BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

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STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS

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.

STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS (cont.)

Description:

Mesenchymal Stem Cells (MSCs):
MSCs can differentiate into a variety of tissue types including various musculoskeletal tissues. MSCs have been investigated for the treatment of orthopedic disorders including damaged cartilage, ligaments, tendons and intervertebral discs. MSCs are associated with the blood vessels within bone marrow, synovium, fat and muscle, where they can be mobilized for endogenous repair as occurs with healing of bone fractures. *Orthobiologics* is a term introduced to describe interventions using cells and biomaterials to support healing and repair. Cell therapy is the application of MSCs directly to a musculoskeletal site. Tissue engineering techniques use MSCs and/or bioactive molecules such as growth factors and scaffold combinations to improve the efficiency of repair or regeneration of damaged musculoskeletal tissues.

Bone marrow aspirate is considered to be the most accessible source and, thus, the most common place to isolate MSCs for treatment of musculoskeletal disease. MSC therapy refers to the procurement, processing and subsequent infusion or implantation of the MSCs into the intended anatomic area to promote healing or regeneration of damaged tissue. Concentrated autologous MSCs do not require approval by the U.S. Food and Drug Administration (FDA).

Allograft Bone Products:
Demineralized bone matrix (DBM) is processed allograft bone that is considered minimally processed tissue and does not require FDA approval. At least 4 commercially available DBM products marketed as containing viable stem cells:

- Allostem®: partially demineralized allograft bone seeded with adipose-derived MSCs
- Map3™: contains cortical cancellous bone chips, DBM and cryopreserved multipotent adult progenitor cells (MAPC®)
- Osteocel Plus®: DBM combined with viable MSCs isolated from allogeneic bone marrow
- Trinity Evolution Matrix™: DBM combined with viable MSCs isolated from allogeneic bone marrow
- Other products contain DBM and ~~are~~ designed to be mixed with bone marrow aspirate include:
    - Fusion Flex™: dehydrated moldable DBM scaffold that will absorb autologous bone marrow aspirate
    - Ignite®: injectable graft with DBM that can be combined with autologous bone marrow aspirate

STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS (cont.)

Description: (cont.)

Combination Products:
DBM combination products are intended to be mixed with bone marrow aspirate:

Product	Matrix Type	Mix with Autologous MSC
Vitoss® Bioactive Foam Bone Graft Substitute	Type I bovine collagen	X
NanOss BVF-E	Nanocrystalline hydroxyapatite	
OrthoBlast® II Demineralized bone matrix putty and paste	Human cancellous bone chips	
CopiOs® Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	X
DBX® Demineralized bone matrix putty, paste and mix	Processed human bone and sodium hyaluronate	X
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Human cancellous bone	X
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen	X
DynaGraft® II Gel and Putty	Processed human bone particles	

MSCs used in the Regenexx-C procedure are considered drugs or biologic products and thus require submission of a new drug application (NDA) or biologic license application (BLA) to FDA. The Regenexx-C procedure originally used stem cells derived from bone marrow or synovial fluid and cultured the cells with autologous platelet lysate in a separate laboratory for culture and other compounds such antibiotics were added before the material was returned to the patient in a separate orthopedic procedure. To date, no NDA or BLA has been approved by FDA for this product. As of 2015, the expanded stem cell procedure is only offered in the Cayman Islands. Regenexx® Stem Cell Procedure is offered through a network of facilities in the United States that provide same-day stem cell and blood platelet procedures, which do not require FDA approval. These procedures, along with the Regenexx® Super Concentrated Platelet Rich Plasma, are marketed as treatments for arthritis and injuries of the knee, hip, shoulder, spine, hand and wrist, foot and ankle and elbow.

STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS (cont.)

Criteria:

- Mesenchymal stem cell therapy for all orthopedic applications is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Repair or regeneration of musculoskeletal tissue

- Allograft bone products containing viable stem cells for all orthopedic applications are 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.

- Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered ***experimental or investigational*** for all orthopedic applications 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.

STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS (cont.)

Resources:

Literature reviewed 08/15/17. 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.

1. 8.01.52 BCBS Association Medical Policy Reference Manual. Orthopedic Applications of Stem Cell Therapy. Re-Issue date 07/13/2017, issue date 04/08/2010.

2. Tirkkonen L, Haimi S, Huttunen S, et al. Osteogenic medium is superior to growth factors in differentiation of human adipose stem cells towards bone-forming cells in 3D culture. *Eur Cell Mater.* 2013;25:144-158.

STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS (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 nílínigíí Blue Cross Blue Shield of Arizona haada yit'éego bína'ídíłkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yína'ídíłkidgo beehaz'áanii hóló díí t'áá hazaadk'ehjí háká a'doowołgo bee haz'ą doo bąąh íłínígóó. Ata' halne'ígíí kojį' bich'į' hodíilnih 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 thêm 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 تساعده أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون اية تكلفة. للتحدث مع مترجم اتصل ب 877-475-4799.

STEM CELL THERAPY, ORTHOPEDIC APPLICATIONS (cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw, o ang iyong tinutulangan, 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 Arizona 에 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 او کمک میکنید ، سوال در مورد Blue Cross Blue Shield of Arizona ، داشته باشید حق این را دارید که کمک و اطلاعات به زبان خود را به طور رایگان دریافت نمایید 877-475-4799
[تماس حاصل نمایید.

Assyrian:

[illegible] Blue Cross Blue Shield of Arizona [illegible]
[illegible] 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: หากคณ หรอคนทคณกาลงชวยเหลอมคาถามเกยวกบ Blue Cross Blue Shield of Arizona
คณมสทธทจะไดรบความชวยเหลอและขอมลในภาษา ของคณไดโดยไมมคาใชจาย พดคยกบลาม โทร 877-475-4799