Section E — Gene Therapy

Source document: Curative Health Plan — Master Clinical Decision Criteria / Unified Reviewer Tool, Version 2.0 (Effective March 4, 2026)

Section: E of G (part of a 7-document set, A–G)

Conditions / procedures in this section: 11

Scope: 11 FDA-approved gene therapy products with product-specific coverage criteria.

Use: Internal utilization-management criteria. Automated systems may approve but must not issue adverse determinations; all denials require licensed clinician review.

SCOPE AND APPLICABILITY This policy covers all FDA-approved gene therapy products that involve direct genetic modification or gene replacement/addition. CAR-T cell therapies are covered under the separate Oncology policy.

PRIOR AUTHORIZATION: Required for ALL gene therapy products. No exceptions. LIFETIME LIMIT: ONE dose per lifetime per product unless otherwise specified by the FDA label. SITE OF CARE: Must be administered at a Curative-designated Center of Excellence or contracted facility with documented gene therapy administration capability. SPECIALIST REQUIREMENT: Must be prescribed by or in consultation with a specialist in the relevant disease area (neurologist, hematologist, ophthalmologist, geneticist, etc.). GENETIC CONFIRMATION: Molecular/genetic testing confirming the specific mutation must be documented for ALL gene therapy products.

GENERAL EXCLUSIONS (apply to all gene therapies):

- Use for indications not approved by the FDA
- Use in patients who do not meet the FDA-approved age/weight criteria
- Repeat administration when the FDA label specifies single-dose/one-time use
- Use in patients with contraindications listed in the FDA prescribing information
- Use at non-designated facilities without documented gene therapy capability
- Gene therapies that are investigational, experimental, or used in clinical trials (unless trial is covered under separate clinical trial policy)

ZOLGENSMA (ONASEMNOGENE ABEPARVOVEC-XIOI) — SPINAL MUSCULAR ATROPHY

ICD-10-CM: G12.0 (infantile spinal muscular atrophy Type I / Werdnig-Hoffmann), G12.1 (other inherited spinal muscular atrophy / SMA Type II-III), G12.8 (other spinal muscular atrophies), G12.9 (spinal muscular atrophy unspecified) Z13.228 (encounter for screening for other metabolic disorders — newborn SMA screening), Z14.8 (genetic carrier of other disease — SMN1 carrier)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL OF THE FOLLOWING (A through G):

A. DIAGNOSIS — Must meet ALL:

- Patient has genetically confirmed spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene
- Genetic testing performed at a CLIA-certified laboratory documenting: homozygous deletion of SMN1 exon 7, OR compound heterozygous mutation (deletion of SMN1 exon 7 on one allele + point mutation on the other allele)
- SMN2 copy number determined by quantitative assay (1-4 copies; patients with ≥5 copies are excluded per most payer policies)

B. AGE — Must meet:

- Patient is less than 2 years of age at the time of infusion (FDA label)
- If premature neonate: full-term gestational age (≥39 weeks 0 days postmenstrual age) must be reached before infusion

C. WEIGHT — Must meet:

- Patient weighs less than 13.5 kg at time of infusion (dosing is weight-based: 1.1×10^{14} vg/kg)

D. DISEASE STATUS — Must meet:

- Patient does NOT have advanced SMA as defined by: complete paralysis of all limbs, AND permanent ventilator dependence (tracheostomy with ≥16 hours/day invasive ventilation)

E. ANTIBODY TESTING — Must meet:

- Anti-adeno-associated virus serotype 9 (anti-AAV9) antibody titer ≤1:50 (per most payer policies; FDA label states results should be

considered in treatment decision)

F. LABORATORY — Must meet ALL:

- Baseline hepatic function within acceptable limits (AST and ALT)
- Platelet count within normal range
- Troponin-I within normal range
- Baseline CBC, CMP, coagulation studies obtained

G. TREATMENT HISTORY — Document:

- ONE dose per lifetime — no repeat administration
- If patient has received prior SMA-modifying therapy (nusinersen/Spinraza, risdiplam/Evrysdi), document and discontinue prior to or

after Zolgensma per clinical judgment

INTENSITY OF SERVICE (IS) — Must meet ≥1:

- Single IV infusion administered over approximately 60 minutes at a designated gene therapy center
- Pre-treatment with systemic corticosteroid (prednisolone 1 mg/kg/day starting 1 day prior to infusion, continuing ≥30 days

post-infusion with taper based on liver function)

- Post-infusion monitoring: minimum 2 hours observation for infusion reactions
- Hepatic monitoring: AST/ALT weekly for first month, then biweekly for second month, then monthly for 12 months
- Troponin-I monitoring for cardiac safety
- Platelet monitoring weekly for first month

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DOES NOT MEET CRITERIA / DENY IF ANY:

- Patient is ≥2 years of age at time of infusion
- Patient weighs ≥13.5 kg
- Patient has advanced SMA (complete limb paralysis + permanent ventilator dependence with tracheostomy)
- SMN1 mutation is NOT confirmed by genetic testing at a CLIA-certified laboratory
- Patient has ≥5 copies of SMN2 (per most payer policies — limited evidence for this population)
- Anti-AAV9 antibody titer >1:50
- Patient has active hepatic disease or significant liver dysfunction (acute hepatitis, ALT/AST >3x ULN)
- Patient has previously received Zolgensma (one dose per lifetime)
- Active untreated infection at time of planned infusion
- Premature neonate who has not yet reached full-term gestational age (≥39 weeks PMA)
- Administration at a facility not designated/contracted for gene therapy
- Request for Zolgensma in combination with another gene therapy product for SMA

NOTE: SMA type classification (Type 0, I, II, III, IV) alone is NOT a basis for denial if the patient meets all criteria above. The FDA label does not restrict by SMA type — it restricts by age (<2 years), bi-allelic SMN1 mutation, and excludes advanced disease.

C. CONTINUED STAY / POST-TREATMENT MONITORING

INPATIENT STAY: Most patients receive Zolgensma as outpatient or 23-hour observation. Inpatient admission justified only if:

- Infusion reaction requiring monitoring beyond 24 hours
- Pre-existing respiratory compromise requiring post-infusion respiratory monitoring
- Hepatotoxicity (ALT/AST elevation >3x ULN requiring IV steroids and monitoring)
- Thrombocytopenia developing post-infusion
- Thrombotic microangiopathy (TMA) — rare but serious complication

POST-INFUSION MONITORING SCHEDULE (outpatient — medically necessary):

- Hepatic panel (AST/ALT): weekly x 4 weeks, biweekly x 4 weeks, monthly x 12 months
- Troponin-I: at baseline, then per clinical judgment
- Platelet count: weekly x 4 weeks, then per clinical judgment
- Systemic corticosteroid taper: prednisolone ≥30 days, taper based on LFTs (do not taper below 0.5 mg/kg until AST/ALT <2x ULN)
- Clinical assessment by neuromuscular specialist: q3 months x 1 year, then q6 months ongoing

- Motor milestone assessment (CHOP-INTEND, Bayley Scales, HFMSE as appropriate)

D. DISCHARGE CRITERIA

- Post-infusion observation period completed (≥2 hours) without adverse reaction
- Vital signs stable
- Prednisolone prescription provided with detailed taper schedule
- Lab monitoring schedule provided to family and PCP/neurologist
- Follow-up with neuromuscular specialist within 1 week
- Family educated on signs of hepatotoxicity (jaundice, vomiting, lethargy, bleeding → return to ED immediately)
- Family educated on signs of TMA (unexplained bruising, pallor, dark urine → return to ED)

E. EVIDENCE SOURCES

1. FDA Prescribing Information: Zolgensma (onasemnogene abeparvovec-xioi). Novartis Gene Therapies. Revised February 2025. 2. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for SMA. NEJM. 2017;377:1713-1722. 3. STR1VE Trial. Day JW, et al. NEJM. 2021;385:427-435. 4. SPR1NT Trial (presymptomatic SMA). Strauss KA, et al. Nat Med. 2022;28:1381-1389. 5. ICER Final Evidence Report: Spinraza and Zolgensma for SMA. Updated May 2019. 6. AAP Expert Consensus: SMA Newborn Screening. Pediatrics. 2020;145:e20200702. 7. Aetna CPB 0953: Onasemnogene Abeparvovec-xioi (Zolgensma). Updated 2025. 8. UnitedHealthcare Medical Policy: Zolgensma. Updated 2025. 9. Mass General Brigham Health Plan: Zolgensma Medical Policy. December 2025.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3399 (injection, onasemnogene abeparvovec-xioi, per treatment)

ICD-10-PCS (if inpatient): XW033G4 (introduction of onasemnogene abeparvovec into peripheral vein, percutaneous approach)

CPT CODES (administration):

- 96413 (chemotherapy administration, IV infusion, first substance, first hour)
- 96415 (each additional hour)

MS-DRG CROSSWALK (if inpatient admission required):

- DRG 013: Tracheostomy for Face/Mouth/Neck Diagnoses or Laryngectomy with MCC (if ventilator-dependent SMA patient)
- DRG 091: Other Disorders of Nervous System w MCC (RW ~1.52) — most common for SMA infusion admission
- DRG 092: w CC (RW ~0.95)
- DRG 093: w/o CC/MCC (RW ~0.71)
- NOTE: Zolgensma is typically outpatient. If inpatient, the drug cost ($2.125 million WAC) will likely qualify as a high-cost outlier.

REVENUE CODES:

- 0250: Pharmacy (Zolgensma product)
- 0260: IV Therapy (infusion services)
- 0300: Laboratory (LFTs, CBC, troponin, genetic testing)
- 0636: Drugs Requiring Detailed Coding (Zolgensma — WAC $2,125,000)
- 0940: Other Services (genetic counseling, neuromuscular assessment)

APPROXIMATE COST: $2,125,000 (one-time, WAC)

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 1-2 days post-infusion observation; total admit 2-5 days Source: FDA Zolgensma label (USPI 2024); CureSMA

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

LUXTURNA (VORETIGENE NEPARVOVEC-RZYL) — RPE65-ASSOCIATED RETINAL DYSTROPHY

ICD-10-CM: H35.50 (unspecified hereditary retinal dystrophy), H35.51 (Stargardt disease — if RPE65-related), H35.52 (pigmentary retinal dystrophy), H35.53 (other dystrophies primarily involving the sensory retina), H35.54 (dystrophies primarily involving the retinal pigment epithelium), H31.20 (hereditary choroidal dystrophy unspecified), H31.21 (choroideremia), H31.29 (other hereditary choroidal dystrophy) Z96.1 (presence of intraocular lens — post-vitrectomy if applicable)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL OF THE FOLLOWING (A through E):

A. DIAGNOSIS — Must meet ALL:

- Patient has confirmed biallelic RPE65 mutation-associated retinal dystrophy, documented by CLIA-certified genetic testing showing

EITHER:

- Single RPE65 pathogenic or likely pathogenic variant in the homozygous state, OR
- Two RPE65 pathogenic or likely pathogenic variants in trans configuration (compound heterozygous), confirmed by segregation analysis when possible
- Diagnosis includes but is not limited to: Leber congenital amaurosis (LCA), retinitis pigmentosa (RP), or other RPE65-associated retinal dystrophy

B. AGE — Must meet:

- Patient is ≥12 months of age (retinal cells still undergoing proliferation <12 months; gene therapy would be diluted/lost)

C. RETINAL VIABILITY — Must meet for EACH eye to be treated:

- Sufficient viable retinal cells as determined by non-invasive means:
- Area of retina within the posterior pole >100 µm thickness on OCT, OR
- ≥3 disc areas of retina without complete atrophy or degeneration on ophthalmoscopy

D. SPECIALIST — Must meet:

- Prescribed by a retinal surgeon with experience in subretinal injection at a Luxturna-designated Center of Excellence

E. TREATMENT — Must meet:

- ONE dose per eye, per lifetime (bilateral treatment = 2 separate procedures, ≥6 days apart)
- Patient has not previously received Luxturna or any other gene therapy for retinal dystrophy

INTENSITY OF SERVICE (IS) — Must meet ≥1:

- Subretinal injection performed under general anesthesia or monitored sedation in operating room
- Vitrectomy to access the subretinal space
- Pre-treatment with systemic corticosteroid (prednisone 1 mg/kg/day x 7 days starting 3 days before each procedure, with 10-day taper)
- Post-operative ophthalmic monitoring (IOP, retinal assessment)

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DOES NOT MEET CRITERIA / DENY IF ANY:

- RPE65 mutation is NOT confirmed by genetic testing (clinical diagnosis alone insufficient)
- Monoallelic (single copy) RPE65 mutation only — must be biallelic
- Patient is less than 12 months of age
- No viable retinal cells in the eye to be treated (complete retinal atrophy)

- Patient has previously received Luxturna in the eye being requested
- Pre-existing conditions that prevent safe subretinal injection (active ocular infection, advanced glaucoma with no light perception)
- Retinal dystrophy caused by mutations in genes OTHER than RPE65 (e.g., RPGR, CNGB3, CNGA3)
- Administration at a facility not designated for Luxturna

C. CONTINUED STAY / POST-TREATMENT MONITORING

INPATIENT: Luxturna is typically outpatient surgical procedure. Inpatient admission justified only for: bilateral general anesthesia concerns in pediatric patient, post-operative complication (retinal detachment, elevated IOP, endophthalmitis), medical comorbidity requiring inpatient monitoring.

POST-TREATMENT MONITORING: Ophthalmic exam day 1 post-op, week 1, month 1, month 3, month 6, annually. Visual function assessment. IOP monitoring.

D. DISCHARGE CRITERIA

- Post-operative ophthalmic exam satisfactory (no retinal detachment, IOP controlled)
- Patient/caregiver educated on steroid taper and post-op activity restrictions
- Follow-up with retinal surgeon within 1 week scheduled
- Second eye treatment scheduled ≥6 days after first eye (if bilateral)

E. EVIDENCE SOURCES

1. FDA PI: Luxturna. Spark Therapeutics. 2017, updated 2023. 2. Russell S, Bennett J, Wellman JA, et al. Efficacy/safety of voretigene neparvovec (AAV2-hRPE65v2) in RPE65 mutation. Lancet. 2017;390:849-860. 3. Maguire AM, et al. Phase 1 and 3 trials results. Ophthalmology. 2019;126:1273-1285. 4. CMS LCD L37863: Voretigene Neparvovec-rzyl (Luxturna). 5. Anthem MED.00120: Gene Therapy for Ocular Conditions. 6. BCBS Florida MCG: Voretigene Neparvovec-rzyl (Luxturna).

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3398 (injection, voretigene neparvovec-rzyl, 1 billion vector genomes)

CPT CODES:

- 67028 (intravitreal injection of pharmacologic agent) — or
- 67113 (repair of retinal detachment, vitrectomy with subretinal injection) — per procedure type
- 67036 (vitrectomy, mechanical, pars plana approach)

MS-DRG (if inpatient): DRG 116 (Intraocular Procedures w CC/MCC, RW ~1.28), DRG 117 (w/o CC/MCC, RW ~0.82)

REVENUE CODES:

- 0360: Operating Room
- 0370: Anesthesiology
- 0250: Pharmacy (Luxturna product)
- 0636: Drugs Requiring Detailed Coding (Luxturna — WAC ~$425,000 per eye, $850,000 bilateral)

APPROXIMATE COST: $425,000 per eye ($850,000 total bilateral)

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: Outpatient or 23-hr; admit only for complications Source: FDA Luxturna label (USPI 2022)

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

CASGEVY (EXAGAMGLOGENE AUTOTEMCEL) — SICKLE CELL DISEASE & BETA-THALASSEMIA

ICD-10-CM: D57.00 (Hb-SS disease with crisis unspecified), D57.01 (Hb-SS with acute chest syndrome), D57.02 (Hb-SS with splenic sequestration), D57.03 (Hb-SS with cerebral vascular involvement), D57.09 (Hb-SS with crisis with other specified complication), D57.1 (Hb-SS disease without crisis), D57.211 (sickle-cell/Hb-C with acute chest syndrome), D57.212 (with splenic sequestration), D57.219 (sickle-cell/Hb-C with crisis unspecified), D57.20 (sickle-cell/Hb-C without crisis), D57.40 (sickle-cell thalassemia without crisis), D57.411 (sickle-cell thalassemia with acute chest syndrome), D57.419 (with crisis unspecified), D57.80 (other sickle-cell disorders without crisis), D57.811 (other sickle-cell with acute chest syndrome), D57.819 (with crisis unspecified) D56.1 (beta thalassemia), D56.5 (hemoglobin E-beta thalassemia), D56.9 (thalassemia unspecified)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

SICKLE CELL DISEASE — APPROVAL REQUIRES ALL (A through F):

A. DIAGNOSIS — Must meet:

- SCD confirmed by molecular/genetic testing with one of the following genotypes: HbSS, HbS/β0-thalassemia, HbS/β+-thalassemia,

HbSC, or HbSD

B. AGE — Must meet:

- Patient is ≥12 years of age

C. DISEASE SEVERITY — Must meet:

- History of ≥2 severe vaso-occlusive crises (VOCs) per year in the previous 2 years, including: pain crises requiring ED visit or

hospitalization, acute chest syndrome, priapism, or splenic sequestration

D. TREATMENT HISTORY — Must meet ≥1:

- Inadequate response to or intolerance of hydroxyurea, OR
- Hydroxyurea is contraindicated, OR
- Patient declined hydroxyurea after informed discussion

E. TRANSPLANT ELIGIBILITY — Must meet:

- Patient is eligible for hematopoietic stem cell transplant (HSCT) but does NOT have an available 10/10 HLA-matched related donor
- Patient has NOT received a prior allogeneic HSCT
- Patient has NOT previously received Casgevy, Lyfgenia, or any other gene therapy

F. TREATMENT — Must meet:

- ONE dose per lifetime
- Administered at a qualified treatment center (QTC) for Casgevy with BMT capability
- Patient will undergo myeloablative conditioning (busulfan) before Casgevy infusion

BETA-THALASSEMIA (TDT) — APPROVAL REQUIRES ALL:

- Diagnosis of transfusion-dependent beta-thalassemia (TDT) confirmed by genetic testing
- Patient is ≥12 years of age
- Requiring ≥8 RBC transfusions per year in each of the preceding 2 years
- No matched related donor for allogeneic HSCT
- ONE dose per lifetime at a qualified treatment center

INTENSITY OF SERVICE (IS) — Must meet ALL:

- Stem cell mobilization (plerixafor + G-CSF) and apheresis for CD34+ cell collection

- Myeloablative conditioning with busulfan prior to Casgevy infusion
- Casgevy infusion (autologous CRISPR-edited CD34+ cells)
- Inpatient BMT unit with protective isolation
- Daily labs, transfusion support, neutropenic precautions

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DOES NOT MEET CRITERIA / DENY IF ANY:

- Patient is <12 years of age
- SCD genotype not confirmed by molecular/genetic testing
- Fewer than 2 VOCs per year in previous 2 years (SCD indication)
- Fewer than 8 RBC transfusions per year in preceding 2 years (TDT indication)
- Patient has an available 10/10 HLA-matched related donor (standard HSCT should be considered first per NHLBI/ASH guidelines)
- Patient has previously received allogeneic HSCT
- Patient has previously received Casgevy, Lyfgenia, or another gene therapy for SCD/TDT
- Active uncontrolled infection
- Myelodysplastic syndrome (MDS) or active malignancy
- Significant organ dysfunction that would preclude myeloablative conditioning (cardiopulmonary, hepatic, renal assessment required)
- Administration at a facility not designated as a Casgevy qualified treatment center

C. CONTINUED STAY / POST-TREATMENT MONITORING

INPATIENT STAY: 4-6 weeks typical (similar to allogeneic BMT). Includes: myeloablative conditioning (busulfan x 4 days), Casgevy infusion (Day 0), neutropenic period (ANC <500 for 14-28 days), engraftment monitoring (ANC >500 x 3 days = engraftment).

CONTINUED STAY IF: ANC <500, active infection, transfusion-dependent, GVHD-like symptoms (rare with autologous but monitor), organ toxicity from conditioning (VOD/SOS, mucositis), unable to tolerate PO.

D. DISCHARGE CRITERIA

- Engraftment achieved (ANC >500 x 3 consecutive days)
- Transfusion-independent ≥48 hours
- Tolerating oral medications and adequate nutrition
- No active untreated infection
- Caregiver available, living within 1 hour of treatment center for first 3 months
- Follow-up: labs 2x/week x 4 weeks, then weekly x 8 weeks, then per protocol
- Long-term monitoring: annual CBC, hemoglobin electrophoresis, HbF levels, organ function, malignancy surveillance (per

REMS/FDA 15-year LTFU)

E. EVIDENCE SOURCES

1. FDA PI: Casgevy (exagamglogene autotemcel). Vertex Pharmaceuticals. December 2023. 2. Frangoul H, et al. CRISPR-Cas9 gene editing for SCD. NEJM. 2021;384:252-260. 3. CLIMB SCD-121 Trial. Locatelli F, et al. NEJM. 2024;390:1649-1662. 4. Aetna CPB 1052: Exagamglogene Autotemcel (Casgevy). Updated 2025. 5. ASH/NHLBI Guidelines: SCD Management. Blood Advances. 2023. 6. ICER Assessment: Gene Therapies for SCD. 2024.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3392 (injection, exagamglogene autotemcel, per treatment)

ICD-10-PCS: XW033L5 (introduction of exagamglogene autotemcel into peripheral vein, percutaneous)

CPT CODES (apheresis/collection):

- 38205 (blood-derived HSC harvesting for transplantation, per collection)
- 38206 (blood-derived HSC harvesting for transplantation, autologous)

MS-DRG: DRG 016 (Autologous Bone Marrow Transplant w CC/MCC, RW ~6.66), DRG 017 (w/o CC/MCC, RW ~4.38). NOTE: CMS has established new technology add-on payment for Casgevy ($1,650,000 add-on for FY2025).

REVENUE CODES:

- 0120: Room & Board (4-6 week stay)
- 0250: Pharmacy (busulfan conditioning, supportive meds)
- 0300: Lab (daily CBC, CMP, hemoglobin electrophoresis, HbF, cultures)
- 0390: Blood Products (transfusion support during aplasia)
- 0636: Drugs Requiring Detailed Coding (Casgevy product)

APPROXIMATE COST: $2,200,000 (drug) + $500,000-800,000 (hospitalization/conditioning) = $2.7-3.0M total episode

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 30-45 days (myeloablative conditioning + engraftment) Source: FDA Casgevy label (USPI 2024); ASTCT

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

LYFGENIA (LOVOTIBEGLOGENE AUTOTEMCEL) — SICKLE CELL DISEASE

ICD-10-CM: D57.00 (Hb-SS with crisis unspecified), D57.01 (Hb-SS with acute chest syndrome), D57.02 (Hb-SS with splenic sequestration), D57.03 (Hb-SS with cerebral vascular involvement), D57.09 (Hb-SS with other crisis), D57.1 (Hb-SS without crisis), D57.211 (sickle-cell/Hb-C with acute chest syndrome), D57.219 (sickle-cell/Hb-C with crisis unspecified), D57.20 (sickle-cell/Hb-C without crisis), D57.411 (sickle-cell thalassemia with ACS), D57.419 (with crisis unspecified), D57.40 (sickle-cell thalassemia without crisis), D57.811 (other sickle-cell with ACS), D57.819 (with crisis unspecified), D57.80 (other sickle-cell without crisis)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL OF THE FOLLOWING:

Same criteria as Casgevy SCD indication (Section A-F above) with the following product-specific differences:

- Lyfgenia uses a lentiviral vector (NOT CRISPR) to deliver $HbA^{T87}v$ gene to patient's own HSCs
- Indicated for SCD in patients ≥12 years with recurrent VOCs (same as Casgevy)
- ONE dose per lifetime
- Myeloablative conditioning with busulfan required before infusion
- Must be administered at a bluebird bio Qualified Treatment Center (QTC)

ADDITIONAL MONITORING REQUIREMENT — Lyfgenia has a boxed warning for hematologic malignancy (MDS/AML). Requires:

- CBC at least every 3 months post-infusion
- Assessment for clonal expansion at least twice in first year, then annually
- Bone marrow evaluation as clinically indicated
- 15-year long-term follow-up per FDA REMS

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

Same exclusions as Casgevy SCD indication PLUS:

- Lyfgenia is NOT indicated for beta-thalassemia (Casgevy and Zynteglo cover TDT)
- Patient with active MDS or hematologic malignancy
- Patient unwilling to comply with 15-year long-term follow-up requirements

C. CONTINUED STAY / POST-TREATMENT MONITORING

Same as Casgevy: Inpatient 4-6 weeks, myeloablative conditioning, engraftment monitoring. ADDITIONAL: Enhanced malignancy surveillance per Lyfgenia REMS.

D. DISCHARGE CRITERIA

Same as Casgevy discharge criteria PLUS:

- Patient enrolled in Lyfgenia long-term follow-up registry per REMS
- Hematology-oncology follow-up with malignancy surveillance schedule established

E. EVIDENCE SOURCES

1. FDA PI: Lyfgenia (lovotibeglogene autotemcel). bluebird bio. December 2023. 2. HGB-206 Trial. Kanter J, et al. Am J Hematol. 2023;98:11-22. 3. FDA Safety Alert: Hematologic Malignancy Risk with Lyfgenia. 2024. 4. ICER: Gene Therapies for SCD Assessment. 2024.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3394 (injection, lovotibeglogene autotemcel, per treatment)

MS-DRG: DRG 016-017 (Autologous BMT). CMS new technology add-on payment: $2,325,000 for FY2025.

REVENUE CODES: Same as Casgevy (0120, 0250, 0300, 0390, 0636)

APPROXIMATE COST: $3,100,000 (drug) + hospitalization = ~$3.5-4.0M total episode

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 30-45 days Source: FDA Lyfgenia label (USPI 2024)

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

ELEVIDYS (DELANDISTROGENE MOXEPARVOVEC-ROKL) — DUCHENNE MUSCULAR DYSTROPHY

ICD-10-CM: G71.01 (Duchenne muscular dystrophy), G71.02 (Becker muscular dystrophy — NOT covered, Elevidys is for DMD only), G71.0 (muscular dystrophy unspecified — must be specified as Duchenne with genetic confirmation)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL OF THE FOLLOWING (A through F):

A. DIAGNOSIS — Must meet:

- Confirmed mutation in the DMD gene by genetic testing at a CLIA-certified laboratory
- Clinical diagnosis of Duchenne muscular dystrophy (NOT Becker muscular dystrophy)

B. AGE — Must meet:

- Patient is ≥4 years of age (FDA-approved for ambulatory patients ≥4 years; accelerated approval for non-ambulatory ≥4 years)

C. ANTIBODY TESTING — Must meet:

- Anti-AAVrh74 total binding antibody titer <1:400

D. MEDICAL STATUS — Must meet ALL:

- No active infection at time of infusion
- No significant liver dysfunction (ALT/AST <3x ULN, no acute hepatic disease)
- No active cardiac disease or clinically significant cardiomyopathy (LVEF within acceptable limits per treating physician)

E. TREATMENT — Must meet:

- ONE dose per lifetime (1.33×10^{14} vg/kg IV infusion)
- Patient has not previously received gene replacement therapy for DMD
- Administered at a Sarepta-designated treatment center

F. CORTICOSTEROID — Must meet:

- Pre-treatment with systemic corticosteroid per Elevidys prescribing protocol
- Post-infusion corticosteroid tapering per protocol

INTENSITY OF SERVICE (IS) — Must meet ≥1:

- Single IV infusion over approximately 1-2 hours
- Post-infusion monitoring for infusion reactions (minimum 3 hours observation)
- Hepatic monitoring (LFTs weekly x 4 weeks, then biweekly x 8 weeks, then monthly x 12 months)
- Cardiac monitoring (troponin, BNP, echo at baseline and post-infusion per protocol)

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DOES NOT MEET CRITERIA / DENY IF ANY:

- Becker muscular dystrophy (G71.02) — Elevidys is NOT indicated for BMD
- Anti-AAVrh74 antibody titer ≥1:400
- Active infection at time of planned infusion
- Significant liver dysfunction or acute hepatic disease
- Prior gene replacement therapy for DMD
- Clinically significant active cardiac disease (cardiomyopathy with LVEF <40%, active myocarditis)
- Administration at non-designated facility

C. CONTINUED STAY / POST-TREATMENT MONITORING

Elevidys is typically outpatient or 23-hour observation. Inpatient admission justified only for: infusion reaction, hepatotoxicity, rhabdomyolysis (rare), cardiac adverse event, pre-existing respiratory compromise requiring post-infusion monitoring.

POST-INFUSION MONITORING: LFTs weekly x 4 wks, biweekly x 8 wks, monthly x 12 mos. Troponin/BNP/echo per protocol. CK monitoring. Motor function assessment (NSAA) q6 months.

D. DISCHARGE CRITERIA

- Post-infusion observation completed without adverse reaction
- Vital signs stable
- Corticosteroid taper schedule provided
- Lab monitoring schedule provided
- Neuromuscular follow-up within 1-2 weeks
- Family educated on hepatotoxicity signs and cardiac monitoring needs

E. EVIDENCE SOURCES

1. FDA PI: Elevidys. Sarepta Therapeutics. 2023, updated 2024. 2. EMBARK Trial (Study 301). Mendell JR, et al. Lancet. 2024. 3. SRP-9001 Phase 1/2 Studies. Mendell JR, et al. JAMA Neurol. 2020;77:1122-1131. 4. Aetna CPB 0911: Gene-Based Therapy for DMD. Updated 2025. 5. BCBS MA: Gene Therapies for DMD. Updated 2025.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J1413 (injection, delandistrogene moxeparvovec-rokl, per therapeutic dose)

CPT CODES: 96365 (IV infusion, initial ≤1 hour), 96366 (each additional hour)

MS-DRG (if inpatient): DRG 091-093 (Other Disorders of Nervous System)

REVENUE CODES: 0250 (Pharmacy), 0260 (IV Therapy), 0300 (Lab), 0636 (Drugs — Elevidys WAC ~$3,200,000)

APPROXIMATE COST: $3,200,000 (one-time, WAC)

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 1-2 days infusion; longer if complications Source: FDA Elevidys label (USPI 2024); PPMD

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

HEMGENIX (ETRANACOGENE DEZAPARVOVEC) — HEMOPHILIA B

ICD-10-CM: D67 (hereditary factor IX deficiency — hemophilia B / Christmas disease)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL OF THE FOLLOWING:

A. DIAGNOSIS — Must meet ALL:

- Confirmed hemophilia B (factor IX deficiency) with FIX activity ≤2 IU/dL (severe/moderately severe) based on one-stage clotting assay or chromogenic assay
- Currently using FIX prophylaxis therapy, OR
- Current or historical life-threatening hemorrhage, OR
- Repeated serious spontaneous bleeding episodes

B. AGE/SEX — Must meet:

- Adult males (≥18 years of age)

C. ANTIBODY TESTING — Must meet:

- No pre-existing anti-AAV5 neutralizing antibodies that would prevent transduction (per Hemgenix prescribing information — no specific titer threshold in label; clinical assessment by hematologist)
- No history of FIX inhibitors (current or prior inhibitor titer ≥0.6 BU)

D. HEPATIC STATUS — Must meet:

- No active hepatitis B or C infection (HBV/HCV screening required)
- No significant liver fibrosis or cirrhosis (FibroScan or equivalent assessment)

E. TREATMENT — Must meet:

- ONE dose per lifetime (2×10^{13} gc/kg IV infusion)

- Administered at a Hemophilia Treatment Center (HTC) experienced in gene therapy

INTENSITY OF SERVICE (IS) — Must meet ≥1:

- Single IV infusion over approximately 1-2 hours
- Post-infusion monitoring for infusion reactions
- Hepatic monitoring: ALT weekly x 26 weeks post-infusion (per label)
- FIX activity monitoring to guide prophylaxis discontinuation
- Corticosteroid per protocol if ALT elevation occurs

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DOES NOT MEET CRITERIA / DENY IF ANY:

- Hemophilia A (factor VIII deficiency) — Hemgenix is for hemophilia B only (Roctavian covers hemophilia A)
- Female patients
- Patients <18 years of age
- Current or historical FIX inhibitor (≥0.6 BU)
- Active hepatitis B or C
- Significant liver disease/cirrhosis
- Prior gene therapy for hemophilia B
- FIX activity >2 IU/dL (mild hemophilia B — insufficient evidence for gene therapy benefit vs risk)

C. CONTINUED STAY / POST-TREATMENT MONITORING

Hemgenix is outpatient infusion. Post-infusion monitoring: ALT weekly x 26 weeks. FIX activity levels serially to guide FIX prophylaxis management (may discontinue prophylaxis if FIX levels sustained).

D. DISCHARGE CRITERIA

- Post-infusion observation completed without adverse reaction
- ALT monitoring schedule established with HTC
- FIX prophylaxis plan documented (continue until FIX activity levels confirm adequate endogenous production)
- Hematology follow-up within 1 week

E. EVIDENCE SOURCES

1. FDA PI: Hemgenix (etranacogene dezaparvovec). CSL Behring. 2022. 2. HOPE-B Trial. Pipe SW, et al. NEJM. 2023;388:706-718. 3. WFH Guidelines: Hemophilia Management. 2020, updated 2024. 4. NHF MASAC Recommendation: Gene Therapy for Hemophilia. 2023.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J1411 (injection, etranacogene dezaparvovec-drlb, per therapeutic dose)

CPT: 96365-96366 (IV infusion)

MS-DRG (if inpatient): DRG 813 (Coagulation Disorders, RW ~1.42)

REVENUE CODES: 0250 (Pharmacy), 0260 (IV Therapy), 0300 (Lab), 0636 (Drugs — Hemgenix WAC $3,500,000)

APPROXIMATE COST: $3,500,000 (one-time, WAC)

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 1-2 days infusion observation Source: FDA Hemgenix label (USPI 2022); WFH

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus

statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

SKYSONA (ELIVALDOGENE AUTOTEMCEL) — CEREBRAL ADRENOLEUKODYSTROPHY (CALD)

ICD-10-CM: E71.520 (childhood cerebral X-linked adrenoleukodystrophy), E71.521 (adolescent X-linked adrenoleukodystrophy), E71.529 (X-linked adrenoleukodystrophy unspecified type), E71.510 (X-linked adrenoleukodystrophy, non-cerebral forms), E71.511 (adrenomyeloneuropathy)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL OF THE FOLLOWING:

- Males 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD)
- Confirmed ABCD1 gene mutation by genetic testing
- Gadolinium enhancement on brain MRI (active demyelination)
- Loes score 0.5-9 (early disease — not too advanced)
- Neurologic function score (NFS) ≤1 (asymptomatic or mildly symptomatic)
- No available 10/10 HLA-matched related donor for allogeneic HSCT
- ONE dose per lifetime
- Myeloablative conditioning (busulfan + fludarabine) required before infusion

IS — Must meet ALL (same as autologous BMT):

- Stem cell mobilization, apheresis, myeloablative conditioning, Skysona infusion, BMT-unit inpatient stay

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DENY IF:

- Female patients
- Age <4 or >17 years
- Loes score >9 (advanced disease)
- NFS >1 (symptomatic beyond mild)
- Available 10/10 HLA-matched related donor (standard allo-HSCT preferred)
- Prior gene therapy or HSCT

BOXED WARNING: Risk of MDS/AML. Enhanced malignancy surveillance required per REMS.

C. CONTINUED STAY / POST-TREATMENT MONITORING

Inpatient 4-6 weeks (autologous BMT protocol). Engraftment monitoring. Enhanced malignancy surveillance: CBC q3 months, clonal expansion assessment 2x in year 1 then annually, bone marrow biopsy as indicated.

D. DISCHARGE CRITERIA

Same as autologous BMT discharge criteria. PLUS: enrolled in Skysona REMS long-term follow-up, neurology and hematology-oncology follow-up established, brain MRI schedule for CALD monitoring.

E. EVIDENCE SOURCES

1. FDA PI: Skysona. bluebird bio. September 2022. 2. ALD-102 Trial. Eichler F, et al. NEJM. 2017;377:1630-1638. 3. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. Brain. 1997;120:1485-1508.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3590 (unclassified biologic) or C9399 (unclassified drug/biological, new technology)

MS-DRG: DRG 016-017 (Autologous BMT, RW ~6.66/4.38)

REVENUE CODES: 0120, 0250, 0300, 0390, 0636

APPROXIMATE COST: $3,000,000 (drug) + hospitalization = ~$3.5-4.0M total episode

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 30-45 days Source: FDA Skysona label (USPI 2022)

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

ZYNTEGLO (BETIBEGLOGENE AUTOTEMCEL) — TRANSFUSION-DEPENDENT BETA-THALASSEMIA

ICD-10-CM: D56.1 (beta thalassemia — beta thalassemia major), D56.5 (hemoglobin E-beta thalassemia), D56.9 (thalassemia unspecified)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL:

- Confirmed beta-thalassemia requiring ≥8 RBC transfusions per year
- No available HLA-matched sibling donor
- Non-β0/β0 genotype (Zynteglo is NOT indicated for β0/β0 genotype patients per FDA label)
- ONE dose per lifetime
- Myeloablative conditioning required
- Age: per FDA label, adults and pediatric patients

IS: Same as autologous BMT (mobilization, apheresis, conditioning, infusion, engraftment)

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DENY IF:

- β0/β0 genotype (not in FDA label)
- Fewer than 8 transfusions/year
- Available HLA-matched sibling donor
- Prior gene therapy or HSCT

C. CONTINUED STAY / POST-TREATMENT MONITORING

Inpatient 4-6 weeks (autologous BMT). Monitor for engraftment, transfusion independence, hemoglobin levels.

D. DISCHARGE CRITERIA

Engraftment achieved, hemoglobin trending upward, transfusion-independent or reduced, enrolled in long-term follow-up.

E. EVIDENCE SOURCES

1. FDA PI: Zynteglo. bluebird bio. August 2022. 2. Northstar-2 Trial. Locatelli F, et al. NEJM. 2022;386:415-427. 3. ICER: Gene Therapy for Beta-Thalassemia. 2022.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3590 or C9399 (unclassified biologic)

MS-DRG: DRG 016-017 (Autologous BMT)

REVENUE CODES: 0120, 0250, 0300, 0390, 0636

APPROXIMATE COST: $2,800,000 (drug) + hospitalization

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 30-45 days Source: FDA Zynteglo label (USPI 2022)

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

KEBILIDI (ELADOCAGENE EXUPARVOVEC-TNEQ) — AADC DEFICIENCY

ICD-10-CM: E70.81 (aromatic L-amino acid decarboxylase deficiency)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL:

- Confirmed AADC deficiency by genetic testing showing biallelic DDC gene mutations AND biochemical confirmation (elevated

3-O-methyldopa, decreased HVA/VMA in CSF)

- Patient is ≥18 months of age
- ONE dose per lifetime
- Delivered by bilateral intraputaminal injection (neurosurgical stereotactic procedure)

IS:

- Stereotactic neurosurgical procedure under general anesthesia
- Inpatient post-operative monitoring (ICU then floor)
- Brain MRI pre- and post-procedure

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DENY IF:

- Age <18 months

- DDC gene mutation not confirmed genetically
- Prior gene therapy for AADC deficiency
- Anatomic contraindication to stereotactic neurosurgery

C. CONTINUED STAY / POST-TREATMENT MONITORING

Inpatient 5-7 days post-neurosurgery. Monitor for: intracranial complications, seizures, dyskinesias (common and expected as dopamine production increases).

D. DISCHARGE CRITERIA

Neurologically stable post-op, seizure-free or controlled, tolerating feeds, MRI satisfactory, neurology follow-up arranged.

E. EVIDENCE SOURCES

1. FDA PI: Kebilidi. PTC Therapeutics. 2023. 2. Phase 1/2 Trial. Chien YH, et al. Science Translational Medicine. 2017. 3. Hwu WL, et al. Gene therapy for AADC deficiency. NEJM. 2012.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3590, C9399

CPT: 61720-61735 (stereotactic procedures)

MS-DRG: DRG 023-025 (Craniotomy/Intracranial Procedures)

REVENUE CODES: 0360 (OR), 0200 (ICU), 0250, 0300, 0610 (MRI), 0636

APPROXIMATE COST: ~$3,200,000 (drug) + hospitalization

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 5-10 days post-procedure observation Source: FDA Kebilidi label (USPI 2024)

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

LENMELDY (ATIDARSAGENE AUTOTEMCEL) — METACHROMATIC LEUKODYSTROPHY (MLD)

ICD-10-CM: E75.25 (metachromatic leukodystrophy)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL:

- Confirmed MLD with biallelic ARSA gene mutations by genetic testing
- Late-infantile form: pre-symptomatic OR early symptomatic (before loss of walking)
- Early juvenile form: pre-symptomatic

- ONE dose per lifetime
- Myeloablative conditioning (busulfan) required

IS: Same as autologous BMT protocol

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DENY IF:

- ARSA mutation not confirmed genetically
- Late-onset (adult) form of MLD (not in FDA label)
- Advanced late-infantile form (non-ambulatory, significant cognitive decline)
- Advanced early juvenile form (symptomatic)
- Prior gene therapy or HSCT

C. CONTINUED STAY / POST-TREATMENT MONITORING

Inpatient 4-6 weeks (autologous BMT). Monitor engraftment, ARSA enzyme activity levels.

D. DISCHARGE CRITERIA

Engraftment achieved, enzyme levels trending upward, neurologically stable, enrolled in long-term follow-up.

E. EVIDENCE SOURCES

1. FDA PI: Lenmeldy. Orchard Therapeutics. March 2024. 2. Biffi A, et al. Lentiviral HSC gene therapy for MLD. Science. 2013;341:1233158. 3. Fumagalli F, et al. MLD gene therapy trial. Lancet. 2022;399:372-383.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J3590, C9399

MS-DRG: DRG 016-017 (Autologous BMT)

REVENUE CODES: 0120, 0250, 0300, 0390, 0636

APPROXIMATE COST: ~$4,250,000 (drug — highest-priced gene therapy in US) + hospitalization

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 30-45 days Source: FDA Lenmeldy label (USPI 2024)

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
- Med-Surg: Post-infusion stable, transitioning to outpatient surveillance, completing pre-discharge labs, immunosuppression taper (where applicable).
- Observation: Outpatient or 23-hour observation may be sufficient for Luxturna subretinal injection or Roctavian/Hemgenix uncomplicated infusion per FDA labels.
- Post-Acute (SNF/IRF/LTAC): Rarely; ALD/MLD/Hurler patients may need IRF for baseline neurologic disability.
- Home (with/without HHA): Stable per FDA label monitoring requirements (labs, immunology, viral shedding precautions), follow-up center every 1–2 weeks initially; HHA for IV therapy and home labs.

LOC Grid Sources: FDA Prescribing Information (USPI) for each product; product-specific REMS programs; ASGCT consensus statements.

I. EXTENDED STAY CRITERIA & GUIDANCE

When Goal LOS is exceeded, continued inpatient stay requires documentation of ONE OR MORE of the following medical-necessity triggers. Document the specific trigger, the clinical evidence supporting it, and the targeted intervention plan.

- Severe adverse event per FDA REMS (hepatotoxicity, TMA, hypersensitivity)
- Failure to meet pre-defined discharge criteria from the FDA label monitoring
- Engraftment delay (autologous HSCT-based therapies)
- Infection or complication of conditioning regimen

Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.

ROCTAVIAN (VALOCTOCOGENE ROXAPARVOVEC) — HEMOPHILIA A

ICD-10-CM: D66 (hereditary factor VIII deficiency — hemophilia A)

A. ADMISSION / TREATMENT CRITERIA — Severity of Illness (SI) / Intensity of Service (IS)

APPROVAL REQUIRES ALL:

- Confirmed severe hemophilia A (FVIII activity <1 IU/dL)
- Adult males (≥18 years)
- Currently using FVIII prophylaxis or history of life-threatening hemorrhage
- No current or prior FVIII inhibitors (≥0.6 BU)
- No anti-AAV5 antibodies (per screening assay)
- No active hepatitis B or C
- No significant liver fibrosis/cirrhosis
- ONE dose per lifetime

IS: Single IV infusion, post-infusion hepatic monitoring (ALT weekly x 52 weeks)

B. DOES NOT MEET CRITERIA / NOT MEDICALLY NECESSARY

DENY IF:

- Hemophilia B (D67) — Roctavian is hemophilia A only
- Female patients
- <18 years
- Current/prior FVIII inhibitor
- Anti-AAV5 antibodies detected
- Active hepatitis B/C
- Significant liver disease
- Prior gene therapy for hemophilia A

NOTE: BioMarin suspended Roctavian in EU market (2024). Verify current US market availability.

C. CONTINUED STAY / POST-TREATMENT MONITORING

Outpatient infusion. ALT monitoring weekly x 52 weeks. FVIII activity levels serially. Corticosteroid if ALT elevation.

D. DISCHARGE CRITERIA

Post-infusion observation complete, monitoring schedule established, hematology follow-up within 1 week.

E. EVIDENCE SOURCES

1. FDA PI: Roctavian. BioMarin. June 2023. 2. GENEr8-1 Trial. Ozelo MC, et al. NEJM. 2022;386:1013-1025.

F. HCPCS/J-CODES, MS-DRG CROSSWALK, CPT CODES & REVENUE CODES

HCPCS/J-CODE: J1412 (injection, valoctocogene roxaparvovec-rvox, per therapeutic dose)

MS-DRG (if inpatient): DRG 813 (Coagulation Disorders)

APPROXIMATE COST: $2,900,000 (WAC)

G. GOAL LENGTH OF STAY (UNCOMPLICATED CASE)

Goal LOS: 1-2 days infusion observation Source: FDA Roctavian label (USPI 2023); WFH

H. LEVEL OF CARE (LOC) GRID — PUBLIC-SOURCE STANDARDIZED CRITERIA

- ICU: Hypersensitivity reaction, hemodynamic instability, hepatotoxicity (e.g., Zolgensma transaminitis with hepatic dysfunction), severe TMA (Lyfgenia/Casgevy busulfan conditioning), respiratory failure.
- Stepdown (Telemetry/PCU): Active infusion (Hemgenix/Roctavian) with q4h vitals, post-conditioning engraftment monitoring (Casgevy/Lyfgenia/Skysona/Zynteglo/Lenmeldy), neurologic monitoring post-Kebilidi intracerebral infusion.
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Extended Stay Sources: Sources: FDA Prescribing Information (USPI) and product-specific REMS documents.