถขอความช่วยเหลือและข้อมูลในภาษาของคุณได้โดยไม่ต้องใช้เงิน โทร 877-475-4799.