Policy Number	**RX501.139**
Policy Effective Date	**12/15/2025**

Treatment of Congenital Athymia

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

Coverage

Allogeneic processed thymus tissue-agdc **may be considered medically necessary** for pediatric individuals with congenital athymia if they meet criteria 1 through 8:

1. Are 21 years old or younger at the time of surgical procedure.
2. Confirmed diagnosis of congenital athymia via flow cytometry documenting fewer than 50 naïve T cells/mm^3 in the peripheral blood or less than 5% of total T cells being naïve in phenotype.
3. Diagnosis of severe combined immunodeficiency has been ruled out.
4. Documentation that following infection control measures can reasonably be maintained until the development of thymic function is established. (See policy guidelines for additional details).
    a. Antimicrobial prophylaxis to prevent bacterial, fungal, and viral infections;
    b. Immunoglobulin replacement therapy;
    c. Strict infection control, sanitation, and isolation protocols to limit exposure to infectious pathogens.
5. Absence of comorbidities, in the opinion of the treating clinician, that are reasonably likely to result in severe complications, including death from administration of allogeneic processed thymus tissue (for example, pre-existing renal impairment, or cytomegalovirus or Epstein-Barr virus infection).
6. Screened for anti-human leukocyte antigen (HLA) antibodies prior to receiving allogeneic processed thymus tissue-agdc. Individuals testing positive for anti-HLA antibodies should receive allogeneic processed thymus tissue-agdc from a donor who does not express those HLA alleles.
7. If the individual has received a prior hematopoietic cell transplantation or a solid organ transplant, HLA matching of allogeneic processed thymus tissue-agdc to recipient alleles that were not expressed in the donor is required.
8. Has not previously received thymus tissue implantation for the treatment of congenital athymia in their lifetime.

Allogeneic processed thymus-agdc **is considered not medically necessary** for pediatric individuals with congenital athymia when the above criteria are not met.

Allogeneic processed thymus-agdc **is considered experimental, investigational and/or unproven** for all other indications.

Repeat treatment with allogeneic processed thymus-agdc **is considered experimental, investigational and/or unproven.**

Policy Guidelines

Recommended Dose

The recommended dose range is 5,000 to 22,000 mm^2 of allogeneic processed thymus tissue-agdc/m^2 recipient body surface area.

Dosing Limits
1 surgical implantation per lifetime.

Other Considerations
- Allogeneic processed thymus tissue-agdc is administered by a single surgical procedure. The dosage is determined by the total surface area of the allogeneic process thymus tissue-agdc slices and recipient body surface area. A slice is defined as the contents on a single fiber membrane; the allogeneic processed thymus tissue-agdc slices are variable in size and shape. The manufacturer calculates the dose in advance of the specific individual; the amount of product provided is adjusted at the manufacturing facility to ensure the maximum dose for the individual cannot be exceeded. Up to 42 cultured allogeneic processed thymus tissue-agdc slices will be provided to each individual. Individuals with evidence of maternal engraftment or an elevated response to phytohemagglutinin should receive allogeneic processed thymus tissue-agdc with immunosuppressive medications.
- To decrease the risk of graft-versus-host disease, immunosuppressive therapy should be administered prior to and/or after treatment according to the disease phenotype and pre-treatment phytohemagglutinin response in accordance with the recommendations in Table 2 and 3 of the product label.
- Immune reconstitution sufficient to protect against infection is unlikely to develop prior to 6 to 12 months after treatment with allogeneic processed thymus tissue-agdc. For some patients, it may take up to 2 years.
- Immunizations should not be administered in patients who receive allogeneic processed thymus tissue-agdc until the individual's immune-function has been restored. It is recommended prescribers reference the following criteria before deciding to administer an inactivated vaccine: immunosuppressive therapies have been discontinued, immunoglobulin replacement therapy has been discontinued, the total $CD4^+$ T cell count is > 200 cells/mm^3, and there are more $CD4^+$ T cells than $CD8^+$ T cells. It is recommended that no more than 2 inactivated vaccines be given per month. Live vaccines should not be administered until individuals have met the recommended criteria for inactivated vaccines and received vaccinations with inactivated agents.

Description

Congenital athymia is an ultra-rare condition in which infants are born without a functioning thymus. The thymus is crucial for the development, selection, and maturation of T cells, which are essential in effectively fighting infection and regulating the immune system. Without a functioning thymus, children develop severe immunodeficiency, susceptible to life-threatening infections. Without adequate medical treatment and management, children with congenital athymia usually do not live past the first few years of life. Multiple genetic and syndrome disorders, mutations and deficiencies are associated with congenital athymia. Supportive care, such as strict prevention measures, prophylactic antimicrobials, immunoglobulin replacement and isolation have been the mainstay management of children with congenital athymia. Rethymic is a regenerative tissue-based therapy that is indicated for immune reconstitution in

pediatric patients with congenital athymia. The reengineered tissue is implanted in the thigh muscle to help a child with congenital athymia build a functioning immune system to reduce the number of potentially life-threatening infections.

Background

Congenital Athymia

Congenital athymia (CA) is an ultra-rare condition in which individuals are born without a functioning thymus. Estimated incidence in the United States is approximately 17 to 24 infants for every 4 million. (1) The thymus is crucial for the development, selection and maturation of T cells, which are essential in effectively fighting infection and regulating the immune system. (2) Without a functioning thymus, individuals are profoundly immunodeficient, have significant increased susceptibility for infection, and have greater tendency to develop autologous graft-versus-host disease (GVHD). These infections and autoimmune conditions can be fatal, and with only supportive care, children with congenital athymia typically do not survive beyond 2 to 3 years of age. (3) Congenital athymia may be associated with other conditions, such as: DiGeorge syndrome (with or without 22q11.2 deletion syndrome); mutations in the genes *TBX1*, *CHD7*, (CHARGE syndrome), and *FOXN1* (FOXN1 deficiency); diabetic embryopathy. (4, 5)

Diagnosis

Currently, all 50 states in the USA offer newborn screening testing that identifies T cell receptor excision circles. This test may identify infants who have congenital athymia in addition to severe combined immunodeficiency (SCID) (6). Confirmatory diagnosis requires confirmation of low naïve T cells by flow cytometry. (6)

Diagnosis of congenital athymia requires confirmation of profoundly low naïve T cells by flow cytometry and genetic evaluation after initial positive results via SCID newborn screening. Individuals with congenital athymia will have less than 50 naïve T cells/mm^3 or naïve T cells comprising less than 5% of the total T cells. However, congenital athymia individuals and a subset of individuals with SCID also present with a lack of T cells but normal levels of B cells and Natural Killer cells (T-B+ NK+). To differentiate these individuals, a genetic panel for known T-B+ NK+ SCID gene mutations, genetic testing to identify gene associated with either condition, or testing of hematopoietic stem cells using an artificial thymic organoid system can be used. Accurate identification of the causes for immunodeficiency in these individuals is important as to ensure appropriate treatment decisions (e.g., receipt of hematopoietic stem cell transplant vs. cultured thymus tissue implantation). (6)

Treatment

Medical treatment of congenital athymia typically focuses on supportive care. Strict infectious disease prevention measures (e.g., masks, sterile gowns, gloves, frequent handwashing), isolation, and antimicrobial prophylaxis to prevent bacterial, viral and fungal infections are critical. Because B cell function is usually reduced, immunoglobulin replacement should be considered. Immunosuppressive agents including steroids or calcineurin inhibitors may be required to manage inflammatory reactions and reduce the risk of autologous GVHD.

Hematopoietic stem cell transplantation has been performed in patients with congenital athymia, but the efficacy is low.

Regulatory Status
On October 8, 2021, allogeneic processed thymus tissue-agdc (Rethymic®; Enzyvant) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of congenital athymia in pediatric patients.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Congenital Athymia
Clinical Context and Therapy Purpose
The purpose of allogeneic processed thymus-agdc in pediatric individuals with congenital athymia is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- Treatment offers a novel mechanism of action or approach that may allow successful treatment of many patients for whom other available treatments are not available.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is pediatric individuals who are diagnosed with congenital athymia.

Interventions
The therapy being considered is allogeneic processed thymus tissue-agdc. The tissue culture is obtained from an unrelated infant donor ≤9 months old undergoing cardiac surgery where thymus tissue removal is necessary. The tissue is aseptically processed and cultured to reduce donor thymocyte levels and maintain similar overall tissue organization, viability, and retention of cell types necessary for product function. Following 12 to 21 days of culture, the tissue slices are collected for transplantation. These slices are then surgically implanted into patients with congenital athymia. The treatment is intended to reconstitute immunity in patients who are athymic. The proposed mechanism of action involves the migration of recipient T cell progenitors from the bone marrow to the implanted tissue slices, where they develop into naïve immunocompetent recipient T cells. Evidence of thymic function can be observed with the development of naïve T cells in the peripheral blood; this is unlikely to be observed prior to 6-12 months after treatment with allogeneic processed thymus tissue-agdc.

Comparators
Prior to the availability of allogeneic processed thymus tissue-agdc, there was no U.S. Food and Drug Administration (FDA) approved treatment for congenital athymia. Medical management focused on supportive care such as infectious disease prevention measures, antimicrobial prophylaxis, isolation, immunoglobulin replacement and immunosuppressive management.

Outcomes
The general outcomes of interest are disease-specific survival, change in disease status, quality of life, treatment-related mortality and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs).
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Nonrandomized Studies
Primary evidence of safety and effectiveness was based on accumulated data from multiple clinical trials conducted over a period of 28 years at a single center, Duke University. The evidence included integrated data from 10 prospective, single-center, open-label studies that evaluating a total of 105 patients. Ninety-five patients were included in the primary efficacy

analysis. (7, 8) Trial characteristics and results are summarized in Tables 1 and 2, respectively. Patient demographics and baseline characteristics were similar between studies. Median age was 8.5 months (range: 33 days to 2.9 years); 59% were male; 70% White, 22% Black, 4% Asian/Pacific Islander, 2% American Indian/Alaskan Native and 2% multi-race. Immunosuppressive therapy was administered to patients based on disease phenotype and pre-allogeneic processed thymus tissue-agdc phytohemagglutinin (PHA) response. No re-treatment occurred.

The primary evidence of efficacy is based on a comparison of 1-year survival between the study participants and natural history populations. Natural history data were obtained from a contemporaneous population of 49 patients with congenital athymia who were observed from 1991-2017 and received only supportive care. (8, 9) The natural history population was sufficiently similar to the study populations who received the intervention. The Kaplan-Meier estimated survival rates for the study participants who received allogeneic processed thymus tissue was 77% (95% confidence interval [CI], 0.670 to 0.841) at 1 year and 76% (95% CI, 0.658 to 0.832) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. In comparison, the 2-year survival rate was 6%, with all patients dying by 3 years of age in the external historical control. In addition to the observed survival benefit, the efficacy is also supported by evidence of immune reconstitution based on decreased frequency and severity of infections, evidence of thymopoiesis on biopsy, increasing numbers of naïve CD3, CD4 and CD8 T-cells, emergence of diverse T-cell receptor variable beta repertoires and increased T cell proliferation in response to antigen/mitogen. Outcomes related to infection are summarized in Table 2. Based on the Wilcoxon signed-rank test, there was a significant difference in the frequency of infection with an onset within 6 months versus an onset within 6 to 12 months post-transplantation ($p<.001$). Reduction in the frequency of infections and serious infections in year 2 compared to year 1 was also significant. Infections are clinically meaningful, proximal manifestations of congenital athymia. Therefore, a decrease in frequency of infections and severe infections provides data to support that clinically meaningful immune reconstitution has occurred.

Overall, there were 29 deaths following treatment in the study population. The most common cause of death was infection (14, 48%), and most of these deaths occurred during the first year after treatment, which is not unexpected as immune reconstitution following treatment takes about 6-12 months after transplantation. There were 3 deaths possibly related to study treatment; 2 were attributed to immunosuppressive agents, and 1 was due to CMV that may have been acquired from the donor thymus tissue.

Table 1a. Key Characteristics Summary of Pivotal Trial

Study	Study Type	Country	Sites	Dates
Markert et al. (2022) (7)	Prospective, single-center, open-label studies	United States	1 Site	1993-2020

Table 1b. Key Characteristics Summary of Pivotal Trial

Study	Participants	Treatment	Follow-Up
Markert et al. (2022) (7)	N=105 (N=95 in the primary efficacy analysis)[a] *Inclusion Criteria* • Congenital aythmia[b] • Confirmed athymia[c] *Exclusion Criteria* • Heart surgery within 4 weeks before administration of CTT or anticipated within 3 months after administration of CTT • Poor surgical candidacy as determined by the surgeon or anesthesiologist • HIV infection • Prior attempts at immune reconstitution • Ventilator dependence • CMV infection for patients requiring immunosuppression	Allogeneic processed thymus tissue-agdc in a single surgical procedure at a dose of 4,900 to 24,000 mm^2/recipient BSA in m^2.	Median follow-up of 10.7 years

BSA: body surface area; CMV: cytomegalovirus; CTT: cultured thymus tissue; HIV: human immunodeficiency virus.

[a] Ten patients were excluded from the primary efficacy analysis: 2 because they were ultimately diagnosed with SCID, 6 because they received a previous hematopoietic stem cell transplantation or fetal transplant and 2 because their diagnosis was not definitive.

[b] Defined as cDGA in which patients had athymia plus either a congenital heart defect or hypocalcemia/hypoparathyroidism or *FOXN1* deficiency. cDGA included 22q11.2ds, CHARGE syndrome, other genetic defects associated with congenital athymia, and diabetic embryopathy.

[c] Athymia defined as circulating $CD3^+CD45RA^+CD62L^+$ T-cell count lower than 50/mm^3 or less than 5% of the total T-cell count on 2 separate flow cytometry analyses (1 performed within 3 months and 1 performed within 1 month before administration of cultured thymus tissue), unless they were enrolled in the expanded access protocol, according to which the naive T-cell could be higher than 50 mm^3.

Table 2a. Summary of Results from Pivotal Studies

Study	Kaplan-Meier Estimated Survival Rate	Infection/Serious Infection	
Prescribing label (8, 9)		<6 months (n=95)	6-12 months (n=80)

Allogeneic processed thymus tissue (n=45)	Year 1: 77% (0.670 to 0.841) Year 2: 76% (0.658 to 0.832)	Number of infections: 346 Number of participants (%): 83 (87.4%) Number of serious infections: 135 Number of participants with serious infections: 55 (57.9%)	Number of infections: 109 Number of participants (%): 45 (56.3%) Number of serious infections: 51 Number of participants with serious infections: 25 (31.3%)
External control (n=45)	Year 2: 6% Year 3: 0	Data not collected/reported	Data not collected/reported

Table 2b. Summary of Results from Pivotal Studies

Study	**Infection/Serious Infection**	
Prescribing label (8, 9)	Year 1 (n=95)	Year 2 (n=73)
Allogeneic processed thymus tissue (n=45)	Number of infections: 455 Number of participants (%): 89 (93.7%) Number of serious infections: 186 Number of participants with serious infections: 63 (66.3%)	Number of infections: 99 Number of participants (%): 34 (46.6%) Number of serious infections: 58 Number of participants with serious infections: 23 (31.2%)
External control (n=45)	Data not collected/reported	Data not collected/reported

The purpose of the study limitations tables is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement. No major limitations in the study relevance were identified. Limitations in study design and conduct relates to the lack of RCTs. However, congenital athymia is an ultra-rare disorder and therefore conducting randomized trials would be challenging. However, the evidence 1) included data from a large number of study participants, especially given the rarity of the disease with a long duration of follow-up (over 25 years), 2) the natural history is uniform and well-characterized, and 3) most importantly, there was a large survival effect that was consistent and persistent in this otherwise rapidly fatal disease, despite the heterogenous underlying genetic anomalies and diverse comorbid conditions.

Table 3. Study Design and Conduct Limitations

Study	**Allocation[a]**	**Blinding[b]**	**Selective Reporting[c]**	**Data Completeness[d]**	**Power[e]**	**Statistical[f]**
Markert et al. (2022) (7)	1. Participants not randomly allocated	1. Not blinded to treatment assignment; 2. Not				

	2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.	blinded outcome assessment; 3. Outcome assessed by treating physician.				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Allogeneic processed thymus tissue-agdc for Congenital Athymia

Primary evidence of safety and effectiveness was based on an integrated analysis from 10 multiple prospective, single-center, open-label studies conducted over a period of 28 years at a single center that included 95 patients with a diagnosis of congenital athymia. The primary evidence for efficacy was based on a comparison of survival between the study participants and natural history populations. Natural history data were obtained from a contemporaneous population of 49 patients with congenital athymia who were observed from 1991-2017 and received only supportive care. The Kaplan-Meier estimated survival rates for the study participants who received allogeneic processed thymus tissue was 77% (95% CI 0.670 to 0.841) at 1 year and 76% (95% CI 0.658 to 0.832) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. In comparison, the 2-year survival rate was 6%, with all patients dying by 3 years of age in the external historical control. In addition to the observed survival benefit, the efficacy is also supported by evidence of immune reconstitution based on decreased frequency and severity of infections. Overall, there were 29 deaths following treatment in the study population. The most common cause of death was infection and most of these deaths occurred during the first year after treatment, which is not unexpected as immune reconstitution following treatment takes about 6-12

months after transplantation. No major limitations in the study relevance were identified. Limitations in study design and conduct relates to the lack of RCTs. Congenital athymia is an ultra-rare disorder and therefore conducting randomized trials would be challenging. The evidence 1) included data from a large number of study participants, especially given the rarity of the disease with a long duration of follow-up (over 25 years), 2) the natural history is uniform and well- characterized, and 3) most importantly, there was a large survival effect that was consistent and persistent in this otherwise rapidly fatal disease, despite the heterogeneous underlying genetic anomalies and diverse comorbid conditions.

Summary of Evidence

For individuals with congenital athymia who received allogeneic processed thymus tissue-agdc, the evidence included 10 prospective, single-center, open-label studies evaluating a total of 95 participants. Relevant outcomes are disease-specific survival, change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The primary evidence of efficacy was based on a comparison of survival between the study participants (n=95) and natural history populations (n=49). Natural history data were obtained from a contemporaneous population with congenital athymia who were observed from 1991-2017 and received only supportive care. The Kaplan-Meier estimated survival rates for the study participants who received allogeneic processed thymus tissue was 77% (95% confidence interval [CI], 0.670 to 0.841) at 1 year and 76% (95% CI, 0.658 to 0.832) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. In comparison, the 2-year survival rate was 6%, with all patients dying by 3 years of age in the external historical control. In addition to the observed survival benefit, the efficacy is also supported by evidence of immune reconstitution based on decreased frequency and severity of infections. Overall, there were 29 deaths following treatment in the study population. The most common cause of death was infection and most of these deaths occurred during the first year after treatment, which is not unexpected as immune reconstitution following treatment takes about 6-12 months after transplantation. No major limitations in the study relevance were identified. Limitations in study design and conduct relates to the lack of randomized controlled trials. Congenital athymia is an ultra-rare disorder and therefore conducting randomized trials would be challenging. The evidence 1) included data from a large number of study participants, especially given the rarity of the disease, with a long duration of follow-up (over 25 years), 2) the natural history is uniform and well-characterized, and 3) most importantly, there was a large survival effect that was consistent and persistent in this otherwise rapidly fatal disease, despite the heterogeneous underlying genetic anomalies and diverse comorbid conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05329935[a]	Congenital Athymia Patient Registry	75	Apr 2026

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J3490, J3590

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/15/2025	Document updated with literature review. Coverage section completely revised. Added references 1-9; others removed. Title changed from "Allogeneic Processed Thymus Tissue-agdc (Rethymic)".
06/15/2024	Reviewed. No changes.
09/15/2023	Document updated with literature review. Coverage unchanged. References updated.
02/01/2023	Document updated. Coverage revised: Rethymic (allogeneic processed thymus tissue-agdc) may be considered medically necessary for immune reconstitution in pediatric patients ages 3 years or younger with congenital athymia when all of the following criteria are met: Patient has a diagnosis of congenital athymia confirmed by a pediatric immunologist; AND Patient does NOT have a diagnosis of severe combined immunodeficiency (SCID); AND Medical record documentation confirming the patient does NOT have pre-existing cytomegalovirus (CMV) infection OR human immunodeficiency virus (HIV) infection; AND Patient has not previously been treated with Rethymic; AND Diagnosis of congenital athymia has been confirmed with documentation of the following: Flow cytometry results demonstrating fewer than 50 naïve T-cells/mm3 (CD45RA+, CD62L+) in the peripheral blood or less than 5% of total T-cells being naïve in phenotype; AND One of the following: Genetic testing confirms 22q11.2 deletion; OR Hematopoietic stem cells (HSCs) successfully differentiate using artificial thymic organoid (ATO) system test; OR Patient has syndromic comorbidities (e.g., palatal anomalies, cardiac abnormalities, hypocalcemia, hearing loss, coloboma, etc.) associated with congenital athymia; AND Patient has documentation of screening for anti-HLA antibodies. Rethymic (allogeneic processed thymus tissue-agdc) is considered not medically necessary in

	patients with pre-existing cytomegalovirus (CMV) infection or human immunodeficiency (HIV) infection or have been previously treated with Rethymic. Dosing and Administration: The Rethymic implantation will not exceed a single, one-time dose (up to 22,000 mm2 of Rethymic surface area per m2 recipient BSA, not to exceed 42 slices) as calculated and supplied by the manufacturer. Rethymic (allogeneic processed thymus tissue-agdc) is considered experimental, investigational and/or unproven for all other indications. Title changed from Rethymic.
07/15/2022	Reviewed. No changes.
04/01/2022	New medical document. Rethymic (allogeneic processed thymus tissue-agdc) may be considered medically necessary for immune reconstitution in pediatric patients with congenital athymia. Rethymic is considered experimental, investigational and/or unproven for all other indications, including but not limited to, severe combined immunodeficiency (SCID).