NONINVASIVE PRENATAL TESTING FOR FETAL ANEUPLOIDIES AND MICRODELETIONS USING CELL FREE FETAL DNA

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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Description:

Fetal chromosomal abnormalities occur in approximately 1 in 160 live births. Most fetal chromosomal abnormalities are aneuploidies, defined as an abnormal number of chromosomes. The trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. The most important risk factor for trisomy syndromes is maternal age. The approximate risk of a trisomy 21 (T21, Down syndrome) affected birth is 1 in 1100 at age 25-29. The risk of a fetus with T21 (at 16 weeks gestation) is about 1 in 250 at age 35 and 1 in 75 at age 40.

Trisomy 21 is the most common cause of human birth defects and provides the impetus for current maternal serum screening programs. Other trisomy syndromes include Trisomy 18 (T18; Edwards syndrome), and trisomy 13 (Patau syndrome), which are the next most common forms of fetal aneuploidy, although the percentage of cases surviving to birth is low and survival beyond birth is limited. The prevalence of these other aneuploidies is much lower than the prevalence of T21 and identifying them is not currently the main intent of prenatal screening programs. Also, the clinical implications of identifying trisomy 18 and 13 are unclear, as survival beyond birth is limited for both conditions.

Sex chromosome aneuploidies (e.g., 45, X [Turner Syndrome]; 47, XXY, 47, XYY) occur in approximately 1 in 400 live births. These aneuploidies are typically diagnosed postnatally, sometimes not until adulthood, such as during an evaluation of diminished fertility. Alternatively, sex chromosome aneuploidies may be diagnosed incidentally during invasive karyotype testing of pregnant women at high-risk for Down syndrome. The net clinical value of prenatal diagnosis of sex chromosome aneuploidies is unclear. Potential benefits of early identification such as the opportunity for early management of the manifestations of the condition must be balanced against potential harms that can include stigmatization and distortion of a family’s view of the child.

Sequencing-based lab tests to determine trisomy 21, 18, 13 or other chromosomal abnormalities include, but are not limited to:

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Test components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmony™ (Roche)</td>
<td>Trisomies 21, 18 and 13</td>
</tr>
<tr>
<td>InformaSeq™ (Integrated Genetics)</td>
<td>Trisomies 21,18 and 13 with optional test for sex chromosome abnormalities</td>
</tr>
<tr>
<td>MaterniT21™ PLUS Test (Sequenom)</td>
<td>Trisomies 21, 18 and 13 and fetal sex aneuploidies. Enhanced sequencing series includes trisomies 16, 22 and 7 and microdeletions</td>
</tr>
<tr>
<td>MaterniT21 Test (Sequenom)</td>
<td>Trisomies 21, 18 and 13 and sex chromosome abnormalities. An extended panel tests for microdeletions</td>
</tr>
<tr>
<td>Panorama™ (Natera)</td>
<td>Trisomies 21, 18 and 13</td>
</tr>
<tr>
<td>Q-Natal Advanced Test (Quest Diagnostics)</td>
<td>Trisomies 21, 18 and 13</td>
</tr>
<tr>
<td>Verifi® Prenatal Test (Integrated Genetics)</td>
<td>Trisomies 21, 18 and 13</td>
</tr>
<tr>
<td>VisibiliT™ (Sequenom)</td>
<td>Trisomies 21 and 18</td>
</tr>
</tbody>
</table>
Definitions:

Microdeletion Syndrome:

Microdeletions (also known as submicroscopic deletions) are defined as chromosomal deletions that are too small to be detected by microscopy or conventional cytogenetic methods. They can be as small as 1 and 3 megabases (Mb) long. Microdeletions, along with microduplications, are collectively known as copy number variations (CNVs). CNVs can lead to disease when the change in copy number of a dose-sensitive gene or genes disrupts the ability of the gene(s) to function and affects the amount of protein produced. A number of genomic disorders associated with microdeletion of been identified. The disorders have distinctive, and in many cases serious clinical features.

Microdeletions include, but are not limited to:

- 1p36 deletion syndrome
- 22q11.2 deletion syndrome
- Angelman/Prader-Willi syndrome
- Cri-du-chat syndrome
- Wolf-Hirschhorn syndrome

Criteria:

COVERAGE FOR MATERNITY IS DEPENDENT UPON BENEFIT PLAN LANGUAGE. REFER TO MEMBER’S SPECIFIC BENEFIT PLAN BOOKLET TO VERIFY BENEFITS.

Although nucleic acid sequencing-based lab testing of maternal serum for chromosome abnormalities with genetic testing panels is considered investigational, there may be individual components of the panel that are medically necessary. Testing for individual components of a genetic panel may be medically necessary in some clinical situations. Other Medical Coverage Guidelines may apply to these individual components.

- If benefit coverage for maternity is available, nucleic acid sequencing-based lab testing of maternal serum for trisomy 21 is considered medically necessary in women with documentation of ALL of the following:
  1. Individual is undergoing screening for trisomy 21
  2. Singleton pregnancy
  3. Individual has received counseling regarding the risk of a false positive test
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Criteria: (cont.)

➢ If benefit coverage for maternity is available, concurrent nucleic acid sequencing-based lab testing of maternal serum for trisomy 13 and/or 18 is considered medically necessary in women who meet criteria for and are undergoing sequencing-based testing of maternal plasma for trisomy 21.

➢ If benefit coverage for maternity is available, nucleic acid sequencing-based lab testing of maternal serum for all other indications not previously listed or if above criteria not met is considered experimental or investigational based upon:

1. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
2. Insufficient evidence to support improvement outside the investigational setting.

These indications include, but are not limited to:

- Fetal sex chromosome aneuploidies
- Microdeletions
- Trisomy 9
- Trisomy 13 and/or 18, other than in the situations specified above
- Trisomy 16
- Trisomy 21 in women with twin or multiple pregnancies
- Trisomy 22

➢ If benefit coverage for maternity is available, nucleic acid sequencing-based lab testing of maternal serum for chromosome abnormalities with genetic testing panels for all indications 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.
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Resources:

Literature reviewed 11/08/16. 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.


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Resources: (cont.)


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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/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield de 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 níilínígíí Blue Cross Blue Shiel’d of Arizona haída yít’éego bínà’idiñídígo éí doodago Háída bíjá aniyyeeédíígi t’áadoo le’é yina’idiñídígo beehaz’áánii hóoló díí t’áa hazaad’ehí háká a’dóowolgó bee haz’a doo bááh ilínígóó. Atá’ halné’ilíi kój koj’ bich’jí’ hodilíih ní 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 thợ dịch viên, xin gọi 877-475-4799.

Arabic: إن كان لديك أو لدى شخص تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فقد الحق في الحصول على المساعدة والموارد الضرورية بلغك من دون أي تكلفة، للتحدث مع مرشح اتصل ب 877-475-4799.
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Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulungan, 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 통역사와 얘기하기 위해서는 877-475-4799 로 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 اطلاعات به زبان خود را به م.SuspendLayout دریافت نمایید 99-475-4799. [پاسخ حاوی تمسیح نماید.]

Assyrian: Blue Cross Blue Shield of Arizona ئەگەر ۆپ دەتوانیت بەندەوە، بەکەوە، بەکەوە، ئەگەر ۆبەرترە بەرەوە، بەکەوە. 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: คุณสามารถสอบถามความข้อมูลลงของ Blue Cross Blue Shield of Arizona คุณสามารถสอบถามความข้อมูลลงของ Blue Cross Blue Shield of Arizona ที่ 877-475-4799.