APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member’s particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member’s benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations, and any state-specific Medicaid mandates. Links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change. Lines of business are also subject to change without notice and are noted on www.wellcare.com. Guidelines are also available on the site by selecting the Provider tab, then “Tools” and “Clinical Guidelines”.

BACKGROUND

DiGeorge syndrome (DGS) is a disorder in which there is a defect in the development of the pharyngeal pouch system. The syndrome is most commonly caused by a chromosomal deletion at 22q11.2. DGS includes many signs and symptoms with the classic three being congenital cardiac anomalies, underdevelopment of the thymus, and hypocalcemia due to parathyroid hypoplasia. Other common findings in DGS patients include, cleft lip or palate, club feet, single kidney, esophageal atresia, butterfly vertebra, rib abnormalities, and laryngomalacia.¹ Thanks to medical advances, improved palliative cardiac repair, and medical management of immunodeficiency, infant mortality in DGS is now approximately 4%.²

Epidemiology - A large population-based study in the United States revealed that chromosome 22q11.2 deletions were relatively common in the general population, making chromosome 22q11.2 deletion syndrome the most common microdeletion
syndrome. The study found that 1 in 5950 live births had a deletion in this chromosomal area, and within the subset of infants, 83 percent had an associated cardiac defect. Other population studies have reported the incidence to be as high as 1 in 4000. Based on the study results, 22qDS is likely underdiagnosed due to the fact that the phenotypic findings may be very mild in some patients.³

**Complete versus Partial DiGeorge Syndrome** – DGS is divided into two subtypes, partial and complete. The patient’s type is based on the level of immunologic function and degree of thymic hypoplasia.³

**Complete DiGeorge Syndrome** – The term complete DiGeorge syndrome is used to describe patients with the syndrome who have profound T-cell deficiency. While in other forms of DiGeorge’s Syndrome, there may be some recovery of T-cell function, it does not occur in the severest form, Complete DiGeorge’s.⁴ Complete This form of severe combined immunodeficiency (SCID), occurs in less than 1 percent of patients with 22q11.2 deletion syndrome. In these patients, the thymus is completely absent and their T-cell count is fewer than 50 T cells/mm³ or fewer than 50 naïve (CD45RA+ CD62L+) T cells/mm³. DGS can be detected by a newborn screening for T-cell lymphopenia or by the development of recurrent severe infections, chronic diarrhea, and failure to thrive.¹⁵ Without early detection and treatment with immunologic reconstitution, complete DGS is fatal within the first year of life with almost all children dying from infections. Patients with complete DGS require immunoreconstitution for survival.⁷

**Atypical Complete DiGeorge Syndrome** – Some patients with severe T-cell deficiency develop a form of SCID called atypical complete DiGeorge Syndrome. These patients have a T-cell count that is higher than normal with complete DGS even though they do not have a thymus. These patients may experience erythrodema (exfoliative dermatitis), oligoclonal T-cell expansion, lymphadenopathy, and or elevated serum immunoglobulin E (IgE) levels. These symptoms can be classified as Omenn syndrome defined by T lymphopenia.¹

**Partial DGS** – The majority of people with DiGeorge Syndrome have partial DGS.⁶ Partial or “leaky” SCID, including Omenn syndrome, is defined by T lymphopenia (age 4 years, SCID, age <2 years, <1000 cells/mm³, age 2–4, cells <800/mm³, ages >4, cell <600 cells/mm³, and PHA values < 30 % of control value).¹⁰ Markert ML, Devlin BH, McCarthy EA. Thymus transplantation. 10 Impaired T-cell production occurs in most patients and is not normally severe. Also, the patient’s CD3+ T-cell counts may gradually improve. Opportunistic infections are not as high as a risk for patients with partial DGS as they are for patients with complete, but many will have recurring sinus and pulmonary infections. Humoral immunodeficiencies are associated with partial DGS and the patient may have an increased prevalence of immunoglobulin A (IgA) deficiency and functional antibody defects. Unlike complete DGS, partial DGS is not life threatening.¹,³

**Genetic analysis** – Although not required for a definite diagnosis, genetic testing is necessary in defining the molecular basis of the patient’s DGS. The first step in testing is typically an assay to check for microdeletion in the DCS region of chromosome 22. These deletions can typically be detected by FISH or a probe specific to the commonly deleted region. The testing can be performed by many laboratories.⁸,⁹,¹⁰

**Treatment** – Cultured postnatal thymic transplant is currently the preferred treatment for infants with complete DGS.¹ Thymus transplantation results in normal immune reconstitution and a median survival rate of 70% up to 4.7 years.⁴ Hematopoietic cell transplantation (HCT) from bone marrow or peripheral blood sources is an easier and more available alternative to thymic transplantation in patients with complete DGS who have an HLA-identical donor.¹¹

**Thymus Transplantation** – A study published in Clinical Immunology followed the transplantation of postnatal allogeneic cultured thymus tissue in sixty subjects under the age of 2 years with complete DiGeorge syndrome. The study participant survival rate was over 70% and naïve T cells developed 3–5 months after transplantation. The transplant recipients were able to discontinue antibiotic prophylaxis, and immunoglobulin replacement. Immunosuppression was used in a subset of subjects and was discontinued when naïve T cells developed.⁷

Another study showed that 43 out of 60 infants treated by cultured postnatal thymic transplantation were alive at the time of reporting. 15 out of 17 of the deaths has occurred within 12 months of the transplant and most were due to infections, with higher risk for mortality-related infection associated with tracheostomies or mechanical ventilation. One of the deaths was related to complications of calcium therapy. For patients with atypical DGC, immunsuppressive therapy was given prior to transplantation to increase the chances of success for tissue engraftment.¹¹

**Hematopoietic cell transplantation** – Transplanting hematopoietic stem cells only, in lieu of stem cells and memory T cells, is not recommended in patients with DGS since donor-derived T cells cannot develop from lymphoid progenitor cells in the absence of thymic tissue. The increase in T cell numbers following HCT in patients with DGS is secondary to expansion of donor memory T cells and not generation of naïve T cells. Therefore, HCT does not restore a full T cell repertoire, it does, however, appear to provide adequate immune function.¹¹
An international survey studied 17 complete DGS patients who underwent HCT from 1995 to 2006. 7 of the 17 participants, 41 percent, were alive at the time of reporting. Only 2 participants did not experience serious adverse events. Of the 10 patients who did not survive, death occurred at an average or 7 months following the HCT transplant. The survival rate was higher, 5 of 7 participants, in patients with an HLA-identical sibling donor. The most common causes of death were related to the underlying disorder and complications from HCT.\textsuperscript{11}

Duke University Medical Center Thymus Transplantation - Currently in the United States, thymus transplantation is performed under an Investigational New Drug application with Food and Drug Administration (FDA). Treatment can be received as part of expanded access at Duke University Medical center and participants must be enrolled in a Phase I/II safety and efficacy study for the treatment of complete DiGeorge anomaly. Eligible participants undergo thymus transplantation and biopsy. Immune function testing is continued for one year post-transplantation.\textsuperscript{12}

Thymus donor screening - All thymus donors and thymus tissue undergo standard donor infectious disease screening as required by the Food and Drug Administration for cell and tissue based products. The donor’s blood is examined by flow cytometry to insure that the donor has greater than 50% naïve (CD45RA+CD62L+) T cells. HLA and ABO typing are done but matching is not required.\textsuperscript{7}

Donor exclusions include: less than 50% naïve (CD45RA+CD62L+) T cells, 22q11.2 hemizygosity or Down syndrome in the thymus donor, and autoimmune disease in primary relatives.\textsuperscript{7}

Thymus tissue processing - Thymus tissue is aseptically sliced into pieces approximately 15 by 15 mm and 0.5 mm thick and held in tissue culture in the laboratory. Transplantation into the recipient occurs after 2–3 weeks of culture and after all evaluations have been completed.\textsuperscript{7}

Thymus transplantation – A pediatric surgeon transplants the donor thymus tissue into both quadriceps muscles of the athymic recipient in the hospital operating room. The surgeon creates individual pockets in the quadriceps muscle for each tissue slice. Immunosuppression therapy is used only in subjects with atypical complete DiGeorge anomaly.\textsuperscript{7}

**POSITION STATEMENT**

**Applicable To:**

- Medicaid – All Markets

WellCare provides coverage for Thymus transplantation for severe combined immunodeficiency syndrome due to DiGeorge syndrome without a prerequisite for a prior failure of hematopoietic cell transplantation (HCT). HLA-identical HCT is may also be considered as a treatment for athymia associated with DiGeorge’s Syndrome. The life expectancy for infants with complete DGS who do not undergo a transplantation procedure is less than one year (Complete DiGeorge syndrome: persistence of profound immunodeficiency.)\textsuperscript{13}

**Exclusions**

1. Unrepaired cyanotic congenital heart disease.
2. Uncontrolled infections (defined by requiring ventilator, dialysis, or vasopressor support or anticipated as requiring such support within 6 months).
3. Pregnancy or refusal to comply with contraceptive measures as indicated in the consent form.
4. HIV infection.
5. Heart surgery conducted less than 4 weeks prior to the projected transplantation date.
6. Heart surgery anticipated within 3 months after the proposed time of transplantation.
7. Rejection by the surgeon or anesthesiologist as a surgical candidate.
8. Lack of sufficient muscle tissue to accept a transplant of 2000 mm\textsuperscript{2} surface area/m\textsuperscript{2} BSA of the recipient.
9. CMV infection - In patients with atypical complete DiGeorge anomaly, CMV infection (CMV PCR result of >500 copies/ml on two consecutive assays or two positive urine cultures) is an exclusion.
10. Ventilator dependence (includes CPAP/BiPAP) for uncontrolled infection or irreversible condition (i.e., airway or central nervous system anomaly).
11. Malignancy

**Coverage**

1. Patient must have Complete or “Atypical” DiGeorge Syndrome (see definition criteria) with poor thymus function as agreed upon by a subject matter expert and the Data and Safety Monitoring Board. Screening for poor thymus function includes review of medical testing laboratory studies and physical examinations; **AND**, 
2. Patient must have an immunodeficiency, or severe autoimmunity for which development of naive T cells would be expected to lead to clinical improvement; **AND**,  
3. Immune criteria as detailed in the protocol must be met; **AND**,  
4. Flow cytometry and PHA studies must be performed twice, once within 3 months of transplantation and once within one month of transplantation. Studies must be performed in a CLIA or CAP certified laboratory, preferably Duke Clinical Immunology Laboratory; **AND**,  
5. Due to limited evidence - following nurse review all requests must be sent to transplant medical director for secondary review regardless of review outcome. *Note for PEGA – All reviews must route to Medical Necessity Not Established Due to Limited Evidence outcome*

**CODING**

**CPT Codes**  *This list may not be all inclusive*

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<td>81422</td>
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<td>B cells, total count</td>
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**ICD-10-PCS Codes**  *This list may not be all inclusive*

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Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member’s benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

**REFERENCES**


**MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS**

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