



MEDICAL COVERAGE GUIDELINES
SECTION: MEDICINE

ORIGINAL EFFECTIVE DATE: 02/05/13
LAST REVIEW DATE: 01/22/19
LAST CRITERIA REVISION DATE: 10/24/17
ARCHIVE DATE:

GENE THERAPY

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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GENE THERAPY (cont.)

Description:

Gene therapy has been investigated as a method to correct a defective gene, or to prevent or treat disease. Approaches include:

- Inserting a normal gene to replace an abnormal gene (most common approach)
- Exchanging an abnormal gene for a normal gene
- Mending an abnormal gene
- Changing the degree to which a gene is turned on or off

Criteria:

For chimeric antigen receptor T (CAR T) cell immunotherapy with Kymriah™ (tisagenlecleucel) criteria, refer to BCBSAZ Medical Coverage Guideline #O1037, “Kymriah™ (tisagenlecleucel)”.

For adoptive immunotherapy and chimeric antigen receptor T (CAR T) cell immunotherapy other than with Kymriah™ (tisagenlecleucel) criteria, refer to BCBSAZ Medical Coverage Guideline #O368, “Immunotherapy, Adoptive”.

- Gene therapy 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.

Resources:

Literature reviewed 01/30/18. We do not include marketing materials, poster boards and non-published literature in our review.

1. Aiuti A, Cassani B, Andolfi G, et al. Multilineage hematopoietic reconstitution without clonal selection in ADA-SCID patients treated with stem cell gene therapy. *J Clin Invest.* 2007 Aug;117(8):2233-2240.
2. Alton EW, Boyd AC, Cheng SH, et al. A randomised, double-blind, placebo-controlled phase IIB clinical trial of repeated application of gene therapy in patients with cystic fibrosis. *Thorax.* Nov 2013;68(11):1075-1077.

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GENE THERAPY (cont.)

Resources: (cont.)

3. Blaese RM. What is the status of gene therapy for primary immunodeficiency? *Immunol Res.* 2007;38(1-3):274-284.
4. Centre for Genetics Education. Gene Therapy Fact Sheet. *The Australasian Genetics Resource Book.* 06/2007.
5. Clinical Trials.gov. Gene Therapy for Chronic Granulomatous Disease NCT00394316. Accessed 07/09/2008.
6. Constable IJ, Lai CM, Magno AL, et al. Gene Therapy in Neovascular Age-related Macular Degeneration: Three-Year Follow-up of a Phase 1 Randomized Dose Escalation Trial. *American journal of ophthalmology.* May 2017;177:150-158.
7. FDA. Human Gene Therapy and The Role of the Food and Drug Administration. 09/2000.
8. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M. Gene therapy of primary T cell immunodeficiencies. *Gene.* Aug 10 2013;525(2):170-173.
9. Gaspar HB, Qasim W, Davies EG, Rao K, Amrolia PJ, Veys P. How I treat severe combined immunodeficiency. *Blood.* Nov 28 2013;122(23):3749-3758.
10. Knight S, Collins M, Takeuchi Y. Insertional mutagenesis by retroviral vectors: current concepts and methods of analysis. *Curr Gene Ther.* Jun 1 2013;13(3):211-227.
11. Loring HS, ElMallah MK, Flotte TR. Development of rAAV2-CFTR: History of the First rAAV Vector Product to be Used in Humans. *Hum Gene Ther Methods.* Apr 2016;27(2):49-58.
12. MedlinePlus. Genes and Gene Therapy. Updated 10/28/2008.
13. Mukherjee S, Thrasher AJ. Gene therapy for PIDs: progress, pitfalls and prospects. *Gene.* Aug 10 2013;525(2):174-181.
14. Nienhuis AW. Development of gene therapy for blood disorders. *Blood.* 2008 May 1;111(9):4431-4444.
15. Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of Antithrombin in Hemophilia A or B with RNAi Therapy. *The New England journal of medicine.* Aug 31 2017;377(9):819-828.
16. Rakoczy EP, Lai CM, Magno AL, et al. Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a phase 1 randomised clinical trial. *Lancet (London, England).* Dec 12 2015;386(10011):2395-2403.

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17. Ryser MF, Roesler J, Gentsch M, Brenner S. Gene therapy for chronic granulomatous disease. *Expert Opin Biol Ther.* 2007 Dec;7(12):1799-1809.
18. Seger RA. Modern management of chronic granulomatous disease. *Br J Haematol.* 2008 Feb;140(3):255-266.
19. Shore ND, Boorjian SA, Canter DJ, et al. Intravesical rAd-IFNalpha/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin-Refractory or Relapsed Non-Muscle-Invasive Bladder Cancer: A Phase II Randomized Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Oct 20 2017;35(30):3410-3416.
20. Simunovic MP, Xue K, Jolly JK, MacLaren RE. Structural and Functional Recovery Following Limited Iatrogenic Macular Detachment for Retinal Gene Therapy. *JAMA ophthalmology.* Mar 1 2017;135(3):234-241.
21. U.S. National Library of Medicine®. What is Gene Therapy? *Genetics Home Reference.* 10/24/2008.
22. U.S. National Library of Medicine®. What are the Ethical Issues Surrounding Gene Therapy? *Genetics Home Reference.* 10/24/2008.
23. U.S. National Library of Medicine®. Is Gene Therapy Available to Treat My Disorder? *Genetics Home Reference.* 10/24/2008.
24. Up to Date. X-Linked Severe Combined Immunodeficiency (SCID). 12/2013.
25. UpToDate.com. Chronic Granulomatous Disease: Treatment and Prognosis. 07/14/2015, 12/01/2013.
26. UpToDate.com. Adenovirus pathogenesis and vector applications. Last updated 10/18/2017.
27. UpToDate.com. Cystic fibrosis: Investigational therapies. Last updated 06/14/2017.
28. UpToDate.com. Hemophilia A and B: Routine management including prophylaxis. Last updated 12/22/2017.
29. Westphal M, Yla-Herttuala S, Martin J, et al. Adenovirus-mediated gene therapy with sitimagene ceradenovec followed by intravenous ganciclovir for patients with operable high-grade glioma (ASPECT): a randomised, open-label, phase 3 trial. *Lancet Oncol.* Aug 2013;14(9):823-833.
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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/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 nilinígíí Blue Cross Blue Shield of Arizona haada yit'éego bina'idííkidgo éí doodago Háida bíjá anilyeedígíí t'áadoo le'é yina'idííkidgo beehaz'áanii hólg díí t'áa hazaadk'ehjí háká a'doowołgo bee haz'ą doo baqah ilínígóó. Ata' halne'ígíí kojí' bich'í' 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 تساعد أسئلة بخصوص Blue Cross Blue Shield of Arizona، فلديك الحق في الحصول على المساعدة والمعلومات الضرورية بلغتك من دون أية تكلفة. للتحدث مع مترجم اتصل بـ 877-475-4799.

