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REVIEW

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Five-year durability in cell and gene therapy: evidence review and implications for payer coverage

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ABSTRACT

Introduction: Cell and gene therapies (CGTs) offer the potential for durable clinical benefit following a single administration. Although early regulatory approvals were often based on limited follow-up, an increasing number of U.S. Food and Drug Administration (FDA)-approved CGTs now report extended durability data from clinical trials and real-world evidence (RWE) studies.

Areas covered: This report synthesizes publicly available long-term follow-up (LTFU) evidence for FDA-approved CGTs in the United States, with a focus on durability of clinical benefit and the implications for payer coverage and reimbursement. Long-term efficacy and safety data for marketed CGTs were identified through a review of peer-reviewed publications and publicly available conference abstracts and presentations. As of December 2025, 21 therapies (62%) report follow-up extending to 5 years or longer. The review examines the available durability evidence and explores its relevance to ongoing discussions around durability-related uncertainty and the role of LTFU and real-world evidence in assessing CGT outcomes.

Expert opinion: Growing LTFU evidence suggests that durable clinical benefit can be achieved across multiple CGT platforms and disease settings. While uncertainties remain, accumulating data may help reduce durability-related uncertainty and inform payer coverage, reimbursement, and value assessment discussions.

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Adeno-associated viral (AAV) gene therapy; cell and gene therapy (CGT); chimeric antigen receptor (CAR) T-cell therapy; lentiviral vector (LVV) gene therapy; long-term follow-up (LTFU); payer coverage; real-world evidence (RWE); therapeutic durability

1. Introduction

Cell and gene therapies (CGTs) are a novel class of advanced therapeutic modalities designed to modify, replace, or supplement biological function at the cellular or genetic level [1]. Since the first U.S. Food and Drug Administration (FDA) CGT approval in 2017, the field has expanded across malignant and nonmalignant hematologic disorders, neuromuscular conditions, and rare genetic diseases. As of December 2025, 48 CGTs have received FDA approval in the United States (US), with more than 2,000 products in active development and dozens more approvals anticipated over the coming decade [2–4].

The rapid expansion of the CGT pipeline, however, has intensified concerns regarding the affordability of these treatments. Most CGTs are administered once or over a short treatment course and are associated with substantial upfront costs, with some therapies exceeding $4 million per treatment [5]. Notably, the wholesale acquisition costs (WACs) for chimeric antigen receptor (CAR) T-cell therapies have increased steadily since their respective launch dates. Among currently marketed products, initial launch prices ranged from $373,000 to $465,000, while 2025 WACs ranged from $462,000 to above $590,000, reflecting annual price increases of approximately 3–7% [6]. These upward trends, combined with the upfront concentration of costs at the time of treatment, can create significant short-term financial challenges, even when long-term value may be anticipated.

For payers, economic rationale for coverage and reimbursement decisions is closely tied to evidence of clinical efficacy and safety, as well as confidence in the persistence of benefit over time. The key concern is not merely whether these therapies work, but whether clinical benefit is sufficiently durable to justify the high cost [4]. Previous analyses have suggested that at least five years of durable benefit may represent an important evidence threshold to support reimbursement of these one-time, high-cost therapies [4].

The evidentiary landscape, however, is evolving. Consistent with FDA recommendations for 5 to 15 years of post-marketing follow-up, an increasing number of FDA-approved CGTs now report outcomes extending to 5 years or longer [7]. The purpose of this report aims to consolidate and interpret the growing body of publicly available long-term follow-up (LTFU) analyses for FDA-approved CGTs in the US. By summarizing the available durability evidence, we examine how the accumulating body of LTFU data may inform ongoing discussions regarding durability-related uncertainty, its implications for payer coverage and reimbursement strategy, and the continued importance of LTFU and real-world evidence (RWE) generation in assessing CGT outcomes.

2. Assessing the maturity of the CGT landscape

2.1. Cohort identification

To characterize the 5-year durability landscape of CGTs in the US, we conducted an evidence review of all products listed on the FDA Approved Cellular and Gene Therapy Products list as of 31 December 2025 [2]. To focus specifically on high-technology

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Article highlights

- As of December 2025, 21 out of 34 (62%) U.S. Food and Drug Administration (FDA)-approved cell and gene therapies (CGTs), excluding cord blood and tissue-engineered products, now report published analyses demonstrating outcomes with at least 5 years of follow-up.
- Seven cell-based treatments, including multiple cluster of differentiation (CD)19- and B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell products, as well as tumor-infiltrating lymphocyte (TIL) therapies, now have ≥5-year follow-up analyses showing durable survival and prolonged remission across multiple malignancy types.
- Fourteen FDA-approved gene therapies report ≥5 years of follow-up, with sustained functional outcomes observed across rare genetic, neuromuscular, and hematologic diseases.
- The growing body of long-term data suggests that outcomes for many approved CGTs are becoming increasingly well characterized, although important uncertainties remain regarding the consistency and duration of benefit.
- Continued long-term follow-up and real-world evidence generation remain important for assessing long-term benefit-risk profiles and informing payer decision-making.

medicinal products for systemic or targeted disease modification, we only considered marketed CGTs including CAR T-cell therapies, adeno-associated virus (AAV)-based gene therapies, lentiviral vector (LVV)-based gene therapies, tumor-infiltrating lymphocytes (TILs), oncolytic viruses, and other genetically modified cell- and gene-based therapies. Hematopoietic progenitor cell cord-blood and tissue-engineered products were excluded, yielding 34 eligible CGTs, Figure 1.

A PubMed literature search through 31 December 2025 was conducted for each eligible CGT product. Searches combined generic and brand names with durability-related terms (e.g. long-term follow-up, 5-year follow-up, durability, efficacy, and safety). Records with an electronic publication (e-pub) date after 31 December 2025, were excluded. Studies conducted exclusively outside the US were excluded unless they constituted part of the pivotal study supporting FDA review or approval of the product. Peer-reviewed publications and eligible conference reports were included if they reported product-specific clinical efficacy and/or safety outcomes from a cohort- or study-level follow-up analysis evaluating outcomes at 5 years or longer after treatment, or reported a cohort mean or median follow-up of at least 5 years with clinical outcomes. Reports were not considered eligible solely because isolated individual patients within a cohort had reached ≥5 years of follow-up in the absence of cohort-level outcomes reported at that time point. Retrospective studies, reviews, editorials, economic evaluations, modeling studies, nonclinical publications, and other reports for products lacking qualifying clinical durability outcomes were excluded.

The PubMed search identified 3,043 records. Removal of 779 duplicate records and exclusion of 232 publications with e-pub dates after 12/31/2025 left 2,032 records that underwent title and abstract screening. Of these, 1,687 records were excluded leaving 345 reports advancing to full-text eligibility assessment. Following full-text review, 17 peer-reviewed publications representing 13 therapies met the predefined criteria and were included in the evidence analysis.

In parallel, conference abstracts and posters from major medical and scientific congresses (e.g. ASCO, ASH, ASGCT, EHA, and other relevant specialty meetings) were searched separately to identify additional publicly available long-term efficacy and safety datasets through 31 December 2025. Therapies lacking an eligible peer-reviewed publication remained eligible if qualifying ≥5-year durability data were available from these sources. Fifteen records were identified and screened, of which 12 reports, representing 8 additional therapies, met predefined durability criteria and were included in the evidence analysis. A therapy-level summary of included and excluded products, evidence sources, and reasons for exclusion is provided in Table 1.

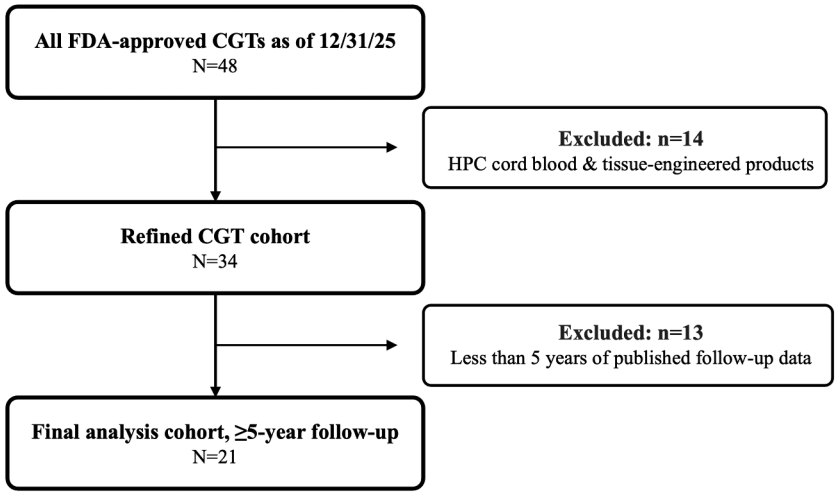

Figure 1. Cohort generation.

After excluding HPC cord blood and tissue engineered products, 34 of 48 approved CGTs were included in this analysis. Of these, 21 (62%) have 5 or more years of LTFU outcomes in at least 1 indication.

Abbreviations: CGTs = cell and gene therapies; FDA = U.S. Food and Drug Administration; HPC = hematopoietic progenitor cells; LTFU = long-term follow-up.

Short Description: Selection of FDA-approved CGTs for analysis based on product type and availability of ≥5 years of published follow-up data.

Table 1. Identification and selection of FDA-approved cell and gene therapies for assessment of ≥5-year long-term durability outcomes.

Therapy	Met review eligibility criteria	Evidence type	Supporting study/evidence source	Basis for inclusion or non-inclusion
Cell Therapies				
Afamitresgene autoleucel	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Axicabtagene ciloleucel	Yes	Peer-reviewed publications	Neelapu et al. (ZUMA-1) [11]; Neelapu et al. (ZUMA-5) [15]; Jain et al. (US Lymphoma CAR-T Consortium) [12]	Qualifying ≥5-year efficacy and safety outcomes reported.
Azficel-T	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Brexucabtagene autoleucel	Yes	Conference abstract/ posters	Wang et al. (ASH 2024, ZUMA-2) [17]; Oluwole et al. (EHA 2025, ZUMA-3) [21]	Qualifying ≥5-year efficacy and safety outcomes reported.
Ciltacabtagene autoleucel	Yes	Peer-reviewed publication	Jagannath et al. (CARTITUDE-1) [26]	Qualifying ≥5-year efficacy and safety outcomes reported.
Donislecel	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Idecabtagene vicleucel	Yes	Conference poster	Anderson et al. (KarMMa; IMS 2024) [30]	Qualifying ≥5-year efficacy and safety outcomes reported.
Lifileucel	Yes	Peer-reviewed publication	Medina et al. (C-144–01) [43]	Qualifying ≥5-year efficacy and safety outcomes reported.
Lisocabtagene maraleucel	Yes	Conference abstracts	Abramson et al. (TRANSCEND NHL 001; ASH 2024) [34]	Qualifying ≥5-year efficacy and safety outcomes reported.
Obecabtagene autoleucel	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Omidubicel-onlv	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Remestemcel-L-rknd	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Sipuleucel-T	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Tisagenlecleucel	Yes	Peer-reviewed publications/ Conference abstract	Maziarz et al. (JULIET) [38]; Rives et al. (ELIANA) [36]	Qualifying ≥5-year efficacy and safety outcomes reported.
Gene Therapies				
Atidarsagene autotemcel	Yes	Peer-reviewed publication	Fumagalli et al. [76]	Qualifying ≥5-year efficacy and safety outcomes reported.
Beremagene geperpavec-svdt	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Betibeglogene autotemcel	Yes	Conference abstract	Kwiatkowski et al. (ASH 2024 LTF-303) [81]; Thompson et al (ASH 2023) [82]; Olson et al. (ASTCT 2025) [83]	Qualifying ≥5-year efficacy and safety outcomes reported.
Delandistrogene moxeparvovec-rokl	Yes	Conference poster	Mendell et al. (WMS 2024 Study 101) [47]	Qualifying ≥5-year efficacy and safety outcomes reported.
Eladocagene exuparvovec-tneq	Yes	Peer-reviewed publication	Tai et al. [50]	Qualifying ≥5-year efficacy and safety outcomes reported.
Elivaldogene autotemcel	Yes	Peer-reviewed publication	Eichler et al. [85]	Qualifying ≥5-year efficacy and safety outcomes reported.
Etranacogene dezaparvovec-drlb	Yes	Peer-reviewed publications	Pipe et al. (HOPE-B) [53]; von Drygalski et al. [54]	Qualifying ≥5-year efficacy and safety outcomes reported.
Etuvetidigene autotemcel	Yes	Conference abstract	Ferrua et al. (ASH 2025) [88]	Qualifying ≥5-year efficacy and safety outcomes reported.
Exagamglogene autotemcel	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Fidanacogene elaparvovec-dzkt*	No	Peer-reviewed publication identified	NA	Product withdrawn from market and excluded from the analysis.
Lovotibeglogene autotemcel	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Nadofaragene firadenovec-vncg	Yes	Peer-reviewed publication	Narayan et al. [57]	Qualifying ≥5-year efficacy and safety outcomes reported.

(*Continued*)

Table 1. (Continued).

Therapy	Met review eligibility criteria	Evidence type	Supporting study/evidence source	Basis for inclusion or non-inclusion
Onasemnogene abeparvovec-brve	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.
Onasemnogene abeparvovec-xioi	Yes	Peer-reviewed publication	Mendell et al. (START/LT-001) [60]	Qualifying ≥5-year efficacy and safety outcomes reported.
Prademagene zamikeracel	Yes	Peer-reviewed publication	So et al. [90]	Qualifying ≥5-year efficacy and safety outcomes reported.
Revakinagene taroretcel-lwey	Yes	Peer-reviewed publication	Singerman et al. [91]	Qualifying ≥5-year efficacy and safety outcomes reported.
Talimogene laherparepvec	Yes	Peer-reviewed publications	Chesney et al. [96]; Dummer et al. [95]	Qualifying ≥5-year efficacy and safety outcomes reported.
Valoctocogene roxaparvovec-rvox	Yes	Conference poster	Leavitt et al. (ISTH 2025 GENEr8-1) [70]	Qualifying ≥5-year efficacy and safety outcomes reported.
Voretigene neparvovec-rzyl	Yes	Conference presentation	Russell et al. (ASRS 2024) [74]	Qualifying ≥5-year efficacy and safety outcomes reported.
Zopapogene imadenovec-drba	No	None identified	None identified	No qualifying ≥5-year clinical durability evidence identified as of December 31, 2025.

*Long-term clinical outcomes have been reported for fidanacogene elaparvovec, but the therapy was excluded from the analysis as it was withdrawn from the market before December 31, 2025.

ASH = American Society of Hematology; ASRS = American Society of Retina Specialists; CAR-T = Chimeric Antigen Receptor T-cell; EHA = European Hematology Association; IMS = International Myeloma Society; ISTH = International Society on Thrombosis and Hemostasis; LBCL = Large B-cell Lymphoma; LTF = Long-Term Follow-up; MacTel = Macular Telangiectasia Type 2; TIL = Tumor-Infiltrating Lymphocyte; WAS = Wiskott-Aldrich Syndrome; WMS = World Muscle Society.

2.2. Outcomes definitions and analysis

Outcomes of interest were therapy-specific. Examples of efficacy outcomes for cell therapy products included overall survival (OS), duration of response (DoR), and progression-free survival (PFS). Efficacy outcomes for gene therapy products included, but were not limited to, durability of effect (e.g. transfusion independence [TI], annualized bleeding rate [ABR]) or functional/motor milestones (e.g. ambulation, North Star Ambulatory Assessment [NSAA] scores). Safety outcomes included incidence of late adverse events (AEs), secondary malignancies, and vector-related oncogenicity.

3. A maturing landscape of long-term evidence

As of 31 December 2025, 34 of the 48 FDA-approved CGT products met eligibility criteria for inclusion in our analysis. Within this cohort, 21 (62%) therapies have established clinical follow-up data extending to 5 years or longer (Tables 2 and 3). Of these therapies, 13 (38%) had data available in full peer-reviewed publications, whereas 8 (24%) were supported by conference abstracts or other brief scientific reports only (Table 1).

3.1. LTFU in cell therapies

3.1.1. Axicabtagene ciloleucel

Axicabtagene ciloleucel (axi-cel) was the first CAR T-cell therapy approved for relapsed/refractory (R/R) large B-cell lymphoma (LBCL) [8]. As of July 2025, over 25,000 patients have been treated globally with axi-cel since its FDA approval in 2017 [9]. The pivotal ZUMA-1 trial (NCT02348216) demonstrated an initial overall response rate (ORR) of 83% (58% complete response [CR]) in 101 patients treated with axi-cel [10]. Five-year follow-up (median 63.1 months [range, 58.9–68.4 months]) demonstrated a median OS of 25.8 months (95% confidence interval [CI], 12.8 months to not estimable), an estimated 5-year OS rate of 42.6% (95% CI, 32.8%-51.9%), and a disease-specific survival rate of 51% (95% CI, 40.4%-60.6%) [11]. For patients who achieved a CR, the 5-year OS rate was notably higher at 64.4% (95% CI, 50.9%-75.1%). At 5 years, responses remained ongoing in 31% of the original treated population, with 30% in ongoing CR. Safety data showed that most serious AEs occurred early (e.g. cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]). No secondary malignancies related to axi-cel were reported.

Consistent with the long-term efficacy findings from ZUMA-1, a 5-year real-world analysis from the US Lymphoma CAR T Consortium evaluated 275 patients with R/R LBCL treated with standard-of-care axi-cel after ≥2 prior lines of therapy [12]. After a median follow-up of 58 months, estimated 5-year PFS, OS, and lymphoma-specific survival rates were 29%, 40%, and 53%, respectively, supporting the durability observed in ZUMA-1. However, unlike the pivotal trial, long-term follow-up in the real-world cohort identified a 5-year non-relapse mortality rate of 16.2%, with infections and subsequent malignant neoplasms among the leading causes of late non-relapse death.

Additionally, axi-cel was evaluated in the Phase II ZUMA-5 trial (NCT03105336), demonstrating a 92% (95% CI, 85%-97%) ORR in patients with follicular lymphoma (FL) or marginal zone lymphoma (MZL); among the 96 patients with a response, 77 (74%) had a CR [13,14]. The 5-year follow-up analysis of ZUMA-5 included 159 patients and confirmed its durable outcomes and curative potential [15]. At a median 64.6 months (range,

Table 2. Key clinical trials of cell therapies with published ≥5-year follow-up analyses.

Therapy	Therapy class	Initial study underlying the LTFU analysis	LTFU study sponsor	Sample size (N)			Indication	Key LTFU clinical outcomes
				Enrolled in initial study/studies	Treated population	Number of patients analyzed in LTFU analysis		
Axicabtagene ciloleucel (axi-cel)	CAR T-cell therapy	ZUMA-1 (Phase II, pivotal, NCT02348216)	Kite Pharma (Kite, a Gilead Company)	111	101	101	R/R LBCL	5-year analysis: • Median OS: 25.8 mo • OS rate: 42.6% • CR patients OS rate: 64.4% • ~30% ongoing CR
		US Lymphoma CAR-T Consortium (RWE)	Not available	298	275	275	R/R LBCL	5-year analysis: • PFS: 29% • OS: 40% • Lymphoma-specific survival: 53%
		ZUMA-5 (Phase II, pivotal, NCT03105336)	Kite Pharma (Kite, a Gilead Company)	159	152	159*	R/R FL/MZL	5-year analysis: • ORR 92%; CR 74% • Median DoR 60.4 mo • Median PFS 62.2 mo • Median OS: NR
Brexucabtagene autoleucel (brexu-cel)	CAR T-cell therapy	ZUMA-2 (Phase II, pivotal, NCT02601313)	Kite Pharma (Kite, a Gilead Company)	91	82	82	R/R MCL	5-year analysis: • Median OS: ○ 46.5 mo for cohort 1 ○ NR for cohort 2 • OS rate: 38.5%-53.6% for cohorts 1 and 2, respectively
		ZUMA-3 (Phase II, pivotal, NCT02614066)	Not available	125	78†	78	R/R B-ALL	5-year analysis: • Median OS 25.6 mo • OS rate: 40% • Responders median OS: 60.4 mo
Ciltacabtagene autoleucel (cilta-cel)	CAR T-cell therapy	CARTITUDE-1 (Phase Ib/II, pivotal, NCT03548207)	Johnson & Johnson and Legend Biotech U.S.A. Inc.	113	97	97	R/R MM	5-year analysis: • Median OS: 60.7 mo • 33% of patients remained progression-free ○ 97% achieved ≥5 years with sCR • 100% sustained MRD negativity in evaluable patients
Idecabtagene vicleucel (ide-cel)	CAR T-cell therapy	KarMMa (Phase II, pivotal, NCT03361748)	2seventy bio and Celgene, a Bristol Myers Squibb Company	149	137	137	R/R MM	5-year analysis: • ORR 76.6%; CR 34.3% • Median DoR: 11.3 mo • Median PFS: 10.8 mo • Median OS: 28.2 mo
Lifileucel	Tumor-infiltrating lymphocyte	C-144–01 (Phase II, pivotal, NCT02360579)	Iovance Biotherapeutics, Inc.	189	153	153	Advanced melanoma	5-year analysis: • ORR 31.4% • Median DoR 36.5 mo • OS rate: 19.7% • Median OS: 13.9 mo

(*Continued*)

Table 2. (Continued).

Therapy	Therapy class	Initial study underlying the LTFU analysis	LTFU study sponsor	Sample size (N)			Indication	Key LTFU clinical outcomes
				Enrolled in initial study/studies	Treated population	Number of patients analyzed in LTFU analysis		
Lisocabtagene maraleucel (liso-cel)	CAR T-cell therapy	TRANSCEND NHL 001 (Phase I, pivotal, NCT02631044)	Not available	345	270	270	R/R LBCL	5-year analysis: • Median OS: 27.5 mo • OS rate: 38.1% ○ CR patients: OS rate of 55.9%
Tisagenlecleucel (tis-cel)	CAR T-cell therapy	ELIANA (Phase II, pivotal, NCT02435849)	Not available	97	79	79	R/R B-ALL	5-year analysis: • RFS rate: 49% • Median RFS: NR • OS rate: 55% • Median OS: NR
		JULIET (Phase II, pivotal, NCT02445248)	Novartis Pharmaceuticals	165	115	115	R/R LBCL	5-year analysis: • ORR: 53%; CR 39.1% • Median OS: 11.1 mo ○ Median OS of 76.5 mo among CR/PR patients • Median DoR: NR • 5-year OS rate: 32% • PFS rate: 28%

*Long-term efficacy analyses were reported in the enrolled/leukapheresed population (N = 159). Of these, 152 patients received axi-cel (124 with follicular lymphoma and 28 with marginal zone lymphoma).
†The 5-year analysis included only Phase 1 and Phase 2 patients who received the pivotal brexu-cel dose (1×10^6 CAR T cells/kg); therefore, the analyzed population represents a subset of all patients enrolled in ZUMA-3.
Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; CAR = chimeric antigen receptor; CAR T = chimeric antigen receptor T-cell; CR = complete response; DoR = duration of response; FL = follicular lymphoma; LBCL = large B-cell lymphoma; MCL = mantle cell lymphoma; mo = months; MRD = minimal residual disease; MZL = marginal zone lymphoma; N = number; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; R/R = relapsed/refractory; RFS = relapse-free survival; sCR = stringent complete response.

Table 3. Key clinical trials of gene therapies with published ≥5-year follow-up analyses.

Therapy	Vector type	Initial study underlying the LTFU analysis	LTFU Study sponsor	Sample size: Enrolled in initial study/ studies	Sample size: Treated population	Sample size: Number of patients analyzed in LTFU analysis	Indication	Key LTFU clinical outcomes
Atidarsagene autotemcel	LVV	Integrated studies (Phase I/II NCT01560182, Phase II/III NCT03392987, and expanded-access programs)*	Orchard Therapeutics	39	39	39 treated / 49 untreated control*	MLD	At a median of 6.8 years of f/up: • Survival without severe motor impairment: ○ 100% vs 0% at 6 years of age (late-infantile) ○ 80%–87.5% vs 11.2% at 10 years of age (juvenile)
Betibeglogene autotemcel (beti-cel)	LVV	Phase I/II: Northstar/HGB-204, (NCT01745120) and HGB-205 (NCT02151526); Phase III (pivotal): Northstar-2/HGB-207 (NCT02906202) and Northstar-3/HGB-212 (NCT03207009); LTF-303 (NCT02633943) †	Not available	63	63	63†	TDT	≥5-year analysis with up to 10 years of f/up: • TI maintained in 90% of Phase III patients • TI maintained in 64% of Phase I/II patients • ≥5-year f/up in 81% • Chelation discontinued in 76% of Phase III patients
Delandistrogene moxeparvovec-rokl	AAV	Study 101 (Phase I/II, NCT03375164)	Sarepta Therapeutics	4	4	4	DMD	5-year analysis: • NSAA increased from 20.5 at baseline to 27.5 • TTR, 10MW/R, and ambulatory status maintained
Eladocagene exuparvovec-tneq	AAV	Phase I/II (NCT01395641), Phase IIb (NCT02926066), and compassionate use trials	PTC Therapeutics	26	26	26 ‡	AADC	5-year analysis: • PDMS-2 score improved from 10.4 to 116.1 • AIMS score improved from 1.8 to 24.5 • Improved cognition/language and decreased dyskinesia over time
Elivaldogene autotemcel (eli-cel)	LVV	STARBEAM ALD-102 (Phase II/III, pivotal, NCT01896102); LTF-304 (NCT02698579)	bluebird bio	32	32	32	CALD	≥5-year analysis: • 81% of patients free of major functional disabilities • Neurologic stability achieved in 94% of patients (median of 6 years of f/up) • 1 case of MDS (vector-related)
Etranacogene dezaparvovec-drlb	AAV	HOPE-B (Phase III, pivotal, NCT03569891)	uniQure and CSL Behring	67	54	54§	Hemophilia B	5-year analysis: • FIX level: 36.1 IU/dL • ABR decreased by 63% • Joint bleeds decreased by 85% • 94% of patients off prophylaxis • No treated bleeds in 82% of patients
		Phase IIb (NCT03489291)	CSL Behring	3	3	3	Hemophilia B	5-year analysis: • Normal or near-normal FIX activity (45.7 IU/dL) • Remained free of routine prophylaxis • No late-emergent safety events

(*Continued*)

Table 3. (Continued).

Therapy	Vector type	Initial study underlying the LTFU analysis	LTFU Study sponsor	Sample size: Enrolled in initial study/ studies	Sample size: Treated population	Sample size: Number of patients analyzed in LTFU analysis	Indication	Key LTFU clinical outcomes
Etuvetidigene autotemcel (etu-cel)	LVV	Integrated studies (Phase I/II NCT01515462, Phase III NCT03837483, and extended-access programs)	Not available	27	27	27	WAS	At a median of 5.7 years of f/up: • OS: 96% • Severe infections reduced from 2.00 to 0.05 events/PYO > 5 years post-treatment
Nadofaragene firadenovec-vncg	AAV	CS-003 (Phase III, pivotal, NCT02773849)	Ferring Pharmaceuticals Ltd.	157	157	157[¶]	NMIBC (CIS + Ta/T1)	5-year analysis: • OS in 80% of patients • Cystectomy-free survival in 49% of patients • Progression to muscle-invasive disease: 3.3%
Onasemnogene abeparvovec-xioi	AAV	START (Phase I, NCT02122952) + LT-001 (NCT03421977)	Novartis Gene Therapies, Inc.	15	15	13[‖]	SMA	5-year analysis: • 100% survival • 100% ventilator-free • 100% milestones maintained or gained
Prademagene zamikeracel	Retroviral	Phase I/II study (NCT01263379); VIITAL (Phase III, pivotal, NCT04227106)	Abeona Therapeutics	7	7	7	RDEB	5-year analysis: • ≥50% wound healing in 70% of patients • Pain/pruritus decreased over time
Revakinagene taroretcel-lwey (NT-501)	Genetically modified allogeneic retinal pigment epithelial cells	Phase I extension study (long-term extension of NCT01327911)	Neurotech Pharmaceuticals and the Lowy Medical Research Institute	7	7	6	MacTel type 2	9-year follow-up analysis • All implants retained through final visit • No serious ocular treatment-related safety signals; no treated eyes experienced ≥15-letter vision loss
Talimogene laherparepvec (T-VEC)	Oncolytic HSV-1	Phase II neoadiuvant study (NCT02211131)	Amgen	150	150	150 (76 T-VEC + surgery; 74 surgery alone)[#]	Resectable stage IIIB-IVM1a melanoma	5-year analysis: • Recurrence-free survival: 22.3% vs 15.2% • OS: 77.3% vs 62.7%
		Randomized phase II study (NCT01740297)	Amgen	198	190	198 (98 T-VEC + ipilimumab; 100 ipilimumab) **	Unresectable stage IIIB-IV melanoma	5-year analysis: • ORR 35.7% vs 16.0% • Median DoR 69.2 mo • OS 54.7% vs 48.4%
Valoctocogene roxaparvovec-rvox	AAV	GENEr8-1 (Phase III, pivotal, NCT03370913)	BioMarin Pharmaceutical Inc.	144	134	134	Hemophilia A	5-year analysis: • 81.3% of patients off prophylaxis • ABR decreased by 87.5% • FVIII use decreased by 92%

(*Continued*)

Table 3. (Continued).

Therapy	Vector type	Initial study underlying the LTFU analysis	LTFU Study sponsor	Sample size: Enrolled in initial study/ studies	Sample size: Treated population	Sample size: Number of patients analyzed in LTFU analysis	Indication	Key LTFU clinical outcomes
Voretigene neparvovec-rzyl	AAV	Phase III, pivotal (NCT00999609) and LTFU studies	Not available	31	29	29	RPE 65 retinal dystrophy	• ≥5-year analysis: • Mean bilateral MLMT change score = 1.7.±.1.1, OI group at Year 4 • Mean bilateral MLMT change score = 2.4.±.1.5, DI group at Year 3 • Improvements were sustained through Years 8 (DI) and 9 (OI) post-administration

*The integrated analysis included 39 Atidarsagene autotemcel–treated patients and 49 untreated patients from a natural history cohort. Efficacy analyses were conducted in 37 treated patients following independent review committee review; all 39 treated patients were included in the safety analysis.

†Sixty-three participants received beti-cel in HGB-204, HGB-205, HGB-207, or HGB-212 and enrolled in LTF-303. Long-term efficacy and safety analyses included all 63 participants; 51 (81.0%) had at least 5 years of follow-up.

‡The pooled analysis included 26 treated patients. Fifteen patients had > 5 years since treatment at data cutoff; however, formal 5-year motor assessments (PDMS-2 and AIMS) were available for 11 patients.

§Fifty-three patients received the full dose, and 1 patient received approximately 10% of the dose. Fifty participants (93%) completed 5 years of follow-up. Four participants did not complete the study because of death (n = 2), liver transplantation ($n = 1$), or withdrawal of consent ($n = 1$).

¶The safety population included all 157 treated patients. The efficacy analysis population included 151 patients who met protocol-defined BCG-unresponsive NMIBC criteria; 6 patients were excluded after enrollment.

‖The long-term follow-up cohort included 13 of 15 patients treated in START. Efficacy conclusions regarding durability of the approved dose were based primarily on the therapeutic-dose cohort ($n = 10$).

#The 5-year analyses were conducted in the intention-to-treat population comprising all 150 randomized patients (T-VEC plus surgery, $n = 76$; surgery alone, $n = 74$).

** The safety analysis set included 95 patients in each arm (190 total) who received ≥1 dose of study treatment. The publication does not explain the discrepancy between the 198-patient ITT population and the 190-patient safety population; therefore, the reported safety population is used as the treated population. Efficacy and 5-year outcomes were analyzed in the ITT population comprising all 198 randomized patients.

Abbreviations: AADC = aromatic L-amino acid decarboxylase deficiency; ABR = annualized bleed rate; AAV = adeno-associated virus; AIMS = Alberta Infant Motor Scale; ALD = adrenoleukodystrophy; CALD = cerebral adrenoleukodystrophy; CIS = carcinoma in situ; DMD = Duchenne muscular dystrophy; DI = delayed intervention; f/up = follow-up; FIX = coagulation factor IX; FVIII = coagulation factor VIII; HSV = herpes simplex virus; IU/dL = international units per deciliter; LTFU = long-term follow-up; LVV = lentiviral vector; MLD = metachromatic leukodystrophy; MLMT = multi-luminance mobility test; MDS = myelodysplastic syndrome; NMIBC = non-muscle invasive bladder cancer; NSAA = North Star Ambulatory Assessment; OI = original intervention; OS = overall survival; PDMS-2 = Peabody Developmental Motor Scales, Second Edition; PYO = person-year of observation; RDEB = recessive dystrophic epidermolysis bullosa; RPE65 = retinal pigment epithelium-specific protein 65 kDa; SMA = spinal muscular atrophy; TDT = transfusion-dependent beta-thalassemia; TI = transfusion independence; TTR = time to rise; 10MW/R = 10-meter walk/run.

32.3–81.4 months) follow-up, median DoR was 60.4 months; median PFS was 62.2 months (34.9 to not evaluable), with 50.4% (range, 41.3%-58.7%) of patients achieving 60 months of follow-up [15]. The 60-month OS estimate was 69% and median OS was not reached [15]. Safety data showed no new safety signals or unexpected toxicities with axi-cel. However, a small number (4%) of second primary malignancies were observed.

3.1.2. Brexucabtagene autoleucel

Brexucabtagene autoleucel (brexu-cel) was the first CAR T-cell therapy approved in adult patients with R/R mantel cell lymphoma (MCL) [16]. The pivotal ZUMA-2 trial (NCT02601313) evaluated a heavily pretreated population with a median of 3 prior lines of therapy [17]. The 5-year analysis of ZUMA-2, including 82 patients treated with brexu-cel, confirmed the durability of response and showed a median OS of 46.5 months (range, 24.9–60.2 months) in cohort 1 (median follow-up 67.8 months; $n = 68$) and not reached (9.4 months to not evaluable) in cohort 2 (median follow-up 72.3 months; $n = 14$). The 60-month OS rate was 38.5% (range, 26.7%-50.1%) for cohort 1 and 53.6% (range, 23.8%-76.2%) for cohort 2 [17]. Long-term safety monitoring revealed no new safety signals, although late-onset cytopenias and hypogammaglobulinemia were reported.

Additionally, brexu-cel received FDA approval for patients with B-cell acute lymphoblastic leukemia (B-ALL) based on data from the ZUMA-3 trial (NCT02614066) that demonstrated a 71% (95% CI, 57%-82%) rate for complete remission or complete remission with incomplete hematologic recovery [18–20]. Five-year survival data from the ZUMA-3 trial in 78 infused patients with a median 65.7 months (range, 56.7–94.3 months) of follow-up demonstrated a median OS of 25.6 months (95% CI, 16.2–60.4 months) and a 5-year OS rate of 40% (95% CI, 28.4%-51.3%) [21]. Among responders, the median OS was 60.4 months (95% CI, 23.2 months to not estimable), which was similar to the 4-year analysis [22]. Safety data showed 1 new AE and death following the 4-year analysis, both in the same patient and unrelated to brexu-cel. No secondary T-cell malignancies occurred.

3.1.3. Ciltacabtagene autoleucel

Ciltacabtagene autoleucel (cilta-cel) was the second B-cell maturation antigen (BCMA)-directed CAR T-cell therapy approved for R/R multiple myeloma (MM); it is differentiated by its 2 BCMA-targeting single-domain antibodies [23,24]. Its approval was supported with outcomes of the CARTITUDE-1 trial (NCT03548207) that evaluated cilta-cel in patients with heavily pre-treated R/R MM [23,25]. Among the 97 patients in LTFU treated with cilta-cel in CARTITUDE-1 (median study follow-up of 61.3 months), the median OS was 60.7 months (95% CI, 41.9 months to not estimable) [26]. One-third (32/97, 33%) of patients remained progression-free for 5 or more years after cilta-cel infusion and required no further antimyeloma therapy. Of these patients, 97% achieved stringent CR (sCR). Among patients with serial minimal residual disease testing ($n = 12$), all were measurable residual disease-negative at Year 5. Secondary primary malignancy occurred in 2 patients. No new cases of parkinsonism or cranial palsies were observed. As of December 2025, over 9,000 patients have been treated with cilta-cel globally, reflecting substantial post-approval clinical experience with this therapy [27].

3.1.4. Idecabtagene vicleucel

Idecabtagene vicleucel (ide-cel) was the first BCMA-directed CAR T-cell therapy approved for adults with R/R MM [28]. Ide-cel received FDA approval based on the pivotal Phase II KarMMa trial (NCT03361748), a single-arm design in a heavily pretreated population (median of 6 prior lines of therapy) who demonstrated an ORR of 73% [29]. In the 5-year follow-up analysis of the KarMMa trial, among 137 patients with a median follow-up of 63.6 months, ORR was 76.6% (95% CI, 69.6%-83.7%), including a CR rate of 34.3% (95% CI, 26.4%-42.3%), and the median DoR was 11.3 months (range, 10.0–12.6 months) [30]. Median PFS was 10.8 months (95% CI, 6.1–11.9 months) and median OS was 28.2 months (range, 20.2–38.1 months). No new or unexpected AEs were reported. The secondary primary malignancy incidence rate was 3.7% (95% CI, 2.0%-6.9%) per 100 patient-years.

3.1.5. Lisocabtagene maraleucel

Lisocabtagene maraleucel (liso-cel) is a cluster of differentiation (CD)19-directed CAR T-cell therapy differentiated by its defined composition and separate manufacturing of CD4+ and CD8+ CAR-positive T-cells [31]. It received FDA approval for the treatment of R/R LBCL based on data from the Transcend NHL 001 trial (TRANSCEND; NCT02631044) [32]. Patients treated with liso-cel demonstrated high overall and CR rates and a manageable safety profile [33].

Almost half of the liso-cel arm (124/270, 46%) completed the study at the final TRANSCEND data cutoff [34]. In the 5-year follow-up analysis, the median OS was 27.5 months (95% CI, 16.2–47.3 months); the estimated 5-year OS rate was 38.1% (95% CI, 31.6%-44.7%) [34]. Among patients who achieved a CR, the 5-year OS rate was 55.9% (95% CI, 45.8%-64.9%). No new or unexpected AEs were reported. Secondary primary malignancies occurred in 19 patients, including nonmelanoma skin cancer in 7 patients and myelodysplastic syndrome in 9 patients.

3.1.6. Tisagenlecleucel

Tisagenlecleucel (tis-cel) was the first CD19 CAR T-cell therapy approved by the FDA [35]. The pivotal ELIANA trial (NCT02435849) tracked a heavily pretreated R/R B-ALL patient population ($N = 79$), with a median of 3 prior lines of therapy. Early analysis showed an overall remission rate (CR or CR with incomplete hematologic recovery within 3 months following infusion) of 82% (95% CI, 72%-90%) [36]. With 64 patients having 5 years or more of follow-up and a median follow-up time of 5.5 years, the LTFU data from ELIANA support the durability of response. Among patients who achieved remission, the 5-year relapse-free survival rate was 49% (95% CI, 34%-62%) [36]. The 5-year OS rate was 55% (95% CI, 43%-66%) with median OS not yet reached. There were no new or unexpected AEs reported. A majority of patients (82%) received intravenous (IV) immunoglobulin at any time post-infusion.

In the pivotal JULIET trial (NCT02445248), 165 patients with R/R LBCL (excluding primary mediastinal LBCL) who progressed through 2 or more lines of therapy were enrolled to receive tis-cel [37]. After a median follow-up of 74.3 months among 115 treated patients, the ORR was 53%, with 39.1% achieving a CR, and median DoR was not yet reached [38]. The median OS was 11.1 months, and 76.5 months among patients with a CR or partial response ($n = 61$). The estimated PFS and OS rates at 60 months were 28% and 32% respectively. No new safety signals or secondary T-cell malignancies were observed.

3.2. LTFU in TILs

3.2.1. Lifileucel

Lifileucel was the first TIL therapy FDA-approved for R/R unresectable or metastatic melanoma [39]. As of May 2025, over 275 patients in the US have been treated with lifileucel [40]. Its approval was based on results from the pivotal C-144–01 trial (NCT02360579), a Phase II study that evaluated lifileucel in 153 patients with advanced melanoma who had previously received anti-programmed cell death protein 1 (PD-1)/anti-programmed death-ligand 1 (PD-L1) and B-Raf proto-oncogene, serine/threonine kinase (BRAF)/mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor therapies, if *BRAF* V600 mutation positive. The ORR was 31.4% (95% CI, 24.1%-39.4%) [41,42]. The 5-year analysis of the C-144–01 trial showed long-term treatment benefits of lifileucel. At a median follow-up of 57.8 months, the ORR was 31.4% (48/153) and 79.3% (111/140) of patients experienced a reduction in tumor burden [43]. The median DoR was 36.5 months (95% CI, 8.3 months to not reached). The 5-year OS rate was 19.7% and median OS was 13.9 months. No new or unexpected AEs were reported. No secondary malignancies attributable to TIL therapy were reported, up to 5 years past administration.

3.3. LTFU in gene therapies: AAV-based

3.3.1. Delandistrogene moxeparvovec-rokl

Delandistrogene moxeparvovec-rokl was the first gene therapy that received FDA approval for the treatment of Duchenne muscular dystrophy (DMD), and over 1,100 patients have been treated with this therapy globally as of November 2025 [44,45]. Five-year outcomes from the Phase I/IIa Study 101 (NCT03375164), an early-phase (Phase I/IIa) trial primarily designed to evaluate safety, included 4 ambulatory patients (aged ≥4 to <8 years at baseline) who received a single IV infusion. Over 5 years, all 4 patients demonstrated sustained increases in NSAA scores, with mean NSAA total score rising from 20.5 at baseline to 27.5 at Year 4, and a statistically significant and clinically meaningful difference versus an external control cohort at Year 5 [46,47]. Time to rise from the floor and 10-meter walk/run times were maintained, with treated patients remaining ambulant throughout the study, while several patients in the external control cohort lost ambulation [46]. No new safety signals were reported beyond the initial 70 days post-infusion; all treatment-related AEs within this study cohort were mild or moderate and resolved. Specifically among these 4 participants, no serious AEs, study discontinuations, or deaths were observed over the 5-year period [47]. However, in November 2025, the FDA added a boxed warning to the product label and revised the approved indication to limit use to ambulatory patients following reports of acute serious liver injury and fatal acute liver failure in non-ambulatory patients [48].

3.3.2. Eladocagene exuparvovec-tneq

Eladocagene exuparvovec-tneq is the first FDA-approved gene therapy administered directly to the brain and the first for treating aromatic L-amino acid decarboxylase (AADC) deficiency [49]. LTFU from 3 open-label studies (compassionate use, Phase I/II [NCT01395641], and Phase IIb [NCT02926066]) including 26 patients (mean age at treatment: 4.1 years) showed sustained increases in dopamine production, as evidenced by elevated 6-[^{18}F]fluoro-L-3,4 dihydroxyphenylalanine (^{18}F-DOPA) uptake on positron emission tomography (PET) scans and increased cerebrospinal fluid (CSF) homovanillic acid (HVA) levels [50]. Importantly, the studies followed a consistent treatment protocol, except for five patients in the Phase IIb trial who received a 33% higher dose. Among the study cohorts, 15 patients had follow-up extending beyond 5 years; the mean follow-up duration across all participants was 5.4 years. Key motor milestones were durable: the mean Peabody Developmental Motor Scales-Second Edition (PDMS-2) score improved from 10.4 ± 5.4 at baseline to 116.1 ± 59.8 at 5 years post-infusion ($n = 11$), and Alberta Infant Motor Scale (AIMS) scores increased from 1.8 ± 1.8 at baseline to 24.5 ± 15.0 over the same time period [50]. Three patients achieved walking without assistance. Consistent improvement was also observed in cognition and language. Additionally, patient symptoms including mood, sweating, temperature instability, and oculogyric crises improved over time, as did patient growth and caregiver quality of life. Long-term safety was favorable, with the most common late events being dyskinesia, which generally decreased in frequency over time as the brain adjusted to new dopamine levels.

3.3.3. Etranacogene dezaparvovec-drlb

Etranacogene dezaparvovec-drlb was the first AAV-based gene therapy approved for the treatment of moderate to severe hemophilia B, with more than 75 patients treated globally as of December 2025 [51,52]. Approval was based on outcomes from the HOPE-B trial (NCT03569891), which analyzed 54 adult men with severe or moderately severe hemophilia B (factor IX [FIX] activity ≤2 IU/dL). After a single infusion, endogenous FIX expression was sustained over 5 years in 50 patients, with mean FIX activity of 36.1 ± 15.7 IU/dL at Year 5 [53]. The mean ABR decreased by 63%, from 4.16 during the lead-in period to 1.52 during months 7 to 60 post treatment. Joint bleeding events were reduced by 85%, and 94% of participants discontinued continuous FIX prophylaxis. Exogenous FIX consumption dropped by 96%, and 82% of participants had no treated bleeding events in Year 5. The safety profile was favorable, with most treatment-related AEs occurring within the first 6 months. No evidence of late hepatic toxicity, thrombotic events, or FIX inhibitor development was observed.

Three neoplasms (hepatocellular carcinoma, schwannoma, and myelodysplastic syndrome) were reported, but none were attributed to gene therapy after molecular evaluation.

These findings were consistent with the 5-year completion of an earlier phase 2b study (NCT03489291), in which participants ($N = 3$) maintained normal or near-normal FIX activity (45.7 IU/dL at Year 5), remained free of routine prophylaxis, and experienced no late-emergent safety events despite the presence of baseline AAV5 neutralizing antibodies [54].

3.3.4. Nadofaragene firadenovec-vncg

Nadofaragene firadenovec-vncg was the first AAV-based gene therapy approved for bladder cancer [55]. It received its approval for adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) based on data from the pivotal Study rAd-IFN-CS-003 (Study CS-003) trial (NCT02773849), which demonstrated a 53.4% CR rate within 3 months of the first dose in the CIS cohort [56]. At the 60-month analysis of the rAD-IFN-CS-OO3 trial, efficacy analysis included 151 patients (103 CIS, 48 Ta/T1), with a median follow-up of 50.8 months [57]. The Kaplan-Meier estimated OS rate was 80% (95% CI, 71.0%-86.0%), and overall cystectomy-free survival was 49% (95% CI, 40.0%-57.1%) with 43% (95% CI, 32.2%-53.7%) in the CIS cohort and 59% (95% CI, 43.1%-71.4%) in the Ta/T1 cohort. High-grade recurrence-free survival at 57 months was 5.8% (95% CI, 2.2%-12.2%) in the CIS cohort and 15% (95% CI, 6.1%-27.8%) in the Ta/T1 cohort. Bladder preservation was achieved in nearly half of participants at 5 years, and clinical progression to muscle-invasive disease was rare (3.3%). No serious AEs or increased risk of systemic toxicity attributable to the gene therapy were reported.

3.3.5. Onasemnogene abeparvovec-xioi

Onasemnogene abeparvovec-xioi was the first gene therapy approved for spinal muscular atrophy (SMA), with more than 5,000 patients treated globally as of July 2025 [58,59]. Five-year outcomes are reported from the LT-001 (NCT03421977) LTFU study, which enrolled participants from the Phase I START trial (NCT02122952) [60]. At the 5-year interim analysis, 13 START participants (low dose $n = 3$; therapeutic dose $n = 10$) were followed for a median 5.2 years (range, 4.6–6.2 years) after dosing; all 10 therapeutic-dose (1.1×10^{14} vg/kg of body weight) patients were alive and free of permanent ventilation, and all maintained previously achieved motor milestones, with 2 achieving new milestones of standing with assistance during follow-up. Long-term safety remained favorable throughout this period, with serious AEs reported but assessed as unrelated to treatment. Subsequent updates presented from the same START to LT-001 cohort extended durability into later childhood (mean follow-up ~8.3 years in the therapeutic-dose cohort) and demonstrated ongoing survival, ventilator-free status in the therapeutic-dose group, sustained milestone performance (including standing with assistance and walking in subsets), and no new late-emerging safety signals, including hepatotoxicity, thrombotic microangiopathy, dorsal root ganglia toxicity, malignancy, autoimmune, or hematologic disorders [61].

3.3.6. Valoctocogene roxaparvovec-rvox

Valoctocogene roxaparvovec-rvox was the first gene therapy approved for severe hemophilia A [62]. A Phase I-II study (BMN 270–201, NCT02576795) demonstrated that valoctocogene roxaparvovec-rvox enabled durable endogenous factor VIII (FVIII) production and led to sustained reductions in both bleeding episodes and FVIII usage for up to 5 years [63–65]. In the pivotal Phase III GENEr8-1 trial (NCT03370913), 134 adult men with severe hemophilia A received a single infusion of valoctocogene roxaparvovec-rvox at 6×10^{13} vector genomes (vg) per kilogram (kg) of body weight [66]. Prior LTFU data demonstrated that treatment with 6×10^{13} vg/kg valoctocogene roxaparvovec-rvox led to greater protection from bleeding compared with standard FVIII prophylaxis over 4 years [67–69]. Five-year follow-up demonstrated sustained hemostatic efficacy: 81.3% of participants remained off FVIII prophylaxis at year 5, and participants experienced a 92% reduction in FVIII infusion rates and an 87.5% reduction in ABR relative to baseline [70]. Mean FVIII activity levels declined gradually over time but were maintained within the mild hemophilia range at Year 5 (mean 13.7 IU/dL by chromogenic assay), providing ongoing protection from spontaneous bleeding events. Clinically meaningful improvements in health-related quality of life were also sustained through 5 years. Safety monitoring through 60 months revealed no treatment-related malignancies, no FVIII inhibitor development, and no thromboembolic events. Of note, in February 2026, the product's manufacturer voluntarily withdrew valoctocogene roxaparvovec-rvox from the market, primarily due to limited commercial success following post approval experience [71].

3.3.7. Voretigene neparvovec-rzyl

Voretigene neparvovec-rzyl, the first gene therapy approved for an inherited genetic disease (biallelic retinal pigment epithelium-specific protein 65 kDa [RPE65] mutation-associated retinal dystrophy), was approved by the FDA based on data from the Phase III AAV2-hRPE65v2 trial (NCT00999609) that demonstrated a mean bilateral multi-luminance mobility test (MLMT) change score of 1.8 ± 1.1 light levels in the original intervention (OI) group [72]. Long-term data demonstrate sustained efficacy as the mean bilateral MLMT change score was 1.7 ± 1.1 at Year 4 in the OI group and 2.4 ± 1.5 at Year 3 in the delayed intervention (DI) group. Patients maintained significant improvements in the MLMT and full-field stimulus threshold (FST), with approximately 70% of participants maintaining their initial functional gains [72,73]. Extended follow-up of the combined OI and DI cohorts showed that among participants with observations available at Year 5, bilateral MLMT performance remained improved from baseline with a mean score change of nearly 2 ($n = 25$) and a mean FST improvement exceeding 2 $\log_{10}$ units from baseline ($n = 24$) (measured in $\log_{10}$[candela·second per square meter, cd·s/m^2]) [74]. Best-corrected visual acuity (BCVA) remained generally stable at Year 5 ($n = 25$). The number of evaluable participants

differed across endpoints and variability increased after Year 5, in part because of COVID-19 and missed assessments. Nevertheless, among participants with available assessments through Years 8 and 9, improvements in MLMT, FST, and visual field remained above baseline, while BCVA remained generally stable [74]. No systemic toxicities or secondary malignancies have been linked to the AAV2 vector, and the long-term safety profile has remained consistent with the known risks of vitrectomy and subretinal injection.

3.4. LTFU in gene therapies: LVV-based

3.4.1. Atidarsagene autotemcel

Atidarsagene autotemcel (arsa-cel) is the first gene therapy approved for metachromatic leukodystrophy (MLD) [75]. In an integrated analysis of 2 prospective open-label studies (NCT01560182, NCT03392987) and expanded-access programs, which together formed the basis for regulatory approval by the FDA, 39 treated patients were evaluated against a natural history cohort of 49 untreated patients, with a median follow-up of 6.76 years (range, 0.64–12.19 years) [76]. Arsa-cel significantly reduced the risk of severe motor impairment or death versus no treatment across key early-onset subgroups, including presymptomatic late-infantile, presymptomatic early-juvenile, and early-symptomatic early-juvenile MLD. The estimated proportion surviving without severe motor impairment at 6 years of age was 0% in untreated late-infantile MLD versus 100% (37/37) in treated presymptomatic late-infantile MLD. Among early-juvenile MLD patients, the estimated proportion surviving without severe motor impairment at 10 years of age was 11.2% in untreated patients versus 87.5% and 80.0% in treated presymptomatic and early-symptomatic early-juvenile patients, respectively. Long-term safety was favorable, with no evidence of insertional oncogenesis (high clonal diversity, no abnormal clonal proliferation; 251 cumulative patient-years of follow-up) and no replication-competent lentivirus detected. The most common Grade ≥3 AE was febrile neutropenia, anti-ARSA antibodies occurred transiently in 15% (6/39), and 3 deaths were reported, all assessed as unrelated to arsa-cel.

3.4.2. Betibeglogene autotemcel

Betibeglogene autotemcel (beti-cel) was the first gene therapy approved for transfusion-dependent beta-thalassemia (TDT) [77]. Its approval was based on data from 2 pivotal Phase III studies, Northstar-2 (HGB-207 [NCT02906202]) and Northstar-3 (HGB-212 [NCT03207009]), which demonstrated TI (defined as maintaining a weighted average hemoglobin [Hb] ≥9 g/dL without transfusions for at least 12 months) in 89% of patients with TDT [78–80]. In LTFU across Phase I/II (HGB-204 [NCT01745120], HGB-205 [NCT02151526]) and Phase III (HGB-207, HGB-212) studies with subsequent enrollment into the LTF-303 follow-up study (NCT02633943), outcomes have been reported for 63 treated participants with a median follow-up of 60.1 months (range, 23.8–109.5 months) [81,82]. TI was achieved and maintained through last follow-up in 37/41 (90%) of Phase III participants and in 14/22 (64%) of Phase I/II TI responders, respectively.

Updated follow-up from the 63 participants enrolled into LTF-303 indicated that 51/63 (81%) had ≥5 years of follow-up (with a median follow-up of 71.2 months [range, 34.5–121.4 months]), with stable peripheral blood vector copy number and HbAT87Q production after initial post-infusion, demonstrating sustained pharmacodynamic effect up to 10 years in a small subset [83]. Across trials, Hb levels during TI were durable, with comparable performance across age groups and β^0/β^0 versus non-β^0/β^0 genotypes in the updated report. Consistent with reduced transfusion exposure, iron burden measures improved over time among TI responders, and most of the Phase III TI responders were able to discontinue iron chelation therapy (28/37 [75.7%]). Reported long-term safety was consistent with expectations for autologous transplantation and busulfan conditioning. No beti-cel–related serious AEs were reported beyond 2 years post-infusion and no cases of malignancy, insertional oncogenesis, or vector-derived replication-competent lentivirus were reported.

3.4.3. Elivaldogene autotemcel

Elivaldogene autotemcel (eli-cel) was the first gene therapy approved for cerebral adrenoleukodystrophy (CALD) [84]. In the Phase II/III study (STARBEAM ALD-102, NCT01896102), 32 patients received eli-cel and 91% (29/32) completed the 24-month study and entered LTFU through the LTF-304 (NCT02698579) study [85]. At Month 24, 91% (29/32) of patients were alive without any major functional disabilities (primary endpoint), and OS was 94% (30/32). At the most recent assessment (median follow-up of 6 years), neurologic function remained stable versus baseline in 94% (30/32) of patients. Through 5 years of LTFU, 26/32 (81%) were free of major functional disabilities with a median follow-up 60.6 months. Kaplan–Meier estimates at Month 48 showed 94% OS. Key safety considerations included rare eli-cel–attributed AEs (12% overall), and 1 case of myelodysplastic syndrome (MDS), considered to be related to vector insertion. Due to the increased risk of hematologic malignancy, the FDA revised the label indication in August of 2025 to limit use to patients without an available human leukocyte antigen (HLA)-matched allogeneic hematopoietic stem cell (HSC) donor [86].

3.4.4. Etuvetidigene autotemcel

Etuvetidigene autotemcel (etu-cel) is an autologous lentiviral hematopoietic stem and progenitor cell (HSPC) gene therapy approved for the treatment of Wiskott-Aldrich syndrome (WAS) in patients with a mutated WAS gene and lacking a suitable matched donor for allogeneic hematopoietic stem cell transplantation [87]. In an integrated analysis of 27 patients treated across Phase I/II (NCT01515462), Phase III (NCT03837483), and expanded-access studies, overall survival was 96% after a median follow-up of 5.7 years (range, 2.3–13.3 years) [88]. Durable clinical benefit was observed, with the rate of severe infections decreasing from 2.00 events per person-year before gene therapy to 0.05 events per person-year beyond 5 years of follow-up, while moderate or severe bleeding events decreased from 2.00 to 0.02 events per person-year during the same period. Sustained immunoglobulin replacement therapy was discontinued in all treated patients, antimicrobial prophylaxis was discontinued in 92.6% of patients, and median platelet count at Year 5 was 68.3×10^9/L. Long-term safety was favorable, with no treatment-related

adverse events, no engraftment failures, and no evidence of abnormal clonal proliferation, replication-competent lentivirus, or treatment-related malignancy reported through follow-up extending up to 13 years.

3.5. Long-term follow-up in gene therapies: other types of gene therapies

3.5.1. Prademagene zamikeracel

Prademagene zamikeracel is the first cell-based gene therapy for recessive dystrophic epidermolysis bullosa (RDEB) [89]. It utilizes autologous keratinocytes transduced with a retroviral vector to produce type VII collagen. Data from the Phase I/II trial (NCT01263379) show a median follow-up of 5.9 years (range, 4–8 years) and long-term improvements in wound healing, pain, and itch in 7 patients with severe RDEB who received prademagene zamikeracel [90]. Across treated wound sites at year 5, 70% (21/30) achieved ≥50% wound healing compared with baseline and no sites with ≥50% healing were associated with pain or pruritus, compared with 67% (6/9) of sites with <50% healing ($P < .001$) [90]. No cases of squamous cell carcinoma (SCC) were reported in prademagene zamikeracel-treated wound sites, whereas SCC occurred in 4 non-treated sites within the same patient population, suggesting a potential protective effect against the primary cause of death in RDEB. No evidence of insertional oncogenesis or clonal expansion attributable to the retroviral vector was observed over LTFU.

3.5.2. Revakinagene taroretcel-lwey

Revakinagene taroretcel-lwey (NT-501) is an encapsulated cell-based gene therapy approved for macular telangiectasia type 2 (MacTel) [91]. In a Phase I extension study primarily designed to evaluate safety, 6 patients were followed for 108 months after implantation. All implants were retained through the final study visit. Ocular adverse events were limited to mild-to-moderate events, and no treatment-related safety signals emerged over 9 years of follow-up. No treated eyes experienced ≥15-letter vision loss, and structural outcomes favored treated eyes, with lower rates of ellipsoid zone progression compared with untreated fellow eyes, supporting durable safety and long-term preservation of retinal structure.

3.5.3. Talimogene laherparepvec

Talimogene laherparepvec (T-VEC), the first FDA-approved oncolytic virus therapy, is a genetically modified *Herpes simplex* type 1 virus engineered to secrete granulocyte macrophage colony-stimulating factor (GM-CSF) [92]. It is indicated for the treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurring after initial surgery. The OPTiM trial (NCT00769704) evaluated safety and efficacy of neoadjuvant T-VEC in patients with unresectable Stage IIIb, IIIc, or IV melanoma and demonstrated a durable response rate (16.3% vs 2.1%; $P < .001$) [93]. While the final OPTiM analysis did not extend to five years of follow-up, subsequent long-term follow-up studies have demonstrated durable benefit across different melanoma populations and treatment settings [94]. In a Phase II study (NCT02211131) evaluating 150 patients with resectable Stage IIIB to IVM1a melanoma, 76 patients receiving T-VEC prior to surgery showed improved outcomes compared to 74 patients who received surgery alone after a median follow-up of 63.3 months. The 5-year Kaplan-Meier estimates for recurrence-free survival rates were 22.3% vs 15.2% (hazard ratio [HR], 0.76; 80% CI, 0.60–0.97) and OS rates were 77.3% vs 62.7% (HR, 0.54; 80% CI, 0.36–0.81), respectively [95]. In a separate randomized Phase II study (NCT01740297) of 198 patients with unresectable stage IIIB-IV melanoma, T-VEC plus ipilimumab demonstrated higher objective response rates (35.7% vs 16.0%; OR 2.9, 95% CI, 1.5–5.7) and durable response rates (33.7% vs 13.0%; OR 3.4, 95% CI, 1.7–7.0) compared with ipilimumab alone [96]. Among responders, median duration of response was 69.2 months (95% CI, 38.5 months to not estimable), and estimated 5-year OS was 54.7% (95% CI, 43.9%-64.2%) vs 48.4% (95% CI, 37.9%-58.1%) with ipilimumab alone.

4. Limitations

Several limitations should be considered when interpreting these findings. Although a structured literature review was conducted, the objective was to characterize the breadth of publicly available durability evidence rather than provide an exhaustive inventory of all ≥5-year follow-up studies. As a result, some relevant reports may not have been captured. Additionally, conference abstracts and presentations were included to broaden evidence-capture and reduce publication bias; however, these sources often provide less methodological detail than peer-reviewed publications and may be subject to future updates. Accordingly, findings were categorized by evidence source, and peer-reviewed evidence was assessed separately (Table 1). In addition, this review was limited to FDA-approved CGTs, for which long-term outcomes are more likely to be collected and reported than for products discontinued during clinical development.

The included studies were also highly heterogeneous, including multiple therapeutic platforms, diseases, patient populations, endpoints, study designs, and follow-up durations. Cohort sizes were often small, reflecting the rarity of several indications, which may limit the generalizability of findings. Importantly, durability is not uniform across therapies, indications, or patients, and the presence of ≥5-year follow-up data should not be interpreted as evidence of sustained benefit for all treated individuals. Finally, while 5-year follow-up represents an important benchmark, it does not fully characterize lifetime benefit. Continued long-term data collection remains necessary to assess effectiveness and safety over the course of a patient's lifespan.

5. Conclusion

The field of CGT has rapidly evolved from early proof-of-concept studies to a robust clinical reality, with an expanding portfolio of FDA-approved products now supported by 5-year and longer follow-up data. Collectively, the available evidence suggests that durable clinical benefit can be achieved across multiple therapeutic platforms and disease settings and offers a more comprehensive understanding of long-term safety outcomes. Although

many uncertainties remain, the accumulation of long-term evidence can help refine expectations regarding both the magnitude and extent of clinical benefit. As additional long-term data emerge, continued surveillance and real-world evidence generation will further inform the long-term benefit-risk profile of CGTs and their role in clinical practice.

6. Expert opinion

The growing body of 5-year follow-up evidence suggests that long-term CGT outcomes are becoming increasingly well characterized across the landscape of approved CGTs. Among 34 FDA-approved CGTs evaluated, 21 therapies were identified with publicly available efficacy and safety outcomes extending to at least 5 years after treatment. These analyses spanned diverse therapeutic modalities and disease settings, with several therapies now reporting follow-up approaching a decade. Importantly, the current body of ≥5-year evidence represents only a snapshot of an evolving landscape, as more recently approved CGTs are nearing this milestone and are expected to meaningfully expand the understanding of long-term CGT outcomes across more patient populations and disease states [97–99].

At the same time, important questions remain regarding ongoing durability and long-term safety of CGTs. Durable benefit is not universal across therapies or patient populations, and it remains unclear which patients will experience sustained long-term benefit and how consistently those outcomes will be maintained over time. In addition, although serious delayed adverse events appear uncommon, their potential consequences can be severe; these include secondary malignancies following CAR T-cell therapy, insertional oncogenesis and hematologic malignancies associated with integrating vectors, hepatotoxicity following AAV-based gene therapy, and potential delayed off-target effects with gene-editing platforms.

Nevertheless, accumulating LTFU data is increasingly demonstrating the potential for sustained clinical benefit with CGTs. Across diverse disease states, sustained benefit has been reported in the form of durable remission, prolonged survival, preservation of functional ability, reduced bleeding events, transfusion independence, or reduced reliance on chronic therapy. While continued long-term surveillance and RWE generation remain essential, particularly given the potential for late loss of efficacy and serious delayed adverse events, the growing availability of LTFU data is beginning to provide greater insight into the consistency and persistence of clinical benefit over time, which may help reduce durability-related uncertainty in payer coverage and decision-making.

6.1. Aligning long-term durability evidence with payer coverage and payment design

Many CGTs present a unique reimbursement challenge: treatment costs are incurred upfront, while clinical benefit and potential cost offsets may accrue over years. Because these therapies are typically administered once or over a short treatment course, confidence that clinical benefit will persist over time is critical. Historically, payers have consistently described uncertainty around long-term durability as a key challenge to CGT reimbursement, and sustained benefit through at least 5 years has been cited as an important evidentiary benchmark for supporting coverage of high-cost CGTs [4,100–102]. The growing availability of 5-year and LTFU data provides an opportunity to reevaluate these concerns across different therapies and patient populations. As long-term outcomes become better characterized, the relationship between high upfront cost and realized clinical benefit can be more fully evaluated, helping to inform the design of alternative reimbursement mechanisms for CGTs, including risk-sharing models and outcomes-based arrangements that link reimbursement to observed long-term outcomes.

This is important because payers face coverage continuity constraints in real-world populations. Health plan members typically remain with a given plan for 2 to 3 years on average, and roughly 22% of members undergo churn each year as individuals switch employers, move between markets, or otherwise change coverage arrangements [103,104]. This pattern creates misalignment between when value is realized and who pays for it, as the clinical benefit from these therapies accrues over extended time periods while the upfront costs are borne by a single payer with no guarantee that the member will remain enrolled with the plan. While 5-year durability may be important from a clinical evidence standpoint, health plans may face incentives to structure reimbursement models around the timelines that better reflect typical membership tenure. These considerations point to a need for more payment strategies that incorporate member portability and shared risk across payers, helping to better align reimbursement with long-term value realization.

6.2. Role of RWE and patient-reported outcomes (PROs)

Although 5-year follow-up data provide important insight into CGT durability, they may not fully reflect how these therapies perform in real-world treatment settings. RWE therefore provides important context by helping to assess whether the durability observed in clinical trials is reproducible across heterogeneous patient populations. Realizing the full value of RWE and PROs depends on the ability to integrate long-term monitoring into routine practice; however, capturing long-term outcomes remains challenging. Patients often travel considerable distances to receive CGTs, making sustained longitudinal follow-up increasingly difficult over time [105]. To help address this challenge, registries such as the Center for International Blood and Marrow Transplant Research (CIBMTR) and the World Federation of Hemophilia Gene Therapy Registry have become important mechanisms for post-marketing surveillance and long-term outcomes collection [106]. Nevertheless, several limitations remain. Registry participation is often voluntary, potentially introducing selection bias and incomplete outcomes capture, as reflected by CIBMTR estimates that only 65% of commercial CAR-T utilization is represented within its database [107]. Additional challenges include variability in follow-up practices across treatment institutions and fragmentation of long-term care, especially as pediatric patients transition to adult health systems [108]. To better align access with demonstrated value,

outcomes tracking should evolve toward automated, electronic health record (EHR) integrated platforms that systematically capture patient outcomes with digitized and readily reportable data. Facilitating stronger RWE generation will require more consistent follow-up across centers, improved EHR-to-registry reporting, linkage of clinical outcomes with claims data, and clearer coordination among treatment centers, registries, manufacturers, and payers.

Importantly, long-term clinical durability should not be conflated with commercial viability. Although durable clinical benefit is a key component of value, commercial success is influenced by many different factors, including treatment center infrastructure, patient identification and referral, reimbursement, provider adoption, manufacturing, and patient access. Accordingly, strong long-term clinical outcomes data do not necessarily translate into sustained market uptake, as illustrated by the withdrawal of valoctocogene roxaparvovec-rvox despite durable 5-year clinical outcomes. As the CGT landscape matures, distinguishing between clinical success and commercial success will become increasingly important when evaluating the long-term impact of these therapies.

Overall, the accumulating body of long-term follow-up evidence suggests that durable clinical benefit can be achieved across a growing number of approved CGTs and disease settings. While clinical outcomes appear encouraging, with many patients experiencing prolonged survival or sustained disease symptom improvement, important questions remain regarding long-term safety and the consistency of durable benefit across patient populations. As additional evidence emerges, continued long-term follow-up and real-world evidence generation will remain essential to further characterize long-term benefit and risk and to inform the evolving landscape of payer coverage, reimbursement, and long-term value assessment of CGTs.

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