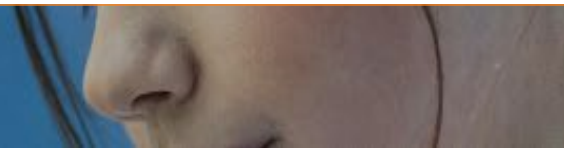


Cell & Gene Therapy – Overview & Setting up the Day

Dr. Surya Singh
Chief Medical Officer



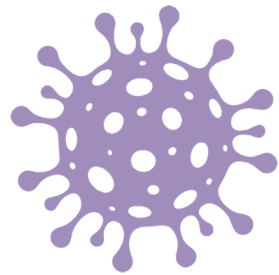
CELL + GENE THERAPY
STAKEHOLDER FORUM



Emerging Therapies to Treat or Cure Disease

Cell Therapy

Transfer of modified live cells into the body



Uses cells from patient: autologous
Uses cells from donor: allogeneic

Gene Therapy

Add new genes (gene addition)
Edit or remove existing genes



Genetically alter outside the body: ex vivo
Direct administration of genetic material: in vivo

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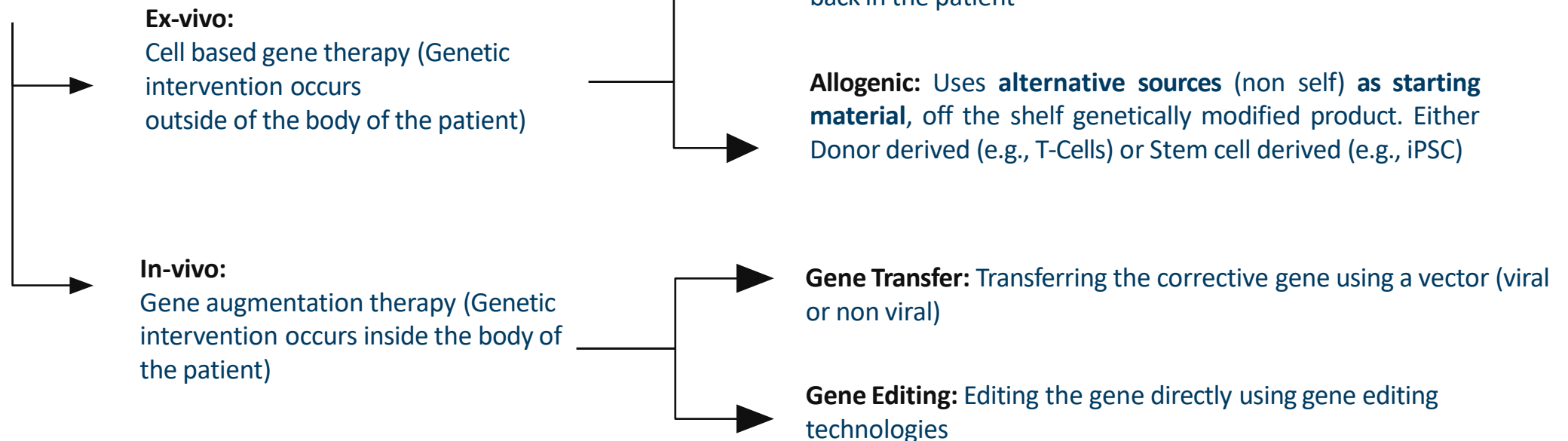
CELL + GENE THERAPY
STAKEHOLDER FORUM

Cell & Gene Therapy: Expanded Definitions

Cell & Gene Therapy

is the introduction, removal, or change in the content of a person's genetic code with the goal to treat or cure a disease. This is achieved by either directly injecting genetic material in their bodies or using modified cells and (re)inserting those as the therapy

Types of cell & gene therapies



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Regulatory Milestones to US FDA Approval

Biologic License Application (BLA)

A request to introduce, or deliver for introduction, a biological product into interstate commerce. The US Food and Drug Administration (FDA) has 90 days from submission to accept the BLA or to request additional information.

Prescription Drug User Fee Act (PDUFA)

Once the FDA has accepted the BLA, a PDUFA date is set by the FDA and is provided to the manufacturer. This is the date by which the FDA must respond to the BLA – either to approve, not approve, or ask for more information.

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Industry Terms & Definitions

FDA	U.S. Food & Drug Administration
CBER	Center for Biologic Evaluation & Research
BLA	Biologic License Application Process of submitting clinical trial data for review/approval by FDA
sBLA	Supplemental Biologic License Application Process for submitting for expanded indications
rBLA	Rolling Biologic License Application Process for submitting some parts of application ahead of BLA filing
PDUFA Date	Prescription Drug User Fee Application Date by which the FDA has to make a decision for approval
ICER	Institute for Clinical & Economic Review Independent non-profit research organization focused on evidence for clinical and economic value of drugs and other therapies

Cell & Gene Therapies

In-vivo

gene therapy directly delivered into the body

Ex-vivo

gene therapy using cells modified outside the body then infused into the patient

CAR-T

chimeric antigen receptor T-cell therapy

TIL

tumor infiltrating lymphocyte therapy

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US FDA Approved Therapies with Condition, Date & Cost*

Therapy Brand Name	Condition(s)	Approval Date	Therapy List Cost**
Cell Therapies			
Kymriah®	Acute lymphoblastic leukemia	August 2017	\$543,828
Yescarta®	Diffuse large B-cell lymphoma, follicular lymphoma	October 2017	\$424,000
Kymriah	Diffuse large B-cell lymphoma	May 2018	\$427,048
Tecartus®	Mantle cell lymphoma	July 2020	\$424,000
Breyanzi®	Diffuse large B-cell lymphoma, follicular lymphoma	February 2021	\$447,227
Abecma®	Multiple myeloma	March 2021	\$457,255
Tecartus®	Acute lymphoblastic leukemia	October 2021	\$424,000
Rethymic®	Congenital athymia	October 2021	\$2,729,500
Carvykti™	Multiple myeloma	February 2022	\$478,950
Kymriah	Follicular lymphoma	May 2022	\$427,048
Omisirge®	Hematologic malignancies (Blood cancers)	April 2023	\$338,000

Therapy Brand Name	Condition(s)	Approval Date	Therapy List Cost**
Gene Therapies (<i>in vivo</i>)			
Luxturna®	Biallelic <i>RPE65</i> mutation associated retinal dystrophy	December 2017	\$425,000 per eye (\$850,000 both eyes)
Zolgensma®	Spinal muscular atrophy	May 2019	\$2,254,412
Hemgenix®	Hemophilia B	November 2022	\$3,500,000
Adstiladrin®	Bladder cancer	December 2022	N/A
Gene Therapies (<i>ex vivo</i>)			
Zynteglo®	Transfusion-dependent beta-thalassemia	August 2022	\$2,800,000
Skysona®	Cerebral adrenoleukodystrophy	September 2022	\$3,000,000
Gene Therapies (<i>Topical</i>)			
Vyjuvek™	Dominant and recessive dystrophic epidermolysis bullosa	May 2023	\$24,250 per vial

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*US Food and Drug Administration (FDA) approved; Prices as of May 2023, and subject to change.

**Please note that list cost for cell & gene therapies does not include any of the care needed to deliver the therapy, such as costs before and after delivery. Administration and associated hospitalizations can range from \$300,000 to \$800,000.

ETS Near-Term Cell & Gene Therapy Pipeline (2023-2024)

Blood Disorders / Hematology

- Hemophilia A (gene, in-vivo) PDUFA 6/30/23
- Transfusion dependent β -thalassemia (gene, ex-vivo)
- Sickle cell disease (gene, ex-vivo)
- Fanconi anemia (gene, ex-vivo)

Cancers / Oncology

- Epstein-Barr virus-associated post-transplant lymphoproliferative disease (CTL)
- Cervical cancer (TIL)
- Metastatic melanoma (TIL) PDUFA 11/25/23
- Marginal zone lymphoma (CAR-T/expanded indications)
- Myxoid/round cell liposarcoma (TCR)
- Synovial sarcoma (TCR)
- Multiple myeloma (CAR-T/expand-move up in line) PDUFA 12/16/23

Musculoskeletal Disorders

- Duchenne muscular dystrophy (gene, in-vivo) PDUFA 6/22/2023

Skin Disorders / Dermatology

- Recessive Dystrophic epidermolysis bullosa (gene)

Inherited Immunodeficiencies / Immunology

- Leukocyte adhesion deficiency type 1 (gene, ex-vivo)

Metabolic Disorders

- Metachromatic leukodystrophy (gene, ex-vivo)
- Mucopolysaccharidosis type II (gene, in-vivo)
- Mucopolysaccharidosis type IIIa (gene, in-vivo)

Inherited Retinal Disease & Ocular Disorders

- Leber hereditary optic neuropathy (gene, in-vivo)
- X-linked retinitis pigmentosa (gene, in-vivo)
- Wet age related-macular degeneration (gene, in-vivo)

Neurodegenerative Disorders

- Aromatic L-amino acid decarboxylase deficiency (gene, in-vivo)
- Amyotrophic lateral sclerosis (autologous, MSC)

Other

- Acute graft versus host disease (allogeneic, MSC) PDUFA 8/02/23

Conditions with Approved Therapies

- | | |
|---|--|
| • Acute lymphoblastic lymphoma | • Follicular lymphoma |
| • Biallelic RPE65 mutation associated retinal dystrophy | • Hemophilia B |
| • Bladder cancer | • Mantle cell lymphoma |
| • Cerebral adrenoleukodystrophy | • Multiple myeloma |
| • Diffuse large B-cell lymphoma | • Spinal muscular atrophy |
| • Dystrophic epidermolysis bullosa | • Transfusion dependent beta-thalassemia |

Cell Therapy Types

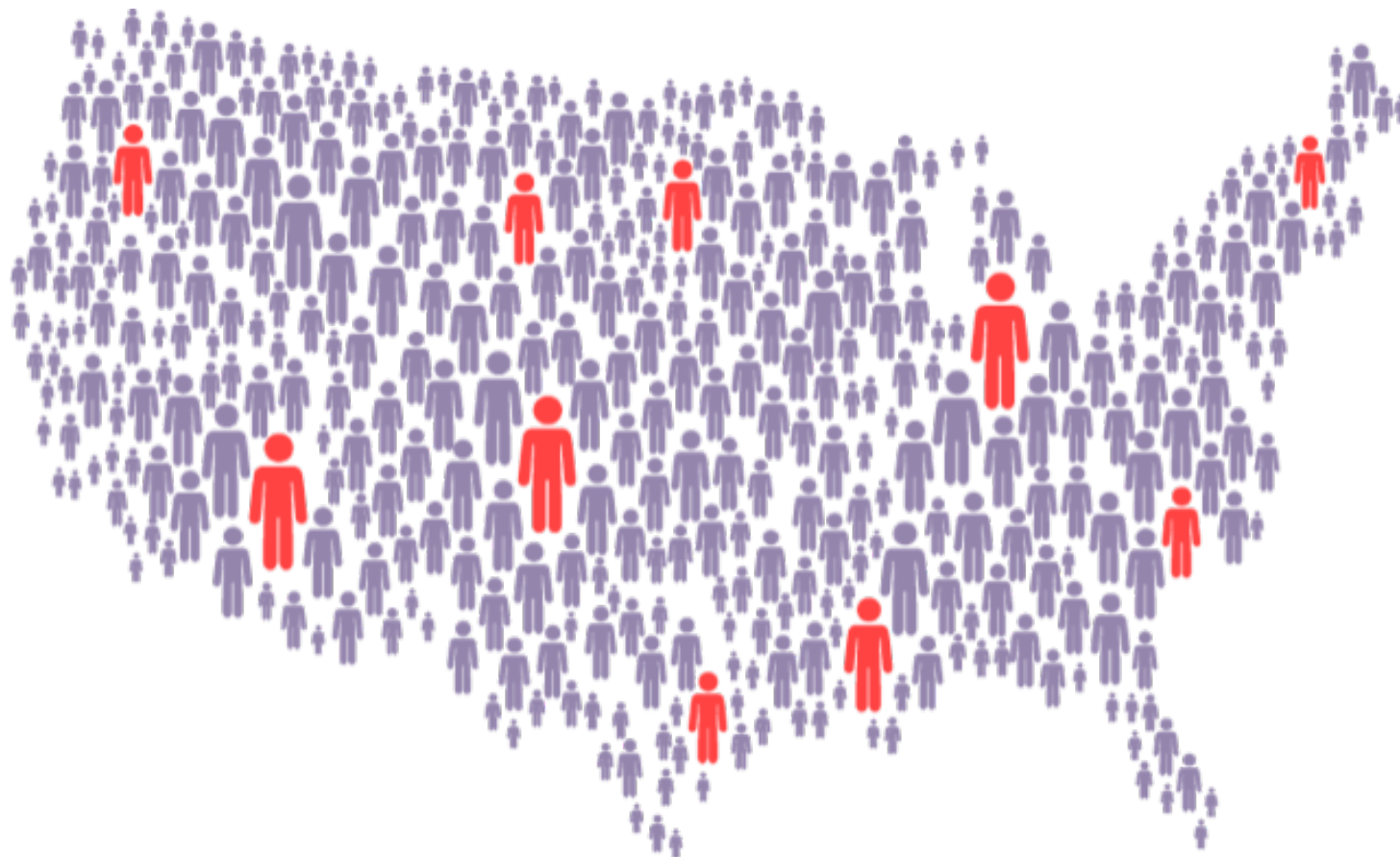
- CAR-T = chimeric antigen receptor T-cell
- TCR = T-cell receptor
- TIL = Tumor infiltrating lymphocyte
- CTL = EBV-cytotoxic T lymphocyte (CTL)
- MSC = Mesenchymal stem cell

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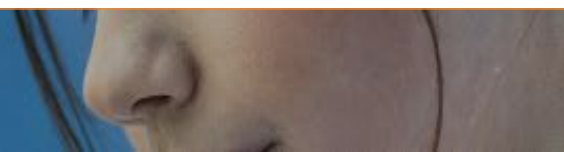
Typical Commercial 1M Life Plan



In 2023,
30-100+
Cases
(minimum)

Based on ETS 2023 proprietary calculations

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Framing the Day – CGT Payment Considerations



- Fair pricing
- Affordability & budget impact



- Concordance / discordance between evidence and label



- Network / COE approach
- Preventing excessive product mark-up in the supply chain
- Increasing predictability of non-product / administration costs



- Establishing outcomes / metrics for monitoring performance & durability
- Warranties and outcomes-based agreements (“OBA’s”)



- Tracking & monitoring outcomes
- Data & analytics

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Stakeholder specific considerations for CGT

Manufacturer

- Ensure product access to label
- Support COE to drive outcomes
- Clinically appropriate patient access – removal of financial barriers

Providers

- Fair reimbursement for administration / prof services
- Achieve COE status with enough volume to justify investment, particularly if buy-and-bill is not an option

Patients

- Access to novel therapies
- Ancillary services and holistic care
- Caregiver support
- Minimize OOP for in-network treatment

Primary payor

- Contract specialist providers through COE
- Expert maintained medical policies
- Ensure fair price for product & admin
- Durability → Warranty via OBA

Secondary payor

- Specialist providers through COE
- Predictability
- Access to OBA and pro rata warranty

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A female scientist with dark hair, wearing a white lab coat over a pink shirt and blue gloves, is focused on using a pipette in a laboratory. The background is a blurred lab environment with blue lighting. The text 'Session Take Aways' is overlaid in white, underlined with a red line.

Session Take Aways

Key themes from the day

Cell & Gene Therapies: Key Takeaways

- It's a transformational moment; it's hard to overstate the opportunity for treatment of rare diseases
 - CGT does not fit the existing, traditional supply chain model (and shouldn't go through this model)
 - A new model is emerging because the current framework for existing drugs is not sustainable for CGT
 - CGT lends itself to outcomes-based (values-based) agreements to address payer uncertainties – better outcomes at less cost with potentially millions of dollars in savings per patient relative to standard of care; right patient/right location/right price
 - Stakeholder needs are not aligned in support of patients, payers and treatment centers; methodology must change
 - Opportunity exists for transformational solutions that align all stakeholder interests to advance patient access to care
 - Do we need a common network of CGT quality treatment centers with criteria?
- Plan document language must match and represent plan sponsors decisions and intentions
 - Patient and family treatment experience is incredibly stressful
 - The CGT treatment breakthroughs “mean nothing” if we can't align the ecosystem – exciting but a lot of work to do
 - CGT treatment is / can be an order of magnitude safer; how are we advancing science and improving care for these CGT patients
 - The question / starting point should be: how can we NOT cover these cell and gene therapies?
 - Need to educate clients; stay ahead of pipeline; have a partner to work with for network access at COEs
 - Risk takers know that lasers are unsustainable as the pipeline grows, but are using now as a tool because they to price for known risk



A female scientist with dark hair, wearing a white lab coat over a pink shirt and blue gloves, is focused on using a pipette in a laboratory. The background is a blurred blue-toned lab environment with various pieces of equipment.

Thank you

For more information contact Ashley Hume
ashley.hume@emergingtherapies.com

Cell and Gene Therapies can offer new treatment options for patients and providers.

Emerging Therapy Solutions® (ETS) closely monitors the cell and gene therapy pipeline to identify noteworthy prospective treatments that our clients should be aware of, with a focus on near-term therapies that are estimated to be coming in the next 15 to 24 months. Below is a brief and limited overview of several investigational cell and gene therapy clinical trials that Emerging Therapy Solutions® (ETS) is monitoring in the United States. For combined administrative and therapy (total) cost estimations, gene therapies are expected to range from between \$1.5 and \$4 million; cell therapies, such as chimeric antigen receptor (CAR) T-cell therapies, are expected to range from \$500,000 to \$1 million in total cost estimations.

Contact ETS to learn more about these therapies: 877.445.4822 | emergingtherapies.com

CELL THERAPIES

THERAPY & MANUFACTURER	CONDITION	CURRENT TREATMENT*	ACTUAL / ANTICIPATED APPROVAL DATE
Kymriah® tisagenlecleucel; tisa-cel Novartis Pharmaceuticals	Acute lymphoblastic leukemia	Multidrug regimen, chimeric antigen receptor (CAR) T-cell therapy	8/30/2017 Approved \$543,828
Yescarta® axicabtagene ciloleucel; axi-cel Kite Pharma	Diffuse large B-cell lymphoma Non-Hodgkin lymphoma Follicular lymphoma	Chemotherapy, bone marrow transplant (BMT), CAR-T therapy	10/18/2017 Approved \$424,000
Kymriah tisagenlecleucel; tisa-cel Novartis Pharmaceuticals	Diffuse large B-cell lymphoma Non-Hodgkin lymphoma	Chemotherapy, BMT, CAR-T therapy	5/1/2018 Approved \$427,048
Tecartus® brexucabtagene autoleucel; brexu-cel Kite Pharma	Mantle cell lymphoma Non-Hodgkin lymphoma	Radiation, chemotherapy, autologous stem cell transplant, CAR-T therapy	7/24/2020 Approved \$424,000
Breyanzi® lisocabtagene maraleucel; liso-cel Bristol Myers Squibb	Diffuse large B-cell lymphoma Follicular lymphoma Non-Hodgkin lymphoma	Chemotherapy, BMT, CAR-T therapy	2/5/2021 Approved \$447,227
Abecma® idecabtagene vicleucel; ide-cel Bristol Myers Squibb/BBB	Multiple myeloma	Chemotherapy, stem cell transplants, surgery, radiation or combination of these options, CAR-T therapy	3/26/2021 Approved \$457,255
Tecartus brexucabtagene autoleucel; brexu-cel Kite Pharma	Acute lymphoblastic leukemia	Multidrug regimen, CAR-T therapy	10/1/2021 Approved \$424,000
Rethymic® Allogeneic Processed Thymus Tissue Enzyvant Therapeutics	Congenital athymia	Strict isolation, prophylactic infection control, immunoglobulins and in some situations, immunosuppression	10/8/2021 \$2,729,500 Approved
Carvykti™ ciltacabtagene autoleucel; cilta-cel Janssen/Legend Biotech	Multiple myeloma	Chemotherapy, stem cell transplants, surgery, radiation or combination of these options, CAR-T therapy	2/28/2022 Approved \$465,000
Yescarta axicabtagene ciloleucel; axi-cel Kite Pharma	Large B-cell lymphoma in the second-line setting	Chemotherapy, BMT, CAR-T therapy	4/1/2022 Approved \$424,000
Kymriah tisagenlecleucel; tisa-cel Novartis Pharmaceuticals	Follicular lymphoma	Chemotherapy, BMT, CAR-T therapy	5/27/2022 Approved \$427,048
Breyanzi lisocabtagene maraleucel; liso-cel Bristol Myers Squibb	Large B-cell lymphoma in the second-line setting	Chemotherapy, BMT, CAR-T therapy	6/24/2022 Approved \$410,300
Omisirge® omidubicel-onlv Gamida Cell	Hematologic malignancies (Blood cancers)	Umbilical cord blood transplantation (UCBT)	4/17/2023 Approved \$338,000
Abecma – Moving up in line Carvykti – Second line	Multiple myeloma	Chemotherapy, stem cell transplants, surgery, radiation or combination of these options, CAR-T therapy	PDUFA - 12/16/23 Q4 2023
Afami-cel afamitresgene autoleucel; ADP-A2M4 Adaptimmune Therapeutics	Synovial sarcoma	Surgical excision, chemotherapy, radiation therapy	H2 2023
Afami-cel afamitresgene autoleucel; ADP-A2M4 Adaptimmune Therapeutics	Myxoid/round cell liposarcoma	Surgical excision, pre-operative chemotherapy, pre-operative or post-operative radiotherapy	H2 2023
Tab-cel® tabelecleucel; ATA129/EBV-CTL Atara Biotherapeutics	Epstein-Barr virus-associated post-transplant lymphoproliferative disease	Immunotherapy, rituximab, radiation & antiviral therapy, immunochemotherapy	H2 2023
Lifileucel LN-144 Iovance Biotherapeutics	Metastatic melanoma	Surgical excision, removal of affected lymph nodes, chemotherapy, radiation, checkpoint inhibitor immunotherapy or targeted therapy drugs	H2 2023
Yescarta axicabtagene ciloleucel; axi-cel Kite Pharma	Marginal zone lymphoma	Active Surveillance, radiation therapy, surgery, rituximab and ibrutinib and chemotherapy	2023
Lifileucel LN-144 Iovance Biotherapeutics	Cervical cancer	Hysterectomy, radiation, chemotherapy	2024

GENE THERAPIES	Therapy & Manufacturer	Condition	Current Treatment*	Actual / Anticipated Approval Date
	Luxturna® <i>in-vivo</i> voretigene neparovovec-rzyl Spark Therapeutics	Biallelic <i>RPE65</i> mutation	<i>In-vivo</i> gene therapy	12/2017 Approved \$425,000 per eye
	Zolgensma® <i>in-vivo</i> onasemnogene abeparovovec Novartis Pharmaceuticals	Spinal muscular atrophy	Spinraza® (nusinersen), Evrysdi® (risdiplam), <i>In-vivo</i> gene therapy	05/2019 Approved \$2,125,000
	Zynteglo® <i>ex-vivo</i> betibeglogene autotemcel; beti-cel bluebird bio	Transfusion-dependent beta-thalassemia	Chronic blood transfusions, BMT, chelation therapy, <i>Ex-vivo</i> gene therapy	8/17/2022 Approved \$2,800,000
	Skysona™ <i>ex-vivo</i> elivaldogene autotemcel; eli-cel bluebird bio	Cerebral adrenoleukodystrophy	BMT, <i>Ex-vivo</i> gene therapy	9/16/2022 Approved \$3,000,000
	Hemgenix® <i>in-vivo</i> etranacogne dezaparovovec; EtranaDez uniQure / CSL Behring	Hemophilia B	Factor replacement, <i>In-vivo</i> gene therapy	11/22/2022 Approved \$3,500,000
	Adstiladrin® <i>in-vivo</i> nadofaragene firadenovoc-vncg Ferring Pharmaceuticals	Bladder cancer	Transurethral resection of bladder tumor (TURBT), intravesical immunotherapy, radiation/chemotherapy, <i>In-vivo</i> gene therapy	12/16/2022 Approved N/A
	Vyjuvek™ <i>Topical</i> beremagene geperpavec; B-VEC; KB103 Krystal Biotech	Dominant and recessive dystrophic epidermolysis bullosa	Wound care	PDUFA 5/19/2023
	SRP-9001** <i>in-vivo</i> delandistrogene moxeparovovec Sarepta	Duchenne muscular dystrophy	Medications include Amondys 45, Exondys 51, and Vyondys 53, otherwise treatment is symptomatic	PDUFA 5/29/2023
	Roctavian® <i>in-vivo</i> valoctocogene roxaparovovec; Valrox BioMarin Pharmaceutical Inc.	Hemophilia A	Factor replacement or Hemlibra® (emicizumab)	PDUFA 6/30/2023
	Remestemcel-L Mesoblast Limited	Acute graft versus host disease	Immunosuppressive prevention; corticosteroid	PDUFA 8/02/2023
	Libmeldy® <i>ex-vivo</i> atidarsagene autotemcel; OTL-200 Orchard Therapeutics	Metachromatic leukodystrophy	BMT	Q3 2023
	Lovo-cel <i>ex-vivo</i> lovotibeglogene autotemcel; bb1111 bluebird bio	Sickle cell disease	BMT	Q3 2023
	Exa-cel <i>ex-vivo</i> exagamglogene autotemcel; CTX001™ CRISPR/Vertex	Sickle cell disease	BMT	Q3 2023
	Exa-cel <i>ex-vivo</i> exagamglogene autotemcel; CTX001 CRISPR/Vertex	Transfusion-dependent beta-thalassemia	Chronic blood transfusions, BMT, chelation therapy, <i>Ex-vivo</i> gene therapy	Q3 2023
	RP-L201 <i>ex-vivo</i> Rocket Pharmaceuticals	Leukocyte adhesion deficiency type I	BMT, antibiotic therapy	Q4 2023
	EB-101 <i>keratinocyte sheets</i> Abeona Therapeutics	Recessive dystrophic epidermolysis bullosa	Wound care	2023
	Olenasuflogene relduparovovec <i>in-vivo</i> Lysogene; UX111 (fka ABO-102) Ultragenyx	Mucopolysaccharidosis type III	Limited to none (Treating symptoms)	2023 – 2024
	RP-L102 <i>ex-vivo</i> Rocket Pharmaceuticals	Fanconi anemia	BMT, oxymetholone	H1 2024
	ADVM-002 <i>in-vivo</i> , Adverum RGX-314 <i>in-vivo</i> , REGENXBIO HMR59 <i>in-vivo</i> , Hemera	Wet age-related macular degeneration	Intravitreal injection of vascular endothelial growth factor (VEGF), photodynamic therapy, vitamin/mineral formula	2024
Elandocagene exuparovovec <i>in-vivo</i> PTC-AADC; Upstaza EU PTC Therapeutics	Aromatic l-amino acid decarboxylase	Limited to none (Treating symptoms)	2024	
LUMEVOQ <i>in-vivo</i> lenadogene nolparovovec; GS010 GenSight Biologics	Leber hereditary optic neuropathy	Limited to none (Treating symptoms)	2024	
RGX-121 <i>in-vivo</i> REGENXBIO	Mucopolysaccharidosis type II	Limited to none (Treating symptoms)	2024	
AAV-RPGR <i>in-vivo</i> botaretigene sparoparovovec MeiraGTx/Janssen Pharmaceuticals, Inc.	X-linked retinitis pigmentosa	Limited to none (Treating symptoms)	2024	

*Current Treatment here is only a general categorization of generally published and known alternatives and does not reflect that every individual situation will vary. **FDA Advisory Panel scheduled.
NOTE: This content is informational only and is intended for a US audience. This document has been prepared by Emerging Therapy Solutions (ETS) and provides information about prospective cell and gene therapy treatments as of the date of this document. The information provided has been obtained from third-party sources we believe to be reliable, however we may not be able to verify accuracy and make no guarantee, warranty, or representation about this information. Due to the rapidly evolving and changing nature of the content of this document, the information presented, including opinions and estimates, is subject to change without notice and may become quickly outdated. The information presented is not intended to be a recommendation as to medical care, or any form of legal or medical advice. Emerging Therapy Solutions is a trademark of Emerging Therapy Solutions, Inc. All other trademarks referenced herein are the property of their respective owners.