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Financing potential cures

New models for cell and gene therapy breakthroughs

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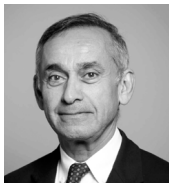
FOREWORD

Health systems worldwide are entering a period of profound transformation. Biomedical advances are making it possible to treat, alter and, in some cases, cure diseases once considered lifelong, debilitating, or fatal. Cell and gene therapies perhaps best exemplify this transformation, with treatments for hematological cancers or spinal muscular atrophy. For patients and their families, these therapies offer hope where little existed. For healthcare systems, however, they present new challenges that test the traditional foundations of healthcare financing.

Most health systems were designed to finance treatments delivered repeatedly over time, not potentially curative therapies that require substantial upfront investment with benefits that may accrue over decades. Healthcare systems are grappling with aging populations, rising demand for care, workforce constraints, and increasing fiscal pressures. These realities raise questions about affordability, budget impact, and how best to ensure timely and equitable access to transformative innovations. As a result, policymakers, payers, manufacturers and other stakeholders are increasingly exploring new financing and reimbursement approaches that can better align payment with long-term value while ensuring healthcare systems remain sustainable.

This report contributes to an important global discussion: how societies can capture the extraordinary promise of biomedical innovation while safeguarding the sustainability of healthcare systems and responding to wider societal health needs. Drawing on international experience, it examines the strengths and limitations of emerging payment models, explores alternative access pathways, and proposes a practical framework to support decision-making across healthcare settings.

Ultimately, the question facing policymakers is not whether transformative therapies should be supported, but how health systems can evolve to accommodate them. The decisions taken today will shape whether future breakthroughs remain scientific achievements accessible to a few, or become sustainable healthcare innovations that can benefit all those who stand to gain from them. This report seeks to inform that debate and provide practical guidance for navigating one of the most important health policy challenges of our time.



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EXECUTIVE SUMMARY

Cell and gene therapies (CGTs) include treatments administered once or over a short course that may cure a disease in some patients or materially alter its progression. CGTs pose distinctive financing and delivery challenges. List prices range from several hundred thousand to several million dollars per patient, while the number of available therapies, approved indications and treated patients continues to increase. Current expenditure remains modest relative to total pharmaceutical spending, but the combination of high prices and rising treatment numbers could place increasing pressure on healthcare budgets over the medium to long term.

DEFINING CGTS

The defining characteristics of CGTs strain the conventional instruments used to secure value for money and affordability. Many reach regulatory and health technology assessments with considerable evidentiary uncertainty, reflecting small and frequently single-arm trials, short follow-up, surrogate endpoints and limited evidence on the durability of treatment effect. This uncertainty extends directly to assessments of long-term value, making estimates of clinical benefit and cost-effectiveness highly sensitive to assumptions about the durability of benefit, long-term survival and quality of life. Nevertheless, favorable assessments based on equity-adjusted Incremental Cost-Effectiveness Ratio (ICER) thresholds may result in the adoption of CGTs. The resulting tension is that, while individual therapies may appear justified, funding them can displace more conventionally cost-effective care. For payers managing large budgets, it is the cumulative impact of a growing class of therapies and its opportunity cost that may call affordability into question, rather than any single claim.

PAYMENT MODELS FOR CGTS

A range of payment models for CGTs has emerged. This report classifies 11 models by the objective they primarily serve – whether value for money or affordability – together with a set of non-conventional models. The report assesses each against a common framework spanning budget impact, clinical uncertainty, operational governance and feasibility, acceptability to payers, incentives for innovation, and equity. It also considers three non-financial approaches that could facilitate access to CGTs. The central finding is that no single mechanism resolves the many challenges CGTs present. Only two of the 11 models could lower the expected cost – price-volume agreements and caps (effective price) and outcomes-based payments (expected payment). Each model carries trade-offs, and its suitability depends on the size and flexibility of the payer's budget, and the institutional features of the health system, such as the degree of centralization, patient mobility, information systems, co-ordination and administrative capacity.

As a result, the appropriate strategy differs by setting. Currently, most high-income countries have the capacity to finance CGTs, although the resources available within health and pharmaceutical budgets remain constrained by competing spending priorities. Also, the ability to fund these therapies within available budgets does

not necessarily imply that their prices offer value for money. The choice of payment model should focus on minimizing uncertainty, securing value for money and keeping coverage of CGTs manageable as part of the wider pharmaceutical budget.

Upper-middle-income countries face sharper trade-offs and may need to prioritize therapies more selectively, taking account of clinical value, affordability, system readiness and the health gains forgone elsewhere in the healthcare system. Many low- and lower-middle-income countries currently lack some of the clinical, regulatory and logistical capabilities needed to deliver CGTs at scale, although capacity varies considerably within and across countries. Conventional payment models alone are unlikely to overcome these constraints. Over the longer term, voluntary licensing, technology transfer and hospital exemptions may offer partial routes to access, particularly where supported by sustained external financing and institutional partnerships. However, the capabilities required to implement these approaches remain absent or incomplete in many settings.

SUSTAINABLE FINANCING FOR CGTS

A broader challenge underlies these findings. Like investments in prevention and health promotion, CGTs require substantial expenditure now against health gains that accrue over decades. Annual budget cycles, short payer horizons and fragmented responsibility for patients hinder the implementation of interventions with this profile, whether preventative or curative. Also, long-term health and societal benefits do not necessarily translate into budget savings: avoided treatment may release capacity without reducing expenditure, and any savings may accrue to a different payer or beyond the budget planning horizon. Sustainable financing therefore requires a medium-term perspective on costs and benefits, with explicit assessment of when, where and under what conditions any anticipated savings can be realized, so that advances capable of extending health are financed sustainably and shared equitably.

SCOPE AND OBJECTIVES

This report investigates the appraisal and financing challenges posed by one-off, potentially curative high-cost therapies. It specifically looks at therapies delivered in a single dose, or over a short, defined course, that either produce a curative effect in a subset of eligible patients or materially alter the natural progression of the disease. In reality, this category is dominated by CGTs.

Section 1 sets out the key clinical, regulatory and economic features of CGTs. It maps the approval landscape and the European Medicines Agency's (EMA) pipeline, and examines how these features strain the conventional value-for-money and affordability instruments of drug coverage, together with the equity adjustments that safeguard access.

Section 2 introduces a taxonomy of the payment models that have emerged, and the framework used to assess them. Section 3 applies that framework to 11 mechanisms, drawing out their strengths, limitations and suitability across contexts, and sets out the policy implications. The section also examines three alternative non-payment pathways that could support access to CGTs.

Section 4 discusses access to CGTs in low- and middle-income countries, covering disease burden, system readiness and manufacturers' launch decisions. Section 5 translates these findings into a decision framework that matches payment models to five payer groups, defined by income level, payer size and whether coverage is public or private. Section 6 proposes a practical application of the framework to Qatar.

Finally, Section 7 sets out conclusions and priority recommendations for payers seeking to secure sustainable access to CGTs:

1. Payers should invest in outcome registries, supported by clear data governance and appropriate safeguards for patient information.
2. Payers should build the epidemiological and legal expertise that price-volume agreements require so they can accurately estimate eligible populations and set credible thresholds. They should define how volumes are verified and rebates enforced.

SECTION 1. CELL AND GENE THERAPIES

Section 1 examines CGTs through their defining characteristics, current and emerging approval trends, and the constraints of traditional evaluation and financing frameworks.

Two trends make the financing of CGTs a pressing policy question. First, list prices run from several hundred thousand to several million dollars per patient.[1] Second, the eligible population is expanding on two fronts: new CGTs continue to reach the market while the take-up and eligible populations of some products have grown substantially over time. For instance, the gene therapy Zolgensma, first marketed in the US in 2019, had been administered to more than 5,500 patients globally by the first half of 2026.[2] It is projected that between 75 and 96 further approvals of durable CGTs are projected for the US by 2033.[3] Although current expenditure on CGTs remains manageable relative to overall pharmaceutical expenditure, the convergence of these two trends could strain budgets in the medium to long term.

DEFINING CHARACTERISTICS OF CELL AND GENE THERAPIES

Regulatory definitions of cell and gene therapies

The European Medicines Agency (EMA) groups gene therapies, somatic cell therapies and tissue-engineered products under a single category of advanced therapy medicinal products (ATMPs).[4] The US Food and Drug Administration (FDA) regulates the equivalent products under two categories: cellular therapy products and human gene therapies.[5] Regulatory classifications and terminology vary across jurisdictions. For the purposes of this report, 'cell and gene therapy' (CGT) is used as a working term to refer to the gene therapy and somatic cell therapy categories common to the EMA and FDA frameworks. Tissue-engineered products are excluded because their list prices have been reported to be much lower than CGTs, so they do not present the same funding challenges.[6]

Eligible patient populations and price implications

In vivo therapies are typically developed for narrow indications, because their benefit derives from correcting a specific genetic lesion, and eligibility is restricted to patients who carry it. Luxturna illustrates this: inherited retinal dystrophy can be caused by mutations in more than 280 genes, but Luxturna is licensed only for the biallelic RPE65 subset, a small fraction of the inherited retinal dystrophy population.[7] The Institute for Clinical and Economic Review estimated between 1,000 and 3,000 people with RPE65-mediated retinal dystrophy in the US.[8] Conversely, chimeric antigen receptor T-cells (CAR-Ts) that address hematological cancers do not target conditions that are rare. Rather, their regulatory approval has generally been confined to patients who have failed several prior treatments, to defined histological subtypes, or to specific age groups. So far, this has limited the number of eligible patients. However, this may change in the future as more trials of CAR-Ts in first or second line are completed. Small populations often result in high price claims from companies eager to recoup research and development costs and extract profits from relatively low sales of one-off therapies.

Clinical evidence available at regulatory review and health technology assessment

The evidentiary package supporting regulatory approval and reimbursement reflects these population constraints. In a systematic review of ATMPs approved in the European Union (EU) – mostly CGTs – Iglesias-Lopez and colleagues found that about 57 percent of pivotal trials were single-arm, 91 percent open-label and 78 percent used a surrogate primary endpoint.[9]

Where required for a health technology assessment (HTA), comparative data are typically generated through indirect treatment comparisons against external controls from registries, prior trials, or natural-history cohorts, rather than head-to-head randomization* against the standard of care.[10] Pivotal trials are also small: in a recent review of authorized ATMPs, the median sample size was 75 patients.[9] Disease severity, ethical constraints on placebo use, and the difficulty of recruiting from small groups often make randomized controlled trials infeasible in ultra-rare monogenic conditions or heavily pre-treated oncology indications; in larger indications they are feasible and increasingly expected, as the randomized second-line CAR-T trials (ZUMA-7, TRANSFORM, KarMMa-3, CARTITUDE-4) show. Pre-approval clinical follow-up is correspondingly short. Median follow-up in pivotal trials generally spans months to a few years, while a CGT's clinical effect is intended to persist far longer.[9,11] Two empirical questions are therefore generally unresolved at the point of approval: the durability of the initial response; and the translation of surrogate endpoints into robust patient-relevant outcomes.

Special regulatory pathways available to CGTs

The evidence supporting the marketing authorization of CGTs is often weaker than that available for conventional drugs. At the same time, these therapies frequently target severe diseases with high burden and substantial unmet need, where the benefits of earlier access to promising therapies may be considerable.[9,12] This creates a tension between expediting access to promising therapies and maintaining patient safety and the rigor of the approval process. In response, regulators have established expedited pathways that grant approval on immature data, with clinical benefit confirmed afterwards. In the EU, conditional marketing authorization permits approval on less comprehensive data where the benefit of earlier access outweighs the risk of incomplete evidence, subject to post-authorization studies.[13] The FDA operates a comparable scheme known as accelerated approval.[14] Japan operates a conditional and time-limited approval pathway for regenerative medical products, allowing approval where safety has been confirmed and efficacy can be predicted, subject to post-marketing evaluation.[15] Separate expedited-review programs, including the EMA's accelerated assessment and the priority review used by the FDA and Australia, shorten regulatory review timelines but do not constitute approval on less comprehensive evidence.[16,17] These mechanisms predated CGTs and often apply to conventional drugs too.

These programs have been applied in practice on several occasions. A study by Iglesias-Lopez and colleagues examined the regulatory pathways of CGTs* approved in Europe, the US or both, up to December 2024.[18] Of the 14 distinct

* The analysis included only CGT products classified as ATMPs under the EMA and FDA criteria. For the EU, only products authorized through the centralized process were considered. The sample included the following therapies: Strimvelis, Kymriah, Yescarta, Zynteglo, Libmeldy (Lenmeldy in the US), Tecartus, Breyanzi, Abecma, Skysona, Carvykti, Casgevy, Lyfgenia, Aucatzyl and Tecelra.

products identified, 12 had been approved by the FDA and 11 by the EMA. In the EU, accelerated assessment was granted to 73% of the products (n = 8/11), while in the US, priority review was granted to 42% (n = 5/12). Standard marketing authorizations accounted for 75% of FDA approvals (n = 9/12) and 55% of EMA approvals (n = 6/11).

Manufacturing economics

The manufacture of CGTs relies on living biological processes rather than chemical synthesis, and the resulting economics differ markedly across product types. In autologous ex vivo therapies, comprising most commercial CAR-T therapies, the patient's own cells are collected, modified and infused back; each dose is therefore manufactured for a specific patient and produced batch by batch. This yields limited economies of scale and high fixed costs for specialized facilities, qualified personnel and cold-chain logistics, all of which drive a very high per-dose cost.[19] In vivo gene therapies, such as Zolgensma and Luxturna, typically rely on viral vectors and are not tied to a specific patient, allowing them to be pre-manufactured off-the-shelf in larger batches. However, their manufacture remains at an early stage of development and does not yet benefit from the economies of scale of mass production or the decades of accumulated knowledge underpinning conventional medicines. Per-dose cost also varies widely with the viral vector used and with the therapy's indication and target organ, which determine the dose required.[20,21,22]

PREREQUISITES TO ADOPT CGTS

Pre-treatment and supportive care

CGTs often entail substantial pre-treatment clinical requirements and management of potentially severe side effects. These requirements vary most markedly between autologous ex vivo and in vivo therapies, as well as across products. Ex vivo therapies require pre-conditioning to enable the infused cells to expand and persist. For example, CAR-Ts typically require lymphodepleting chemotherapy before administration, together with the management of potentially severe and costly adverse effects such as cytokine release syndrome and neurotoxicity post-administration. Hematopoietic stem cell therapies, such as Casgevy for sickle cell disease and beta thalassemia, instead necessitate high-dose chemotherapy to destroy the patient's existing bone marrow. This process is known as myeloablative conditioning, which clears space within the marrow and enables durable engraftment. While the bone marrow is depleted, patients are highly susceptible to infection and require care in a protected environment until immune function recovers.[23] In vivo therapies usually have milder pre-treatment requirements, including pre-screening tests and prophylactic corticosteroid therapy. For instance, for products such as Roctavian, patients are screened for antibodies against adeno-associated virus to ensure they do not possess pre-existing immunity to the viral vector used.[24]

Supply chain logistics, workforce and treatment centers

The pre-treatment requirements, administration and management of toxicity events are complex and demand specialized teams whose expertise is rarely available in routine care. Therefore, multidisciplinary teams are needed that are capable of managing the end-to-end delivery of CGTs. To facilitate combining expertise, CGTs are normally delivered in a small number of specialized treatment

hubs. This presents a dual challenge: first, such treatment hubs may not be easily accessible for a large part of the population due to geographical distance and other constraints; second, the expertise required to deliver CGTs may be unavailable in some regions or countries, especially developing ones.[25]

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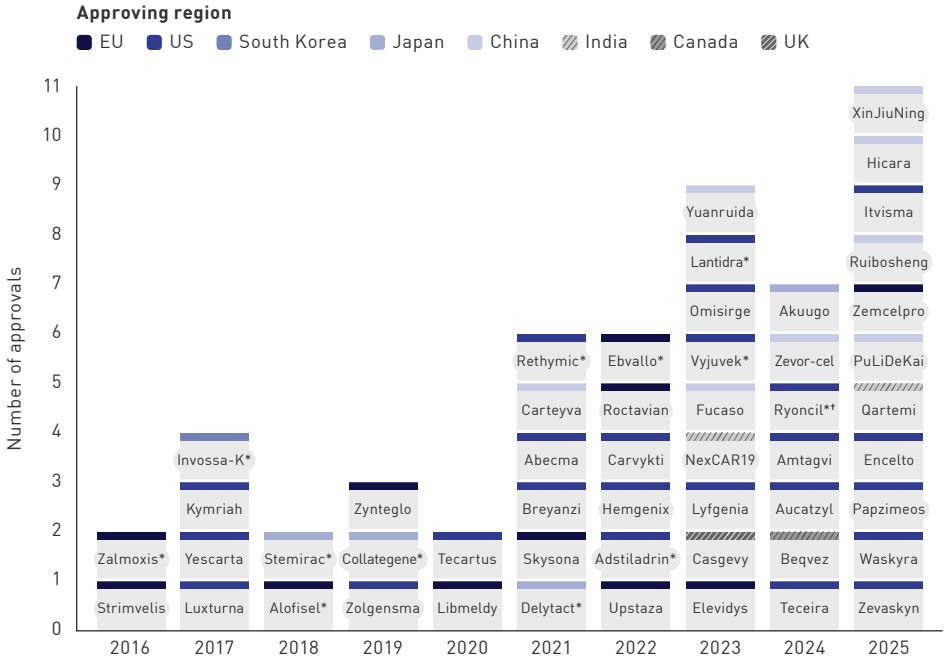
The supporting logistics are equally demanding and, like the clinical requirements, vary considerably across products along the ex vivo and in vivo distinction described above. Autologous CAR-T therapies rely on a vein-to-vein process where cells are collected from the patient, cryopreserved, shipped to a manufacturing facility and returned for infusion up to several weeks later.[26] Transportation requires continuous temperature monitoring and ultra-low temperatures, sometimes below -150°C. In vivo therapies are comparatively simpler to store and transport, although they still require cold storage, with temperatures ranging from -60°C to standard refrigeration, around 2°C–8°C (for example, for Zolgensma and Roctavian).

THE CELL AND GENE THERAPY LANDSCAPE: APPROVALS AND PIPELINE

A decade of CGT approvals (2016–2025)

Figure 1 shows the annual number of CGTs receiving their first regulatory approval over the past decade, with the country/region in which they were first approved. To provide the broadest possible overview of CGT approval trends, it includes all CGTs as previously defined, irrespective of their administration schedule or clinical potential. Further detail is provided in Appendix, Table A1.

Figure 1. CGT first regulatory approvals by year (2016–2025)



Notes: *Represents drugs that are not one-off curative or potentially curative therapies. †Ryoncil (US, 2024) has a similar predecessor, Temcell, approved in Japan in 2015. However, the products are not considered identical due to differences in manufacturing and formulation.

Sources: US Food and Drug Administration; European Medicines Agency's European Public Assessment Reports; Pharmaceuticals and Medical Devices Agency (Japan); National Medical Products Administration (China); Central Drugs Standard Control Organisation (India); American Society of Gene & Cell Therapy (ASGCT)/Citeline Gene, Cell & RNA Therapy Landscape Reports (Q4 2024); CGTLive®; BioInformant; peer-reviewed literature and manufacturer announcements. Where products were first approved in China and India, these were corroborated using regulator listings and ASGCT quarterly reports.

Annual approval activity increased from fewer than three first authorizations per year on average between 2016 and 2020 to at least five in every year from 2021 onwards, reaching a peak of 11 in 2025. The increase in approval activity dates from the authorization within a six-month window in 2017 of the first CAR-T therapies, Kymriah and Yescarta for hematological malignancies, alongside Luxturna for inherited retinal dystrophy and Invossa-K for osteoarthritis in South Korea. The CAR-T class was subsequently extended through Tecartus (2020), Breyanzi (2021), Abecma (2021), Carvykti (2022) and Aucatzyl (2024), with the range of indications widened to mantle-cell lymphoma, multiple myeloma, and B-cell precursor acute lymphoblastic leukemia. The in vivo gene therapy pipeline over the same period consisted of several products including Zolgensma (2019) for spinal muscular atrophy, Hemgenix (2022) for hemophilia B, Roctavian (2022) for hemophilia A, and Vyjuvek (2023) for dystrophic epidermolysis bullosa. Cumulatively, 52 CGTs received first regulatory authorization between 2016 and 2025, with thousands of cell therapies in clinical trials worldwide. However, several products have subsequently had their marketing authorizations withdrawn, revoked or expired, or have been commercially discontinued in certain markets, including Zalmoxis, Invossa-K, Zynteglo, Skysona, Alofisel, Collategene and Beqvez. Consequently, cumulative first approvals do not necessarily reflect the number of therapies currently authorized or commercially available.

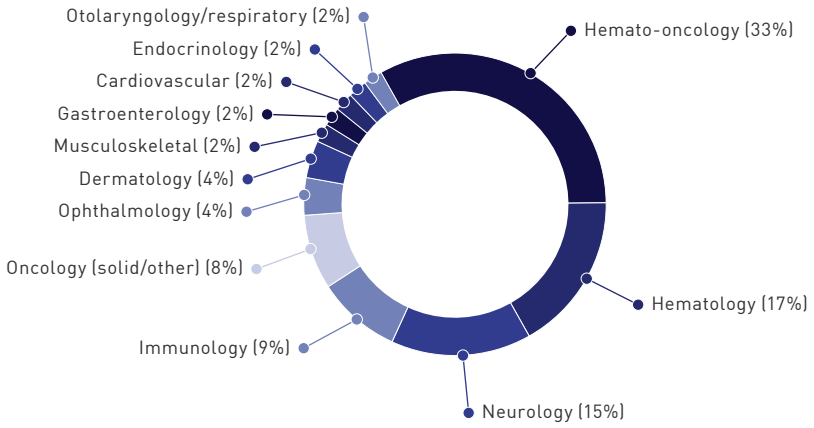
Figure 2 shows the distribution of the 52 CGTs by disease area. Approvals are highly concentrated: hemato-oncology and hematology together account for almost half of all products. Hemato-oncology constitutes the largest disease area (about 33 percent), reflecting the rapid expansion of CAR-T therapies. Hematology accounts for a further 17 percent, including therapies for hemophilia, sickle-cell disease and beta thalassemia (Zynteglo, Hemgenix, Roctavian, Casgevy, Lyfgenia and Beqvez), alongside Omisirge, Zemcelpro and XinJiuNing.

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Neurology forms the next largest cluster (about 16 percent) and covers rare genetic conditions (Zolgensma, Libmeldy, Skysona, Upstaza, Elevidys and Itvisma), as well as acquired neurological injury (Stemirac and Akuugo). Solid-tumor oncology contributes four products (Adstiladrin, Amtagvi, Tecelra and Delytact), while immunology contributes five (Strimvelis, Rethymic, Ryoncil, Waskyra and Ruibosheng). The remaining products are distributed across dermatology (Vyjuvek and Zevaskyn), ophthalmology (Luxturna and Encelto), and musculoskeletal, gastroenterological, cardiovascular, endocrine and otolaryngological indications, each represented by one product (Invossa-K, Alofisel, Collategene, Lantidra and Papzimeos, respectively).

First approvals have also spread geographically since 2021. Until then, the majority of CGTs were authorized first in the US or the EU; from 2021 onwards, China, India, Japan, the UK, Canada and South Korea have each been the country of first approval for at least one product.

Figure 2. Distribution of cell and gene therapy approvals by disease area (2016–2025)



CGTs under EMA review

To map drugs under active regulatory consideration, we analyzed the full list of marketing authorization applications under EMA review as of March 2026.[27] From this list, we retained all CGTs and excluded preventive and prophylactic treatments, vaccines, therapies requiring multiple or lifelong administration, diagnostic

compounds, biosimilars, changes in the modality of administration, labeling updates, manufacturing changes and generics. The analysis was restricted to the EMA because comparable data on active applications under review at the FDA or the UK's Medicines and Healthcare products Regulatory Agency were not available. This identified only three one-course, potentially curative CGTs under EMA review as of March 2026, spanning two oncology indications and one rare human papillomavirus respiratory condition. The individual products and their indications are listed in Appendix Table A2.

VALUE FOR MONEY, AFFORDABILITY AND EQUITY: THE POLICY CHALLENGES POSED BY CGTS

The allocation of financial resources in publicly funded health systems is organized around two interlinked policy objectives:

- Value for money, where the price of a covered drug is aligned with its clinical benefit.
- Affordability, which keeps aggregate pharmaceutical expenditure manageable alongside competing spending needs.

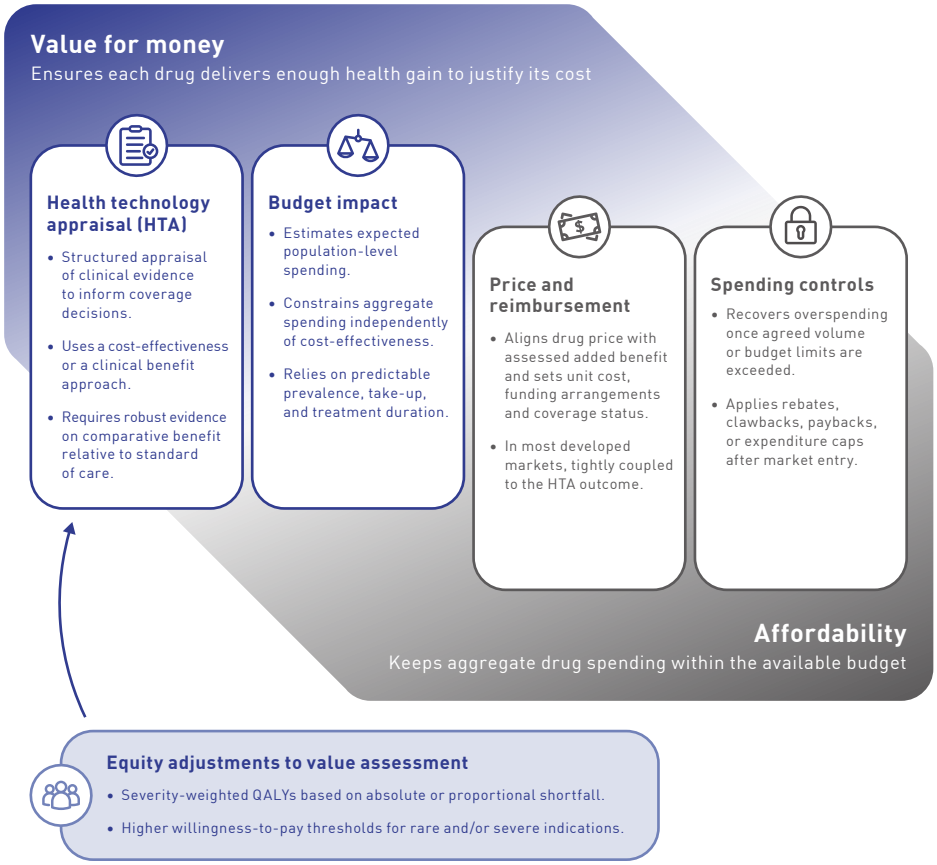
Coverage decisions are also shaped by equity considerations that reflect societal preferences on access for severe, rare, or end-of-life indications, and by the broader objective of responsible drug use.

Figure 3 summarizes the principal instruments that policymakers use to pursue these objectives, together with the equity adjustments that modify the value assessment. These instruments are interconnected: the HTA informs the price negotiation, which in turn shapes the coverage decision. A budget impact assessment links the two, sitting within the HTA process while also informing the negotiation. Spending controls apply once coverage has been granted, containing the expenditure that follows from it.

The defining features of CGTs set out earlier in this section pose unique challenges for each instrument. These processes also need to be connected to budgetary decision-making. Health authorities and payers, in co-ordination with finance authorities, need to reconcile proposed coverage decisions with available annual and medium-term resources.[28] This requires clear responsibilities for approving additional funding or reallocations, and for managing expenditure that exceeds forecasts. HTA and price negotiations inform these choices, but do not replace decisions on how coverage will be financed alongside other health priorities.

The remainder of this section examines each of these instruments, setting out how it operates, how it contributes to the two objectives, and where CGT characteristics constrain its use.

Figure 3. Policy objectives and pharmaceutical resource allocation



Source: The authors.

Value for money as a policy objective

'Value for money' means the price paid for a covered drug is aligned with the clinical benefit it provides. The main instrument is HTA, supplemented by price and reimbursement negotiations that translate its outcomes into net prices. Two philosophies dominate HTA. The first is cost-effectiveness analysis, where added clinical benefit and added cost are assessed jointly through the Incremental Cost-Effectiveness Ratio (ICER), typically expressed in cost per quality-adjusted life-year (QALY), and benchmarked against a willingness-to-pay threshold. Combining benefit and cost in a single metric embeds the value-for-money test within the appraisal. If ICERs at list price exceed the threshold, value for money can be delivered through confidential price negotiations that bring the 'net price ICER' below it. The second is clinical-benefit appraisal, adopted by countries including France and Germany, where costs are not formally weighed at the appraisal stage. Instead, the achieved benefit rating informs the price negotiations. Value for money in both systems is therefore achieved through the combined HTA, price and coverage negotiation stages.

The limits of standard value-for-money tools for CGTs

CGTs come to HTA with significant evidentiary uncertainty. Assessment bodies consistently identify the same sources of uncertainty: limited sample sizes; single-arm designs; and extrapolation from short follow-up.[29] This affects clinical-benefit and cost-effectiveness appraisal: trial size and design constrain the precision of incremental estimates, while lifetime extrapolation bears more narrowly on cost-effectiveness, where it drives ICER uncertainty.

The very small number of eligible patients shapes the size and design of pivotal CGT trials. At these sample sizes, effectiveness estimates carry wide confidence intervals that propagate to the incremental QALY and ICER estimates, widening the range of estimates.† Where only a single-arm trial is available, effectiveness against the standard of care or best supportive care is estimated through indirect comparisons, matching-adjusted analyses, or external controls built from registries.[30] Acceptance of observational comparators has grown, but they remain methodologically weaker than randomized trials since residual confounding by unmeasured factors cannot be ruled out.‡



A further challenge is the durability of treatment effect, which is assumed rather than observed. Cost-effectiveness models for one-off CGTs run over a lifetime horizon, while follow-up at reimbursement rarely extends beyond a few years.

A further challenge is the durability of treatment effect, which is assumed rather than observed. Cost-effectiveness models for one-off CGTs run over a lifetime horizon, while follow-up at reimbursement rarely extends beyond a few years. Lifetime QALY estimates therefore depend on the assumed trajectory beyond the trial; the choice between waning and sustained efficacy is a principal driver, and modest variations produce substantial movements in the ICER.§

Equity considerations in coverage decisions for CGTs

Strict adherence to value for money criteria would require rejecting any drug whose ICER exceeds standard cost-effectiveness thresholds. In practice, HTA bodies that rely on cost-effectiveness analysis routinely relax these thresholds in response to equity concerns. These formal adjustments are largely confined to jurisdictions whose coverage decisions rest on ICERs; agencies that base decisions on clinical added benefit already weigh severity, rarity and unmet need within the benefit assessment itself, and so need fewer separate equity adjustments. Without adjustment, two groups of patients may be disadvantaged:

- Those with severe conditions or in later disease stages, where fewer QALY gains exist, which increases the ICERs.[31]
- Those with rare diseases, whose small eligible populations may drive upper-patient treatment costs and, in turn, the ICERs.

Among countries that formally adopt ICER thresholds, two adjustments are common. The first raises the cost-effectiveness threshold, the maximum a system will pay for a given health gain, for narrowly defined categories such as ultra-rare conditions.

England's Highly Specialised Technologies Programme illustrates this: under strict eligibility criteria that include rarity and unmet need, the National Institute for Health and Care Excellence's (NICE's) willingness-to-pay threshold rises from between £25,000 and £35,000, as of April 2026, to between £100,000 and £300,000 per QALY, depending on the magnitude of the health gain.[32,33] The second adjustment gives extra severity weighting[¶] to the health gains of patients whose disease causes the greatest loss of length and quality of life.[34] How far these adjustments should go, and their criteria, is ultimately a question of what society values.

Affordability as a policy objective in the context of CGTs

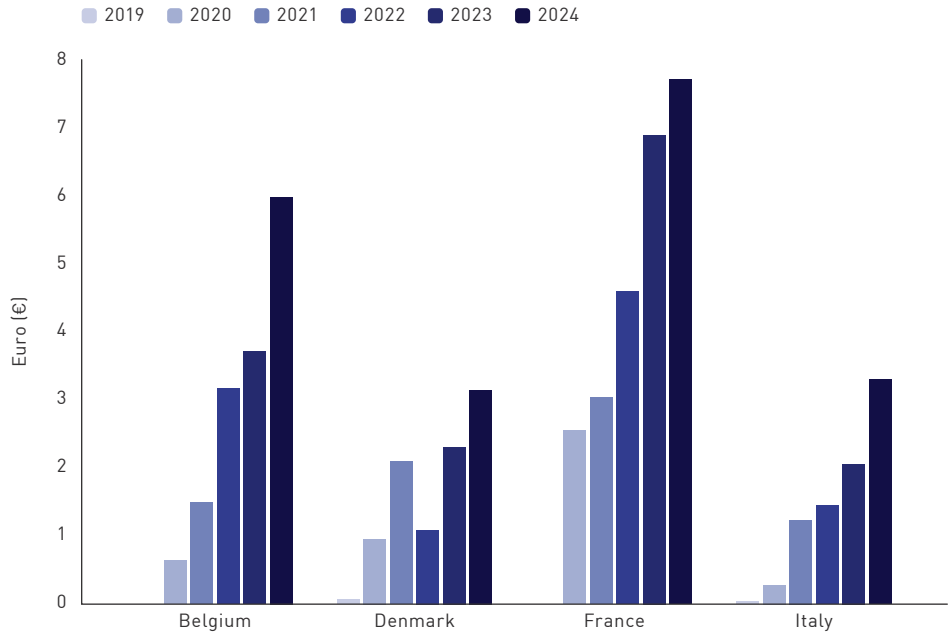
The affordability objective seeks to keep aggregate pharmaceutical expenditure within a manageable share of the healthcare budget. Value for money focuses on the price of individual drugs. Affordability operates across the budget as a whole, asking whether the implication of a coverage decision, together with the cumulative cost of all listed products, fits within the payer's spending objectives. As shown in Figure 3, policymakers usually deploy three tools to achieve this objective: budget impact assessments; payment models to spread risk across time or several payers; and budget ceilings accompanied by rebates, clawbacks or paybacks.

For CGTs, in the short term, affordability is primarily a concern for underfunded payers or small risk pools, for which a relatively small number of high-cost claims may create an unmanageable peak of expenditure so that the entire budget is destabilized. Such situations are best addressed through larger risk pools or reinsurance mechanisms (see sections 3.5 and 3.6). For many large payers, a small number of CGT claims is unlikely to create immediate budgetary concerns. However, this does not preclude a worsening of affordability in subsequent time periods. In the US employer-sponsored insurance market, who first bears the cost of a CGT depends on how the health plan is structured, whether the employer holds separate 'stop-loss' cover that reimburses claims above a set threshold, or participates in a risk-pooling mechanism. Large claims can later push up insurance or stop-loss premiums, and employers then choose whether to absorb the increase, pass part of it to employees, or scale back the benefits they offer.[35] More broadly, as CGT approvals and treatment volumes increase, their cumulative budget impact, rather than the effect of any single claim, is likely to become the more important consideration. Affordability should, therefore, be considered over a medium-term horizon, particularly where payment arrangements generate financial commitments across more than one budget period. These mechanisms may help manage the timing or distribution of expenditure, but they do not remove the need to plan how future obligations will be financed alongside existing commitments and competing health priorities.

CGT approvals have risen steadily over the past decade and are expected to keep doing so, meaning that their cumulative budget impact warrants attention. This matters because CGTs are usually cost-effective only when HTA criteria are relaxed on equity grounds – meaning that funding these therapies within a fixed budget may displace treatments that would otherwise deliver greater aggregate health gains. However, even therapies that meet standard cost-effectiveness criteria may require substantial additional expenditure, creating difficult choices about funding and reallocations. In general, the additional spending arising from any new positive coverage decision needs to be considered alongside other health spending priorities and available budgetary resources. However, there is no universal benchmark for

deciding whether a treatment is inherently unaffordable: affordability depends on the resources available, existing commitments and the opportunity costs society is willing to accept. Budgetary pressures can arise well before expenditure threatens aggregate fiscal sustainability.[36] To gauge the scale of this spending, Figure 4 tracks CGT expenditure per capita over time in Belgium, Denmark, France and Italy.*

Figure 4. Innovative therapy expenditure per capita (€) (2019–2024)



Source: The authors, based on AIFA's 2024 *Report on the Use of Medicines in Italy*, data provided by INAMI (Belgium), SNDS/PMSI (France) data extraction, and expenditure data provided by Amgros.

Notes: All expenditure figures are reported at list prices, except for the expenditure on CAR-Ts in Belgium, which is reported at net prices owing to data availability. The group of reimbursed products varies from country to country. Appendix Table A3 provides a detailed list of the products counted in Figure 4. A further consideration is that CGTs, and CAR-Ts in particular, can carry high administration costs. These fall outside the figures presented above, since they are met from hospital budgets rather than from the pharmaceutical budget, yet they remain a real burden on the wider health system that the payer must ultimately bear. Figure 5 sets out the administration costs of several of the best-selling CAR-Ts in France, which amount to 8 percent to 9 percent of their list price (and about 2 percent for Luxturna) and so represent a significant additional expenditure for payers. These estimates include costs associated with treatment administration, hospitalization and supplementary hospital payments obtained from economic evaluations validated by the French HTA authority, but do not capture the full treatment pathway. Depending on the therapy and the economic evaluation, additional costs may arise from the management of complications and long-term follow-up.

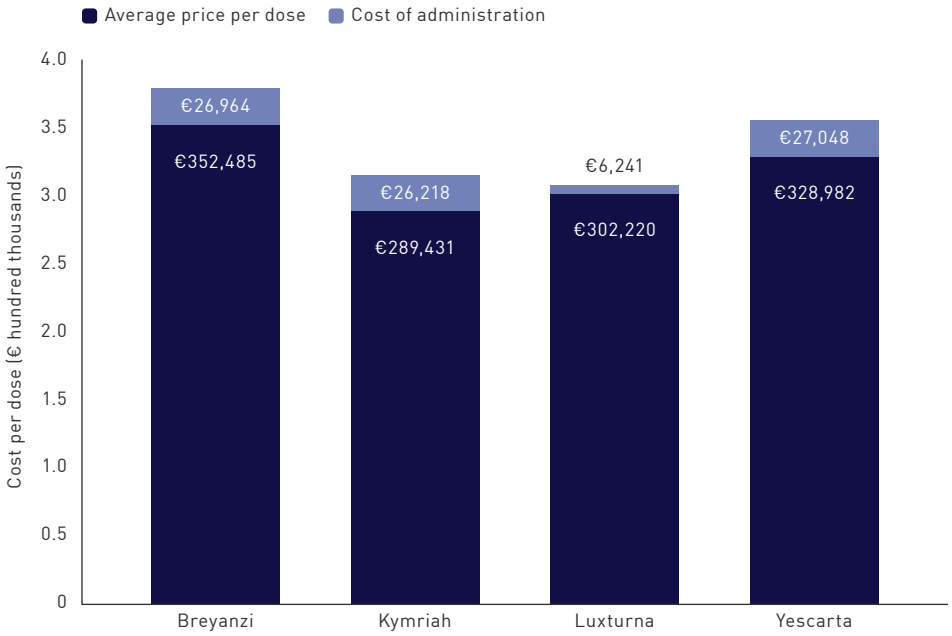
On a per-capita basis, all four countries' expenditures trend upward over 2019 to 2024, though from different starting points and at different speeds. Importantly, data for Belgium and France are only available from 2020. By 2024, per-capita expenditure ranged from roughly €3 to €8 across the four countries, having grown substantially from a low base over the period. In absolute terms, Belgium's expenditure grew from roughly €7.4 million in 2020 to €71.1 million in 2024; Denmark's from €0.42 million in 2019 to €18.84 million in 2024; France's from €172.3 million in 2020 to €529.6 million in 2024; and Italy's from €1.4 million in 2019 to €194.5 million in 2024. These figures

* Countries selected based on data availability.

reflect the volume of treatments administered multiplied by their price, which in turn depends on whether a treatment is included in the benefits basket provided (see Appendix Table A3).

The CGT share of the total pharmaceutical budget cannot be calculated precisely and homogeneously, because countries report overall expenditure in different ways – particularly with respect to list versus net prices, the application of rebates, and the treatment of hospital drug spending. Nonetheless, our analysis estimates this share at between 0.5 percent and 1 percent across all four countries.

Figure 5. Average price and administration cost of selected innovative therapies in France



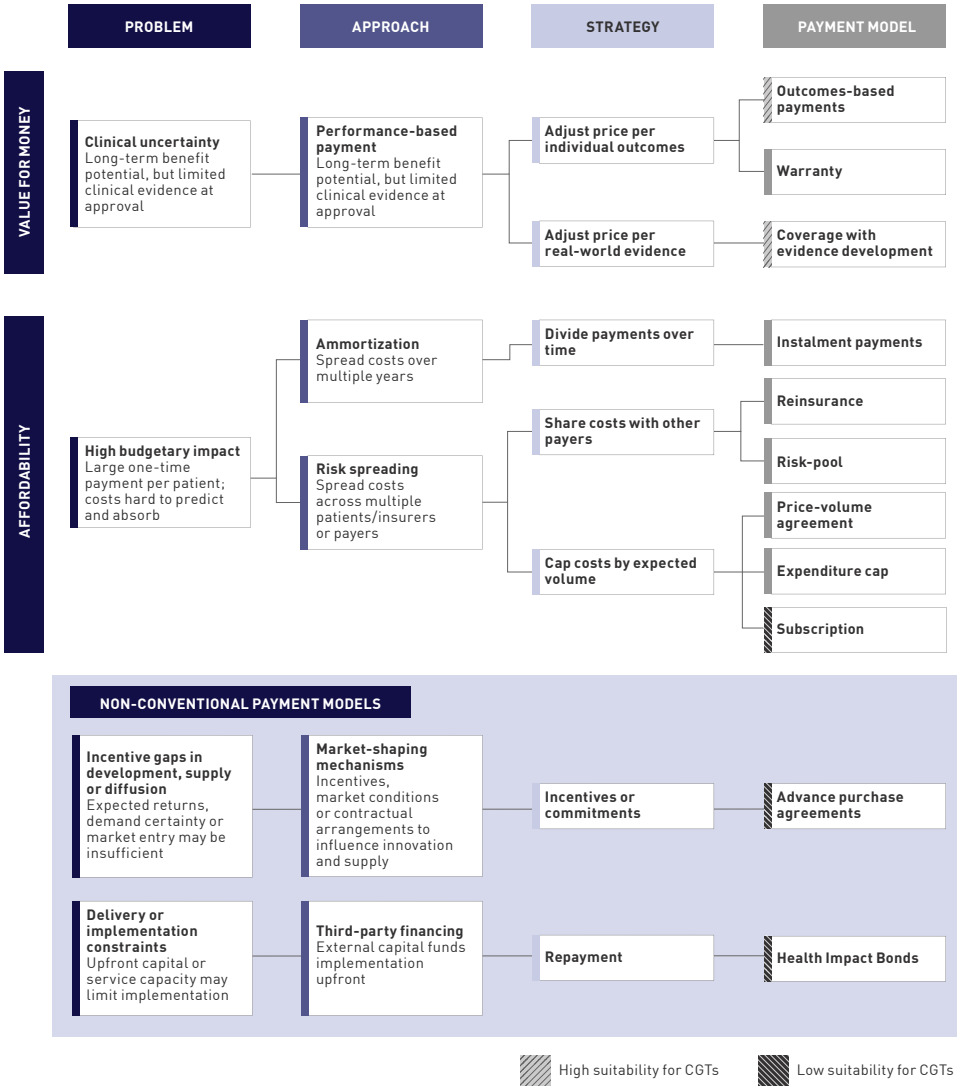
Source: The authors, based on list prices from the 'Liste en sus' (add-on list) and economic assessments by Haute Autorité de Santé (HAS). See Appendix Table A4.

Notes: The figure reports the average price of each molecule between 2020 and 2024 as reported in the Liste en sus, alongside its cost of administration. These administration figures are drawn from the additional economic and budget-impact analyses conducted within the HAS appraisals, which are required only for drugs expected to have a significant impact on public expenditure and claiming a L'Amélioration du Service Médical Rendu (ASMR) rating of I, II or III. As a result, detailed administration costs are available only for the indications expected to have the greatest budget impact. The figures shown should therefore be read as the cost for the specific indication referenced, not as an average across each drug's approved indications, and they are likely to vary slightly from one indication to another (see Appendix Table A4 for further details).

SECTION 2. PAYMENT MODELS FOR CELL AND GENE THERAPIES: A TAXONOMY AND FRAMEWORK FOR EVALUATION

The clinical and economic features of cell and gene therapies (CGTs) set out in Section 1, together with the limits of conventional value-for-money and affordability instruments, have prompted a range of alternative payment models. This section adapts the taxonomy developed by Harrow and Kesselheim,[37] classifying these models into two categories that we selected to mirror the policy objectives outlined in Section 1: value for money; and affordability. The two categories are not mutually exclusive, and a single agreement can combine models from both – for instance, outcomes-based payments and instalments. A third category covers non-conventional models that fall outside this framework. Figure 6 presents the resulting classification.

Figure 6. Taxonomy of payment models for CGTs



Source: The authors, adapted from Horrow and Kesselheim (2023).[37]

Classifying mechanisms by the policy objective they address clarifies what each is designed to achieve, but it does not reveal how well any of them performs in practice. A mechanism may be well suited to its stated objective, yet remain difficult to implement – from the data infrastructure and governance it demands, to the willingness of payers to adopt it. Therefore, whether a mechanism succeeds depends on a wider set of dimensions, each of which can enable or hinder it. The next section assesses the payment models and other non-financial mechanisms for accessing CGTs.

SECTION 3. ASSESSMENT OF PAYMENT MODELS AND NON-FINANCIAL ACCESS MECHANISMS FOR CELL AND GENE THERAPIES

This section assesses 11 payment models and 3 non-financial mechanisms for accessing cell and gene therapies (CGTs).

The payment models are:

1. Outcomes-based payments
2. Warranties
3. Coverage with evidence development
4. Instalments
5. Reinsurance
6. Risk pools for high-cost treatments
7. Price-volume agreements
8. Expenditure caps
9. Subscriptions
10. Advance purchase agreements
11. Health impact bonds

The section then examines three non-financial access mechanisms: hospital exemption; voluntary licensing; and joint procurement. The analysis uses the assessment framework set out in Table 1. The assessment framework provides a structured basis for comparing alternative payment models for CGTs. It draws on prior work on the sustainable financing of innovative therapies, complemented by literature focused specifically on CGTs. Notable resources are Horrow and Kesselheim's[37] review of high costs, clinical uncertainty and payment models for gene therapies, and the systematic review of funding models for breakthrough therapies by Hanna et al.[38] The assessment framework operates at the level of the mechanism rather than the individual therapy, and does not evaluate clinical value or substitute for formal HTA. Instead, it assesses how each mechanism performs across a common set of dimensions: cost to the system; uncertainty around long-term clinical benefit; operational governance and feasibility; acceptability to payers; incentives for innovation; and equity (Table 1). These dimensions allow mechanisms to be compared by the policy problem they address, the conditions their implementation requires, and the trade-offs they create for payers, manufacturers, health systems and patients.

Table 1. Assessment framework for CGT payment models

Dimension	Research endpoint
Budget impact	The degree to which a payment model eases budgetary pressure at two levels: (i) per-patient, by spreading a concentrated one-time payment across multiple budget cycles; and (ii) population-level, by managing aggregate expenditure when multiple patients are eligible within the same period.
Clinical uncertainty	The degree to which an option manages the fact that clinical outcomes remain unknown at the point of initial payment, particularly the long-term durability of treatment effect; and the degree to which it ties the level of payment to the magnitude of the outcome actually achieved, so that greater therapeutic benefit corresponds to greater willingness to pay.
Operational governance and feasibility	Operational feasibility is assessed in terms of how feasible an option is to implement, given the data infrastructure, institutional co-ordination, administrative effort, and contractual governance it requires.
Acceptability to payers and societies	Acceptability to payers is assessed in terms of how readily payers are likely to take up the option, reflecting whether its design aligns with their budgetary, administrative, and other constraints, as a basis for funding future high-cost innovative therapies.
Incentives for innovation	Incentives for innovation are assessed in terms of an option's capacity to maintain manufacturer returns at a level sufficient to sustain continued investment in CGT development.
Equity	Equity is assessed in terms of an option's design and whether it is likely to support or hinder fair access across eligible patients, providers or payer settings. This includes whether the mechanism introduces administrative, data, monitoring or other burdens that may give rise to unequal access.

Table 2 summarizes how the 11 assessed payment models perform against the six dimensions of the framework in Table 1. The ratings are qualitative and reflect the authors' assessment of each mechanism, and should be read alongside sections 3.1 to 3.12.

Table 2. Summary comparison of CGT payment models against the assessment framework

Payment model	Effect on budget impact	Effect on clinical uncertainty	Operational requirements	Degree of payer acceptability	Incentives for innovation	Effect on equity	Illustrative example
Outcomes-based payments	○	▲	▼	▲	▲	?	Kymriah and Yescarta (Italy): The Italian Medicines Agency (AIFA) adopted three milestone-based payments linked to clinical outcomes. Kymriah includes an initial payment at infusion, while Yescarta's payments are entirely deferred and conditional on treatment response.[39]
Warranties	○	▲	▼	▲	▲	?	Roctavian (US): BioMarin offers a four-year warranty reimbursing up to 100% of the acquisition cost if patients fail to respond or lose treatment response, with reimbursement prorated over time.[37]
Coverage with evidence development	○	▲	▼	○	▲	○	Cancer Drugs Fund (England): Provides temporary access to cancer therapies, including CAR-T treatments, while additional clinical evidence is collected to inform subsequent National Institute for Health and Care Excellence (NICE) reassessment and routine commissioning decisions.[40]
Instalments	▲	○	▼	▲	○	?	Yescarta (Belgium): The agreement provides for 87.5% of the cost at administration, followed by two payments of 6.25% at 12 and 20 months, conditional on data submission rather than clinical outcomes.[37]
Reinsurance	▲	○	▼	▲	▲	▲	PreserveRx (US): Insurers pay a per-member fee for financial protection against high-cost gene therapies. For Zolgensma, the reinsurer covers eligible expenditure above the payer's initial $250,000 contribution.[41]

Risk pools	▲	○	?	▲	▲	▲	Embarc Benefit Protection (US): Cigna Healthcare pools fixed per-member contributions to cover eligible gene therapies, with no patient out-of-pocket costs for the therapy itself, although administration costs remain with the health plan.[42,43]
Price-volume agreements	▲	○	▲	▲	▲	○	Zolgensma (Spain): A mixed agreement combines volume-based pricing provisions with outcomes-based conditions monitored through the Spanish National Health's VALTERMED registry, covering an estimated 30 patients annually.[37,44]
Expenditure caps	▲	○	▲	▲	▼	▲	Luxturna (Italy): AIFA established an expenditure ceiling of €21.6 million over 24 months, with spending above the agreed limit recovered through manufacturer paybacks.[45]
Subscriptions	N/A						No relevant CGT example identified.
Advance purchase agreements	N/A						No relevant CGT example identified.
Health impact bonds	N/A						No relevant CGT example identified.

▲ = Favorable; ○ = Neutral; ▼ = Unfavorable; ? = Not assessable; N/A = Not applicable.

Notes: A favorable rating indicates that the mechanism is likely to support the objective underlying the criterion, and an unfavorable rating that its design or implementation requirements are likely to hinder it. A neutral rating indicates no material effect in either direction, and 'not assessable' that the evidence is insufficient to judge. A lot of these judgments are based on what objective the payment method is designed to address. Evidence supporting the ratings is developed in subsections below.

3.1. OUTCOMES-BASED PAYMENTS

Outcomes-based payments (OBPs) link a therapy's payment to a patient achieving a pre-specified outcome after treatment. These outcomes vary depending on the characteristics of the product being reimbursed and the proposed contract terms, but they may include survival or complete response. The fundamental premise is that payment for the therapy is associated with demonstration of clinical benefit to patients. If the therapy does not deliver this benefit, the manufacturer either receives no payment or refunds a patient's pre-payment. OBPs are effective where evidentiary uncertainty at launch is high, as is the case for some CGTs. Italy uses one variant: OBPs paid in instalments for the CAR-T therapies, Kymriah and Yescarta. For Kymriah, the Italian Medicines Agency (AIFA) pays in three instalments: at infusion; at six months; and at 12 months. The last two instalments are due only if the patient has achieved the agreed health benefit. For Yescarta, the structure is similar but less favorable to the manufacturer: the three payments occur at 180 days, 270 days, and 365 days after treatment. No payment is made at infusion, and the manufacturer bears the full cost of any patient who is treated but does not reach the first milestone.[39] In the US, the Centers for Medicare & Medicaid Services' (CMS) Cell and Gene Therapy Access Model uses centrally negotiated, outcomes-based rebates to support Medicaid access to sickle-cell gene therapies across participating state programs.[46]



In fragmented systems, patient movement between institutions can separate responsibility for the initial treatment from subsequent outcome monitoring, creating uncertainty over which institution should verify outcomes and administer any contingent payments or rebates.

This analysis considers only OBPs operated at the individual patient level, where payment depends on whether each treated patient meets the agreed outcome. Population-level variants, which instead settle payment against the average performance of the whole treated cohort, are not examined here. This is because CGT populations are typically small and their outcomes vary significantly across patients, so a cohort average would be imprecise.

By aligning payment with realized benefit, OBPs reduce payment for patients who do not respond within the contractual period. They are not, however, a cost-containment tool: their aim is to secure value for money, not budget control. Nor do they generate generalizable evidence unless the outcome data lead to a formal reappraisal. Overall, OBPs work well when the outcome is clinically meaningful, clearly caused by the therapy, and measurable within a reasonable timeframe.[47] These agreements are, however, complex to operate. The contract must define who is eligible, which outcome counts as success, how and when it is measured, and how payments are reconciled; the system must then track each patient's outcome. Therefore, their feasibility depends on data infrastructure, but also on continuity of institutional responsibility over the period in which outcomes are assessed. In fragmented systems, patient movement between institutions can separate responsibility for the initial treatment from subsequent outcome monitoring, creating uncertainty over which institution should verify outcomes and administer any contingent payments or rebates.[48]

Payers turn to OBPs where the evidence at launch is too weak to justify funding the therapy outright, but the relevant outcomes can still be measured without excessive strain on the system. Manufacturers may welcome them where they secure access that might otherwise be delayed, denied, or won only at a larger discount, while accepting the risk of not being paid in full if clinical milestones are not reached. On equity, OBP can widen access to therapies that payers would otherwise refuse or delay on evidentiary grounds. But they can also create disparities where they rely on data, follow-up or administrative capacity that is unevenly available across centers, regions or payers.

3.2 WARRANTIES

Warranty arrangements operate as a form of patient outcome-based refund, providing financial protection to the payer if a therapy does not achieve the pre-specified outcomes. Warranties may be administered directly by the manufacturer as a performance-based rebate, or through a third-party insurance arrangement where the manufacturer pays the insurance premium and the payer receives any compensation in case of treatment failure.[35] If treatment is unsuccessful, the payer may be reimbursed for all or part of the drug's cost, or for defined medical costs, such as hospitalization, associated with the failure. BioMarin's offer of a warranty to payers in the US for Roctavian, a gene therapy for hemophilia A, shows how a manufacturer-backed warranty works. Payers meet the full cost of treatment upfront, but if the patient does not respond, or loses response within four years of dosing, BioMarin reimburses up to 100 percent of the wholesale acquisition cost, prorated for the time elapsed.[37]

Warranties share many features with OBPs: both are tools for securing value for money by tying payment to clinical performance; neither reduces the list price; and both rely on the same enablers – clear, attributable and verifiable clinical outcomes, and the administrative capacity to implement the payment model. However, they diverge in three respects:

1. **Timing:** An OBP withholds or staggers payment until the outcome is confirmed, whereas a warranty is usually settled in full upfront and refunds the payer if the treatment fails.
2. **Structure:** An OBP is a payment schedule that forms part of the coverage decision, while a warranty is often a separate insurance product whose payout is seen as compensation for treatment failure.
3. **Scope:** Warranties can extend to defined downstream medical costs, not only the drug's price.

For payers, warranties may appeal where they offer meaningful recourse for treatment failure without requiring the payer to manage every element of an outcomes-based contract directly. Where a third-party administrator is used, some patient tracking, monitoring and reconciliation functions can be transferred to the external provider.[49] For manufacturers, they may support coverage while preserving upfront payment and signaling confidence in the product, though premium costs could offset such advantages.

The allocation of risk also shapes which systems each mechanism fits in. OBPs suit centralized systems with strong administrative and monitoring capacity, such as single-payer systems or national health insurers. Warranties suit fragmented, insurer-based systems with multiple payers, such as in the US. These systems may lack capacity but still want recourse against evidentiary uncertainty, since the warranty pays upfront and offloads patient tracking and failure risk to an external insurer or administrator. However, these benefits need to be balanced with the potential risk that patients switch insurer, which would complicate the original payer's ability to receive compensation for treatment failure.

3.3 COVERAGE WITH EVIDENCE DEVELOPMENT

Coverage with evidence development (CED) is a conditional reimbursement arrangement where a payer funds a therapy for a defined interim period while additional evidence is collected, after which the technology is formally reappraised and coverage is continued, restricted or withdrawn.[50] The rationale is that a therapy reaches the market judged plausibly cost-effective or offering a clinically meaningful improvement, but with material uncertainty about its real-world benefit. Given high unmet need or severity, there is a compelling case to fund the therapy before that evidence matures. Therefore, the payer bears the interim risk that the clinical benefit does not materialize, and a definitive appraisal follows once the data have matured.

The Cancer Drugs Fund (CDF) in England is the clearest example, having funded CGTs such as Kymriah and Yescarta since 2018.[51] The CDF funds cancer therapies that cannot yet be recommended for routine use, but whose cost-effectiveness has plausible potential to meet standard thresholds. The CDF provides funds under a managed access agreement that identifies the additional evidence required for subsequent NICE reassessment, which may come from ongoing clinical trials and real-world data collection.[52] By early 2023, of the managed access agreements reappraised by NICE, the substantial majority (26 out of 30, or 87 percent) were recommended for routine commissioning.[40] Importantly, the CDF operates within a spending cap to prevent excessive expenditure; however, this is not always the case with CED mechanisms.

CED does not affect the volume of a treatment. However, it may impact the price by mandating discounts to include the therapies in the CED program, as in the case of England.[40] Its strength lies in addressing clinical uncertainty by mandating evidence generation. However, the payer assumes the interim risk that a therapy funded without robust evidence could fail to deliver the expected benefit. The operation of this scheme is relatively complex: it requires mature data systems, such as dedicated patient registries, and the associated investment in infrastructure and personnel. These costs are borne by the payer or manufacturer depending on the agreement. Acceptability is mixed: payers value the ability to grant access without committing to permanent funding, but are wary of the difficulty of withdrawing coverage once granted.[53] Manufacturers broadly view CED as favorable, as it secures faster market access and can aid trial recruitment, a notable advantage in low-prevalence conditions. Such advantages are contingent on steep price cuts not being imposed on exit from the CED fund. For patients, the principal benefit is faster access. However, this does not improve equity, as availability may be restricted to specialist centers with the necessary registry capacity.

3.4 INSTALMENTS

Instalment arrangements spread the price of a therapy across a defined time period. They are most useful where the main challenge is the concentration of expenditure over a short period, thereby relieving pressure on annual budgets. Therefore, the case is strongest for one-time high-cost therapies like CGTs, where the budget impact is immediate, but the clinical benefit accrues over many years. The profile of the eligible population matters too: instalments suit a group of untreated patients that has accumulated by market entry, where demand is concentrated at launch and incidence is low thereafter. A continuous inflow of new patients makes the mechanism less attractive.

Belgium's arrangement for Yescarta illustrates how instalments operate in practice. Under this scheme, 87.5 percent of the therapy's cost is settled on administration. The remaining balance is disbursed in two equal payments of 6.25 percent, payable at 12 months and 20 months respectively. Disbursement of the payments is contingent on the submission of patient data, but it is not tied to specific clinical outcomes, unlike the Italian scheme discussed in Section 3.1.[37] A key limitation of this mechanism is the lack of a direct link between payments and clinical outcomes. A fixed multiyear payment schedule does not protect the payer if the patient experiences no health benefits.



The value of instalments lies in improving affordability within annual budget constraints, not in lowering the underlying price or volume of treatment.

The value of instalments lies in improving affordability within annual budget constraints, not in lowering the underlying price or volume of treatment. In terms of budget management, instalments ease short-term budget pressure but do not reduce total expenditure, and may even increase it once financing and administrative costs are factored in. Where new patients are treated each year, instalment obligations for successive cohorts accumulate, potentially reducing the budget available for new coverage decisions in subsequent years. Operationally, instalments require clear rules on schedule, duration, invoicing, accounting treatment, and responsibility for future payments.*

Also, implementation may be difficult where annual budgets constrain commitments beyond the current fiscal year, payer responsibility is fragmented, or patients move between payers. In private insurance, multiyear instalments can create administrative difficulties when a patient changes insurer or an employer changes plan. The original payer may remain responsible for outstanding payments, while a successor insurer gains part of the therapy's future benefit.[1]

Instalments are favored where high upfront costs create budgetary concerns, but support depends on whether the resulting obligations remain manageable (see Section 1). Long-term liabilities, data requirements, patient mobility, and uncertainty over responsibility for future payments all weigh against adoption. Acceptability is therefore highest where governance is centralized, payment terms are simple

* Spreading cash payments over several years does not necessarily spread the recognition of expenditure over the same period; this depends on the applicable accounting rules.

and short in duration, and financial exposure is clearly defined. For manufacturers, instalments are broadly neutral as they do not affect price or treatment volumes, while posing few downside risks where contractual obligations are robust and enforceable.

3.5 REINSURANCE

Reinsurance is a contractual arrangement where a payer transfers part of its exposure to high-cost claims to a third-party insurer in exchange for the payment of a premium. This functions as a secondary layer of coverage for primary health insurers and as stop-loss protection for self-funded employers. The insured party is then indemnified for losses above a predefined threshold.[54] Reinsurance is largely confined to the private US health insurance market, where it is most relevant to smaller payers, which are the most exposed to destabilization by CGT claims. PreserveRx, a reinsurance product for gene therapies in the US, illustrates how such arrangements operate in practice. It works by having eligible health insurance plans pay a per-member-per-month fee in exchange for being shielded from the high one-time cost of a covered CGT. The payer absorbs costs up to an attachment point and the reinsurer covers the remainder. At launch (in 2020), PreserveRx covered Luxturna and Zolgensma, with three further therapies expected, and was reinsured by BCS Insurance Company.[41] For Zolgensma, the payer would cover the first $250,000, with PreserveRx reimbursing the remaining cost up to the therapy's $2.125 million list price.[37]

Reinsurance's principal benefit is risk-spreading: it smooths the actuarial risk that a single CGT claim could destabilize a smaller payer, replacing the risk of a high lump-sum expense with a predictable premium.[55] It does not, however, affect the price or volume of treatment. Reinsurance is not concerned with evidentiary uncertainty because indemnification is set by claim size rather than clinical outcomes.

Reinsurance relies on tools that insurers already use to handle rare, very high-cost claims, so it is most readily implemented where infrastructure is already in place.[56] Implementation depends on sound institutional design (a defined reinsurer, a clear contractual basis, transparent eligibility rules, an agreed attachment point, and reliable claims systems) and on safeguards against adverse selection.

Reinsurance is most attractive to smaller payers, including self-insured employers, regional plans, and state programs that must cover eligible therapies yet remain exposed to rare, very high-cost claims. By capping exposure, it makes spending more predictable and lowers reluctance to cover. Its value is lower where payers can exclude the therapy or have the scale to absorb the risk internally. For manufacturers, the mechanism is broadly favorable, since making high-cost claims manageable for smaller payers supports take-up.

Its equity profile is more mixed: it can widen access by enabling smaller payers to cover therapies they could not otherwise sustain; but voluntary participation, high premiums, the exclusion of high-risk patients, and narrow therapy lists can cause unequal access. It is therefore most equity-supportive where participation is broad, coverage rules are standardized, and patient protections guard against exclusion and delay.

On balance, reinsurance allows a payer to transfer the risk of a rare, multimillion-dollar claim to a third party for a premium, capping exposure, but does not affect the price or volume of treatment. For most publicly financed systems it is largely irrelevant: a single national payer is in effect backstopped by the government and can absorb such claims without external insurance.

3.6 RISK POOLS FOR HIGH-COST TREATMENTS

High-cost risk pool (HCRP) financing spreads the cost of eligible high-cost therapies across a large group of policyholders. Our analysis focuses on pools dedicated to very high-cost therapies such as CGTs, which present two problems that ordinary insurance pooling handles poorly: the sheer size of a single treatment cost; and the difficulty of forecasting how many patients will be eligible, given the small numbers involved. Together, these issues lead insurers to restrict or exclude coverage. A dedicated ring-fenced pool, funded by a fixed share or amount of each premium removes the uncertainty of a single large payment for any one insurer and, as the pooled population grows, it improves the accuracy of patient-volume estimates. The same benefit applies to patients, who may otherwise face high deductibles or co-payments, or lack coverage altogether, in the absence of an HCRP.

Embarc Benefit Protection, operated by Cigna Healthcare in the US, illustrates the model: health plans pay a fixed per-member-per-month fee for full coverage of an eligible gene therapy for their policyholders, with no out-of-pocket exposure once prior-authorization criteria are met. The funding pool does not, however, cover administration costs, which fall to the member's plan and may carry a co-payment or deductible amount.[42,43]



By design, pooling redistributes cost rather than reducing it: it converts an unaffordable individual claim into an affordable per-member premium. It improves access, but does not lower the negotiated price or treatment volume.

By design, pooling redistributes cost rather than reducing it: it converts an unaffordable individual claim into an affordable per-member premium. It improves access, but does not lower the negotiated price or treatment volume. It is also neutral on clinical uncertainty, transferring financial risk to the pool without mitigating the risk that long-term benefits fail to materialize.

As with reinsurance, the relevance of a dedicated HCRP depends on how a health system is organized. Risk-pooling is already in place across most publicly funded systems with mandatory contributions: most directly in single-payer systems such as Italy and the UK, where the national payer pools risk across the whole population; but also in managed-competition markets such as the Netherlands and Switzerland, whose risk-equalization provisions compensate sickness funds for high-use patients. A purpose-built HCRP therefore adds little in these settings. The operational question arises most sharply in the private insurance market, where feasibility depends on whether: the pool is large enough to absorb the claims; the benefit design admits the therapy; and the plan can manage prior authorization, utilization review, and case management for a small number of high-cost cases.

Where these conditions are met, acceptability is generally positive, since risk shifts from policyholders and insurers to the pool. Manufacturers also benefit: pools that include CGTs convert an unaffordable list price into a covered benefit, expanding the effective market and supporting incentives for innovation. On equity, pools support equitable access within the population they cover, removing the affordability barrier and applying standardized clinical criteria. Their limits are external, as access depends on whether a patient's employer participates in a pool.

3.7 PRICE-VOLUME AGREEMENTS

Price-volume agreements (PVAs) are a common managed-entry tool used to control expenditure on high-cost or high-volume therapies. Under a PVA, the payer and manufacturer set a volume threshold: if total units sold in a period exceed it, the manufacturer provides a rebate or price reduction on the excess. The effective price per patient declines as more patients are treated. Unlike flat pricing, PVAs allow payers to commit to covering more patients while keeping some budget control, since any increase in demand is partly subsidized by the manufacturer. In Spain, Zolgensma was funded from December 2021 under a mixed arrangement that combined a volume-based agreement with an outcomes-based agreement monitored through the Spanish National Health System's VALTERMED registry. The Ministry of Health published a maximum price of €1.945 million per patient and estimated about 30 patients a year; public procurement records subsequently showed hospitals paying about €1.34 million per treatment.[37,44]



Unlike flat pricing, PVAs allow payers to commit to covering more patients while keeping some budget control, since any increase in demand is partly subsidized by the manufacturer.

PVAs act on price and expenditure rather than on volume. They oblige manufacturers to lower effective prices when usage exceeds pre-agreed levels, which delivers cost savings when treatment volumes increase. The net effect on total cost depends on the balance between volume growth and the reduced price. PVAs do not address clinical uncertainty. For these reasons, PVAs are most effective for high-cost drugs with a demonstrated clinical benefit and relatively large eligible populations, as with Sovaldi in Italy.[57] For manufacturers, PVAs are slightly positive. They preserve the upfront list price and market access while only modestly curbing revenue. A high initial price can be set for units up to the threshold, while rebates, which are frequently confidential, influence the financial return gained from widespread use. PVAs may lead to faster patient access to innovative medicines by improving their affordability to payers.

Therefore, in the context of CGTs, PVAs are best suited to conditions with a measurable and reasonably predictable annual patient population, where payers can set a credible volume threshold. They are less suitable for ultra-rare conditions, where year-on-year incidence is too small and uncertain to forecast: in effect, PVAs require a minimum viable threshold to function.

3.8 EXPENDITURE CAPS

Expenditure caps set a predefined ceiling on spending over a fixed period, with any overspend recovered from the manufacturer through paybacks.[58] They can apply to the entire pharmaceutical budget, to a therapeutic class, or to an individual product.

Italy presents a clear real-world example. National pharmaceutical spending is subject to statutory ceilings expressed as a share of total health expenditure – about 15 percent, with specific sub-caps applied to different subcategories, such as direct purchases of medicines in hospitals.[59] When thresholds are exceeded, a payback is applied proportionately to the respective market share of manufacturers.

Caps can also operate at product level. For Luxturna, AIFA set an ex-factory price of €360,000 per vial (one eye), subject to a confidential discount. An expenditure ceiling of €21.6 million is set over 24 months, and spending above the ceiling is recovered from the manufacturer through payback.[37]

Assuming that manufacturers continue to provide the product for free once the cap is reached, expenditure caps act on price rather than number of patients treated. The per-unit price is unchanged up to the spending limit. Beyond it, the manufacturer rebates all of the excess. Therefore, the price per patient declines as more patients are treated, even though the list price is unchanged. An expenditure cap limits only spending: once the ceiling is reached, the cost of further patients is largely borne by the manufacturer, so there is no budget reason to restrict access and volume may even rise. This would represent a challenge for CGTs due to their high average and marginal costs of production, which make supplying patients beyond the cap at no charge far less sustainable than for conventional drugs.

Spending caps do not address uncertainty on clinical benefits. Operationally, macro caps are simple to run and acceptable to payers, relying on existing expenditure monitoring. Product-level caps require monitoring of expenditure or use against the agreed ceiling, alongside administrative mechanisms to enforce payback obligations. The main trade-off is for innovation, given that the effective price falls as take-up grows, potentially deterring future investments. On equity, the same loosening of the budget constraint can widen access by removing a budget-driven reason to restrict treatment. The extent of this benefit is contingent on the contractual provisions governing supply beyond the agreed ceiling.

3.9 SUBSCRIPTIONS

Under a subscription, the manufacturer receives a fixed fee for the supply of a therapy. This decouples the payer's total cost from the volume of treatment delivered.[60] Paying a flat fee independent of sales volume, rather than per unit, provides an incentive for companies to develop medicines with potentially low sales. To date, the model has mostly been implemented to fund novel antibiotics that address antimicrobial resistance. In June 2022, National Health Service (NHS) England contracted the first two such drugs – Shionogi's cefiderocol and Pfizer's ceftazidime–avibactam – committing to pay each manufacturer up to £10 million a year under initial three-year agreements extendable to 10 years, irrespective of sales.[61]

This mechanism is largely inapplicable to CGTs. A successful subscription model depends on a low marginal cost of production: once the fee is paid, additional treatment courses can be released at negligible cost, which is what allows manufacturers to enter into such agreements. CGTs invert this premise. Each course is complex and expensive to manufacture, so supplying an open-ended number of patients for a fixed fee would expose the manufacturer to substantial costs. This is an arrangement that no manufacturer could reasonably be expected to accept – and subscriptions were designed to address a different problem. This payment mechanism was developed in the antimicrobial market to delink revenue from volume to sustain the supply of drugs whose use must be deliberately restricted to limit resistance. A guaranteed minimum return removes any incentive to promote sales since revenue is protected when volumes are low. That rationale cannot be extrapolated to CGTs. Therefore, subscriptions are likely irrelevant for the funding of these therapies.

3.10 ADVANCE PURCHASE AGREEMENTS

Advance purchase agreements (APAs) are pre-treatment procurement arrangements where a purchaser commits to buying a product that is not yet on the market at a predefined price, quantity or both, depending on the contract. APAs reduce demand risk for the company and secure provision for the purchaser.[62] Where the product is still under development, such commitments are typically conditional on regulatory authorization, development milestones, technical criteria, or a predefined public health emergency. Historically, APAs have been deployed to purchase vaccines. Notable examples are the US and EU's APAs for the Pfizer-BioNTech COVID-19 vaccine candidate. In July 2020, the US Government committed about $1.95 billion, under a firm fixed-price agreement, for the manufacture and delivery of 100 million doses, conditional on FDA approval.[63]

APAs are most useful where payers need to secure supply against firm, predictable demand, as in the case of vaccines. A commitment to purchase large volumes enables the manufacturer to scale up production, which tends to lower average production costs, and may compress the time between authorization and availability. This logic holds for the example above, but it does not extend to CGTs for several reasons:

- Take-up is difficult to model as epidemiological data for CGTs are often uncertain (see Section 1).
- CGTs typically rely on complex, bespoke manufacturing processes where the economics may differ from biologics or small-molecule medicines.
- The bespoke nature of some CGTs makes stockpiling impossible. This implies that any committed but unused treatment yet to be honored under an APA could cost the payer several hundred thousand dollars.

Taken together, these factors make APAs unlikely to succeed in the context of CGTs, and they are not explored further here.

3.11 HEALTH IMPACT BONDS

Health impact bonds (HIBs) are population-level outcomes-based agreements where external investors provide upfront capital for a health intervention, and the public payer repays them only if predefined outcomes are achieved.[64] HIBs work as follows:

- A payer defines a target population and the desired outcomes.
- Investors provide the implementation capital via an intermediary, earning a return only if those outcomes are met.
- A service provider delivers the intervention.
- An independent adjudicator determines whether the outcomes for payment have been achieved.

In practice, HIBs have mostly funded prevention campaigns that avert chronic disease and deliver long-term savings, rather than a pharmaceutical intervention. The following example illustrates such an arrangement.

Region Stockholm issued an HIB to finance a type 2 diabetes prevention program for people with prediabetes. The HIB had a maximum value of SEK 30 million (about $3.5 million) and combined a five-year zero-coupon structure with an outcome-linked return based on cost savings. The intervention was backed by private financial institutions, and delivered via a digital platform and health coaches by Health Integrator, a service supported by the European Institute of Innovation & Technology. The intervention targeted prediabetic patients, and the bond paid out if participants met a series of indicators consistent with a reduced risk of developing type 2 diabetes.[65] More than 50 percent of the target population moved out of the diabetes risk zone, improved their HbA1c (blood sugar) levels, and faced a lower risk of developing type 2 diabetes than those who did not receive the intervention.[66]

Due to the design, the best candidates for HIBs are programs with large upfront costs, those that serve large populations, and those supported by strong evidence of clinical benefit.[64] For CGTs, however, each of these three conditions is called into question. On cost, although CGTs are expensive per patient, a single treatment is unlikely to justify an HIB on its own. Contracts would probably need to span multiple patients, conditions and therapies, creating significant administrative complexity. HIBs also depend on predefined outcomes that can only be set reliably where the evidentiary package is strong at launch, which is often not the case for CGTs. Large populations are also typically needed to achieve statistically meaningful results and to reduce heterogeneity in treatment response. This aspect would also be problematic for CGTs, where response varies widely and patient numbers are small.

Conclusion on the 11 payments models

The payment models assessed above offer different ways of addressing the challenges that policymakers face when allocating resources to pharmaceuticals. With its focus on CGTs, our assessment indicates that PVAs and expenditure caps are the only mechanisms that may reduce or contain total expenditure. The remaining mechanisms primarily redistribute financial risk, spread expenditure over time or support evidence generation, without directly reducing total spending.

3.12 NON-FINANCIAL ACCESS MECHANISMS

The mechanisms that follow sit outside the payment-model framework considered above. Hospital exemption, voluntary licensing and joint procurement instead act on the conditions under which therapies are produced, supplied or purchased. Therefore, these non-financial mechanisms may complement conventional reimbursement where these are insufficient on their own to secure access.

Hospital exemption

The hospital exemption is a provision that allows a hospital to manufacture and administer a CGT on a non-routine basis within its own establishment, without applying for centralized marketing authorization. In Europe, the mechanism operates within a common EU-level legal framework, but its implementation varies considerably across countries.[67] A more harmonized framework for hospital exemption across Member States is expected under the revised EU Pharmaceutical Package which was adopted in September 2026 (pending the European Parliament's final vote). This would maintain the existing hospital exemption eligibility conditions while introducing more explicit requirements for national authorization, annual data reporting and regulatory oversight.[68,69] For example, in Spain, advanced therapy medicinal products (ATMPs) may be authorized for use within a designated hospital, which remains responsible for the product, its administration and safety.[70] Authorization requires manufacturing standards equivalent to those for industrial medicines, plus safety and efficacy data. Similar non-industrial, hospital-based regulatory pathways are also emerging outside Europe. In Chile, the 2026 regulatory framework for advanced therapy medicines recognizes a non-industrial route for hospital-based production alongside the conventional industrial pathway.[67]

The most prominent Spanish example is varnimcabtagene autoleucel (ARI-0001), an academic CD19 marker CAR-T therapy developed by the Hospital Clínic Barcelona for adults with relapsed or refractory acute lymphoblastic leukemia. ARI-0001 builds on A3B1, a monoclonal antibody developed at the Hospital Clínic more than 30 years earlier. Its development was enabled through a combination of public, academic and civil society support. For ARI-0001, the price under the hospital exemption pathway is reported to be roughly a quarter to a third that of commercial CAR-T products available in Spain.[71] However, the scale of any saving will depend on the product, the manufacturing model and the institutional setting.

The Spanish case illustrates that the successful implementation of the hospital exemption relies on a wider institutional ecosystem. Spain combines a dedicated legal route, robust regulatory and oversight capabilities, hospital-based manufacturing compliant with good manufacturing practice (GMP), specialized clinical teams and public or philanthropic support for academic development. Effective implementation appears to depend on four requirements:

- Strong legal and regulatory capabilities
- GMP-compliant manufacturing
- Clinical expertise and specialized care teams to administer the therapies
- Highly sophisticated research teams and institutions that have adequate long-term funding.

These four requirements are demanding, and few settings satisfy them as fully as Spain.

Also, even in high-income countries (HICs), not every commercially available CGT has an academic equivalent developed at a research hub. Where one does exist, manufacturing capacity is frequently too limited to meet national demand. These same constraints apply to low- and middle-income countries (LMICs), which may lack the legal framework required to implement the hospital exemption.



Even in high-income countries, not every commercially available CGT has an academic equivalent developed at a research hub. Where one does exist, manufacturing capacity is frequently too limited to meet national demand.

Clinical capacity is a further constraint, since highly trained personnel are needed to prepare and administer the therapy and to manage the recovery phase. Where the latter two barriers can be mitigated, however, technology transfer from willing research hubs in HICs to LMICs could potentially open access to high-cost CGTs at a substantially reduced cost, albeit likely on a small scale. Such an arrangement would, of course, depend on the willingness of partner institutions to share the technology. More broadly, the potential expansion of the hospital exemption needs to be balanced against its original role as an exceptional, non-routine pathway. As the number of centrally authorized ATMPs increases, greater consistency in how the exemption is interpreted and applied across Member States may become increasingly important, particularly around the meaning of 'non-routine' use.

Voluntary licensing

Voluntary licenses are contractual arrangements where a patent holder authorizes third-party manufacturers to produce, register and supply a branded product under license in defined territories. Licenses may be negotiated bilaterally or through an intermediary, and they vary in territorial scope, sublicensing rights, royalties and access conditions.[72] Unlike the traditional payment models described above, voluntary licenses work by transferring patent rights voluntarily, which widens patient access in countries that could not afford a branded drug at full price. Given their importance in LMICs, we assess their potential for the provision of CGTs.

The Medicines Patent Pool is a non-profit facilitator that negotiates non-exclusive licenses from originator companies and sub-licenses them to several generic manufacturers. These manufacturers then supply the medicines, sometimes in exchange for royalties, across a defined set of developing countries.[73] The Medicines Patent Pool model is illustrated by the voluntary license that ViiV Healthcare issued for long-acting cabotegravir, initially (July 2022) for HIV pre-exposure prophylaxis in 90 countries and, from July 2025, for treatment in 133 countries.[74]

The feasibility of such arrangements, however, depends on the nature of the therapy. Voluntary licenses are most effective when the production process is straightforward, allowing several generic manufacturers to step in and supply the drugs. This is not the case for CGTs, as explained in Section 1. For example, the manufacturing of CAR-T

therapies is complex, tailored to each patient, and expensive on a per-patient basis. Given high fixed costs, it is difficult to imagine a generic manufacturer investing in the manufacture of CGTs at low costs for sales in LMICs.

Beyond cost, the complexity of the manufacturing process is also very high. Gilead-Kite, the manufacturer of Yescarta and Tecartus, has only three facilities licensed to produce its therapies: in Southern California, Maryland and Amsterdam.[75] This represents an expansion from the late 2010s, when CAR-Ts were first introduced and both Kite and Novartis encountered capacity and manufacturing constraints.[76] These constraints point to the substantial technical, regulatory and supply-chain requirements involved in producing these therapies at scale, all of which may be difficult to achieve without direct technology transfers from the originator. Such transfers can involve the originator passing manufacturing know-how to a third party, usually as part of a voluntary license to manufacture complex drugs.

The mRNA Technology Transfer Programme is an example of such transfer, although it did not involve the originator company. It centers on a hub in South Africa, led by the pharmaceutical company Afrigen, which trains personnel and transfers the technology to enable mRNA vaccine production across sites in LMICs.[74] During the COVID-19 pandemic, the program had expected Moderna or Pfizer-BioNTech to share the vaccine technology under a voluntary license, but no such license was issued. The hub therefore relied on publicly available information to replicate the mRNA technology. Although this was possible because Moderna had pledged not to enforce its patent rights during the pandemic, it slowed development and manufacturing. A direct technology transfer could have established manufacturing capacity in roughly six months; without it, producing a ready-to-use vaccine would take at least two and a half years.[75,76] As a result, the vaccine would have arrived too late to contribute meaningfully to the pandemic response. Therefore, the focus shifted to providing long-term mRNA vaccine capacity building instead of COVID-19 pandemic response.

This experience shows that originators may resist technology transfers, even during pandemics, to protect their intellectual property and prevent leakages. The lack of spare production capacity to implement voluntary licenses and the likely reluctance of originators to share the complex, sensitive trade secrets underpinning CGT manufacturing make it unlikely that voluntary licenses will contribute meaningfully to improved access to CGTs.

Joint procurement

Joint procurement refers to a cross-country purchasing arrangement where participating authorities pool demand and contract under shared terms, rather than relying solely on separate national processes.[77] In practice, such arrangements have mainly been used where demand can be planned in advance, products are sufficiently standardized, and countries can agree common tendering and contracting rules. Examples include Nordic joint tenders where Denmark, Iceland and Norway have pooled procurement for selected hospital medicines.[78,79] Beyond Europe, the Pan American Health Organization's Regional Revolving Funds provide a long-standing example of pooled procurement, where participating countries co-ordinate demand through a regional mechanism to improve access, affordability and supply predictability for vaccines, essential medicines and strategic health supplies.[80]

For CGTs, joint procurement is likely to be most valuable for small markets, where domestic demand is insufficient to justify a commercial decision to launch. Aggregating demand across several jurisdictions could create a larger combined market with stronger, more predictable demand, thereby strengthening the commercial case for launch. Joint procurement also has the distinct advantage of increasing the bargaining power of smaller payers by leveraging greater purchase volumes. Its feasibility would depend on prior agreement on the eligible population, expected volume, allocation across participating countries, and rules for managing deviations between expected and actual demand. Joint procurement also requires harmonized or compatible regulatory standards and procurement rules for countries joining the procurement pool. At EU level, the feasibility of such approaches may be strengthened by the proposed Critical Medicines Act, which would provide a framework for voluntary collaborative procurement between Member States, and would extend these provisions to orphan medicines.[81] By enabling countries to aggregate demand and strengthen their collective purchasing position, the framework could be particularly relevant to therapies serving small patient populations. Although it does not resolve value-for-money and affordability concerns for payers, the greater commercial attractiveness of a larger combined market may offer advantages for countries with small markets in terms of access.

A further consideration is the cost of the appraisal process itself. Health technology appraisal is time-consuming and resource-intensive. Also, in very rare diseases, the necessary expertise may be scarce, a constraint felt most acutely by smaller countries. Joint initiatives offer a partial remedy. The Beneluxa Initiative, comprising Belgium, the Netherlands, Luxembourg, Austria and Ireland, seeks to streamline the assessment of innovative products and negotiate prices jointly for selected therapies. The Initiative has already applied price negotiations to CGT: in 2021, Belgium, Ireland and the Netherlands concluded a joint price negotiation for Zolgensma.[80] Such arrangements are likely to be relevant to CGTs, and particularly to securing access in smaller countries. Qatar presents another setting where a similar arrangement could potentially be highly beneficial through a partnership with the Gulf Health Council. However, the scalability of such programs is limited, since participating countries need to be reasonably similar in population size and ability to pay for a single negotiated price to be acceptable to all countries.

SECTION 4. THE AVAILABILITY OF CELL AND GENE THERAPIES

GLOBAL ACCESS TO CGTS DOES NOT REFLECT THE TRUE BURDEN OF DISEASE

While industry typically launches products in developed countries that have the ability to pay, many CGTs remain unavailable in low- and middle-income countries (LMICs). However, this does not mean that LMICs do not have a high burden of disease; for some conditions, the disease burden in LMICs is disproportionately high.

This pattern is clearest for the hemoglobinopathies. These inherited disorders of hemoglobin are concentrated in parts of Africa, Asia and the Middle East, which account for a disproportionately high share of affected births worldwide. The contrast is particularly marked for sickle cell disease (SCD). In 2021, an estimated 7.7 million people were living with the disease globally, including 5.68 million in Sub-Saharan Africa. The region also accounted for 405,000 affected births, equivalent to 79 percent of global incidence at birth.[82] By comparison, about 100,000 people are living with SCD in the US, and an estimated 28,821 to 48,928 across 12 EU Member States.[83] This uneven distribution extends to other inherited conditions, such as beta thalassemia, which affects about 68,000 children each year, with the highest mutation prevalence reported in Mediterranean, Middle Eastern, Southeast Asian and Central Asian populations.[84]

The burden of advanced hematological cancers in LMICs is harder to quantify. Accurate data are scarce, particularly for the indications targeted by CAR-Ts, which are typically second- or third-line therapies with few eligible patients in any single country. The broader oncology burden is growing fastest in lower-resource settings. GLOBOCAN-based projections suggest that cancer incidence and mortality will rise disproportionately in developing countries over the coming decades. More recent estimates point to an increase of 142 percent in cases and 146 percent in deaths in low Human Development Index (HDI) countries between 2022 and 2050, against rises of about 42 percent and 57 percent in very-high-HDI countries.[85]

MANY CGTS REQUIRE ROBUST HEALTH SYSTEM INFRASTRUCTURE TO REACH PATIENTS

Within the limited scope of this report, a detailed assessment of system readiness by country, or even by region, was not feasible. Nonetheless, a number of general observations can be made.

First, early diagnosis through newborn screening is needed for the effective use of some CGTs, such as Zolgensma. Yet the availability of such screening and the range of conditions it covers are uneven and heavily concentrated in HICs, and newborn screening is unavailable in many LMICs. The situation is the same for cancer screening.[86]

Second, the availability of well-equipped treatment hubs, staffed by a highly specialized workforce who are able to manage severe adverse events, represents a significant constraint for LMICs. HICs generally have advanced university centers equipped to meet these requirements. Some upper-middle-income countries (UMICs), such as China, Brazil or Türkiye, also have hospital centers with comparable capabilities. In LMICs, however, such capacity is rarely available. The following example illustrates why. A clinic delivering gene therapy for SCD, for instance, must be equipped to measure hemoglobin levels and the resulting red blood cell function, and to manage vaso-occlusive crises (where the crescent-shaped blood cells block normal flow). Clinics also need to be able to bring patients within the published clinical parameters required before blood stem cells can be collected and gene therapy initiated and administered. Each of these activities depends on a combination of clinical protocols, trained staff, medicines, diagnostics, reagents, monitoring equipment, and shared data elements and platforms that enable care to be monitored and adjusted in real time. In many LMICs, access to these underlying capabilities remains limited.[87]

Third, the pre-conditioning regimens required before some CGTs are administered, particularly those for hematological conditions, may be unavailable in LMICs. Where they do exist, they tend to be concentrated in urban centers.[86] Access to these treatments is expected to be much greater in UMICs and HICs.

LACK OF CGT AVAILABILITY IN LOW- AND MIDDLE-INCOME COUNTRIES

CGTs are largely unavailable in low- and middle-income countries, as companies do not launch them and payers do not reimburse them.

Manufacturers' appetite to launch in any given country is difficult to gauge, as these decisions rest on commercial and strategic considerations that are complex and largely confidential. This includes the sequencing of future product launches, international reference pricing, and a health system's willingness to pay. We therefore refrain from broad characterizations, and instead draw tentative conclusions from the empirical data available on drug availability. It should be noted that regulatory approval, where secured, does not necessarily translate into patient access through public coverage.

This situation is exemplified in UMICs, where CGTs may hold a marketing authorization yet lack public funding. In Brazil, for instance, nine CGTs had been approved up to 2024, but only Zolgensma was publicly reimbursed.[86] Interestingly, manufacturers appear not to have sought public reimbursement for most of these therapies, with only Luxturna having been formally evaluated and rejected. Likewise, as of 2025, no CGT had been included in Mexico's public reimbursement schemes. In this case, it is because no CAR-T or gene therapy has yet obtained full marketing authorization in the country.[87] This points to a challenge likely to be common across the larger UMICs: countries that possess the infrastructure and clinical expertise to deliver CGTs, but are unable to meet the high prices required for these therapies.

The picture in LMICs appears different, with both regulatory approval and reimbursement absent. As of 2021, only three of the 20 gene therapies approved worldwide had secured approval in any LMIC.[88] Casgevy, a CGT that has demonstrated substantial clinical benefit in patients with SCD and transfusion-dependent beta

thalassemia, was first approved in the UK in 2023. While SCD is among the conditions with the widest mismatch between unmet need and therapy availability, Casgevy is not approved in any LMIC.[89] The same is true of Lyfgenia, a further SCD therapy currently approved only in the US. This lack of patient access is especially concerning given the high disease burden of these conditions in some LMICs, which gives rise to high unmet need. Similarly, as of early 2026, CAR-Ts were not yet approved in Africa, although the US Federal Government was exploring their adoption.[90] Whether the principal barrier to access is limited regulatory, infrastructural or clinical capacity, or an inability to meet the price of these therapies, is difficult to establish conclusively. In all likelihood, it is a combination of these factors that contributes to the limited access in LMICs.

THE REIMBURSEMENT OF CGTS AS AN INSTRUMENT OF INDUSTRIAL POLICY

In recent years, policymakers have increasingly framed biotechnology as a strategic sector. In Europe, the Draghi report on EU competitiveness and the proposed European Biotech Act highlight the strategic importance of biotechnology and advanced therapies. They call for stronger research, development and manufacturing capacity, and for faster translation of scientific advances into products that reach the market.[91,92] Within this interpretation framework, coverage decisions may play a role in research and development (R&D) investments in individual countries, among other important determinants of R&D location choices.

While we recognize these considerations, the aim of this report is to assess payment models that help payers achieve value for money and affordability. The wider effects on industrial competitiveness are therefore not considered further in this analysis.

SECTION 5. FROM THEORY TO PRACTICE: A DECISION FRAMEWORK

Section 3 assessed each payment model in isolation and found that none, on its own, resolves the challenges posed by CGTs. This section translates that assessment into a decision framework for policymakers to use to select payment models across health system archetypes. The framework is depicted in Figure 7. The framework proceeds in three steps. Step 1 confirms that the delivery prerequisites set out in sections 1 and 4 are in place. Where they are not, the payment model is premature and delivery barriers should be addressed first.

Step 2 identifies the challenge a therapy presents and selects the corresponding tool through a single key question.

- The first challenge is clinical uncertainty over the magnitude or durability of benefit. Where the payer is willing and able to track each patient's outcome within a contractable horizon and link payment to it, outcomes-based payments, including warranties, are appropriate. Where payers cannot do so, a simple confidential discount (reflecting the level of uncertainty over clinical benefit) is a realistic alternative.
- The second challenge is uncertainty over the eligible population and take-up. Price-volume agreements suit therapies whose annual volumes can be reliably forecast. Expenditure caps suit those whose volumes cannot be forecast, or where total exposure is the main concern.
- The third challenge is the exposure of small risk pools to rare, very high-cost claims. This arises most acutely in private multipayer insurance, but also in publicly financed systems where regional, state or hospital budgets bear the cost, since only national single payers pool risk across the whole population. High-cost risk pools address exposure shared by many small payers. Reinsurance addresses exposure specific to individual payers.

Step 3 matches these tools to five payer groups, defined by income level, payer size and whether coverage is public or private. All public payers share concerns over evidentiary uncertainty at launch, the opportunity cost of coverage and budget impact. The selections therefore reflect each group's specific circumstances. Some mechanisms may not be applicable in certain contexts, while others may be combined to address different policy objectives.

- **High-income large public payers** have large populations and budgets, established registries and, most often, health technology assessment HTA bodies. They also have a single contracting authority, although their willingness to run product-level contracts varies.
- **High-income small public payers** have small national cohorts that are easy to follow, advanced health systems and potentially high willingness to pay, but limited bargaining power, and small, variable treatment volumes.

- **Upper-middle-income large public payers** have large eligible populations and enough scale to invest in infrastructure, but tighter fiscal constraints and less predictable take-up.
- **Upper-middle-income small public payers** have small markets, limited administrative capacity and limited scope to develop patient tracking systems.
- **Private multipayer insurers** operate many small, fragmented risk pools, with frequent patient movement between plans. They do not have a single purchaser negotiating on behalf of all insurers.

Figure 7. Decision framework for selecting financing mechanisms for CGTs

STEP 1: CONFIRM THAT THE THERAPY CAN BE DELIVERED

Prerequisites	If not in place, payment model choice is premature
Authorization, specialized centers, conditioning and toxicity management, trained workforce, cold chain (temperature-controlled supply chain)	Build capacity first, supported by hospital exemption, technology transfer or joint procurement

STEP 2: FOR EACH CHALLENGE THAT APPLIES, SELECT THE APPROPRIATE TOOL

Not every therapy raises all three challenges, so select a tool only for those that apply.

A. Clinical uncertainty over the magnitude or durability of benefit
Key question: Is the payer willing and able to track each patient's outcome within a contractable horizon and link payment to it?
Answer: Yes
Outcomes-based payment How it works: Part of the price is paid, withheld or rebated per patient Requirements: Patient-level follow-up and authority to withhold or reclaim payment; an endpoint observable within a reasonable timeframe to enable contracting; pre-agreed rules for missing or disputed outcomes
Answer: No
Simple discount How it works: A confidential price discount that reflects the level of uncertainty over clinical benefit Requirements: Contracting capacity only. However, an HTA may strengthen the payer in the negotiations

B. Budget uncertainty over the eligible population and take-up

Key question: Can annual treated volumes be reliably forecast?

Answer: Yes

Price-volume payment
How it works: Effective price falls once volume exceeds an agreed threshold

Requirements: A credible threshold and volume monitoring

Answer: No, or total exposure is the main concern

Expenditure cap
How it works: After an agreed ceiling is reached, the manufacturer keeps supplying the therapy but is subject to a payback

Requirements: Patient counting, expenditure monitoring, enforcement of payback obligations

C. Small risk pool exposed to rare, very high-cost claims

Applies to multipayer insurance and single payers where no centralized risk pooling exists.

Key question: Is the exposure shared by many small payers, or is it specific to individual payers?

Answer: Shared by many small payers

High-cost risk pool or outlier fund
How it works: A ring-fenced fund, financed per member and covering eligible claims

Requirements: A regulator or central fund and standard eligibility rules

Answer: Specific to individual payers

Reinsurance
How it works: Claims above an attachment point are transferred to a reinsurer for a premium

Requirements: Reliable insurance markets, as well as legal and claims systems

STEP 3: MATCH THE TOOL TO THE PAYER GROUP

Payer group	A. Clinical uncertainty	B. Budget uncertainty	C. Small risk pool
High-income large public payers e.g. England, France, Italy, Japan, Germany, Saudi Arabia, Chile Specific circumstances: Established registries and contracting capacity, though willingness to use outcomes-based payments varies	**Outcomes-based payment** Registries and developed legal systems allow patient-level outcomes to be tracked and settled nationally	**Price-volume agreement** Eligible populations are large enough for credible volume thresholds	**Not applicable** Risk is pooled nationally and backstopped by the state
High-income small public payers e.g. Qatar (nationals), UAE Specific circumstances: Small cohorts, potentially limited bargaining power compared to larger payers, but potentially high willingness to pay	**Outcomes-based payment** Small-scale and advanced health systems allow for individual patient tracking	**Simple discount** Volumes likely too small and variable for credible PVA thresholds or expenditure caps	
Upper-middle-income large public payers e.g. Brazil, Türkiye, Argentina Specific circumstances: Tighter fiscal constraints requiring more selective prioritization	**Outcomes-based payment** Scale can justify building outcome tracking. Simple discount as second best where contracting capacity is lacking	**Price-volume agreement** Eligible populations are large enough for credible volume thresholds, although take-up may be unpredictable	
Upper-middle-income small public payers e.g. Serbia, Montenegro Specific circumstances: Small market and less developed administrative capacity	**Simple discount** Patient tracking systems are unlikely to be in place, so payment cannot be linked to individual outcomes	**Simple discount** Volumes are too small and variable for credible PVA thresholds or expenditure caps	

Payer group	A. Clinical uncertainty	B. Budget uncertainty	C. Small risk pool
Private multipayer insurance e.g. US commercial plans, Gulf expatriate schemes Specific circumstances: Patients move between insurers and pools are fragmented	**Outcomes-based payment (including warranties)** Patient tracking is feasible for sophisticated insurers; however, rebates are difficult to administer when patients change insurer	**Not applicable** PVAs and expenditure caps are uncommon in private insurance, where coverage restrictions are used instead	**Risk pools and reinsurance** Preferred, as it spreads risk across all plans under common rules. Reinsurance can protect individual plans where no pool exists

Selections reflect the authors' assessment.

Notes: Small risk pool: Where both options to address small risk pools are feasible, establishing a high-cost risk pool or outlier fund is preferred to reinsurance because it spreads risk across all payers under common rules, rather than leaving cover to each payer's voluntary purchase.

SECTION 6. PRACTICAL APPLICATION OF THE FRAMEWORK TO QATAR

This brief case study applies the decision framework to Qatar, a small high-income country. It focuses on the universal coverage that Qatar provides to its citizens, rather than on the mandatory private insurance market covering the resident expatriate population. Access to CGTs for expatriates depends on the benefits defined under the mandatory health insurance scheme established by Law No. 22 of 2021, which is being implemented in phases.[93,94]

Delivering CGTs requires specialized treatment centers able to manage conditioning and severe toxicities, a trained multidisciplinary workforce and reliable cold-chain (temperature-controlled supply chain) logistics (see Section 1). Outcomes-based payment, the option Figure 7 identifies for this payer type, further requires an outcomes registry linked to reimbursement, and state authorities able to disburse or withhold payment depending on the achieved outcomes. While a small population and geographical area do not create these capabilities themselves, they can make them easier to build, particularly if adequate funding is available. Expertise and infrastructure can be concentrated in a small number of specialist centers accessible to most of the population. Also, the number of treated patients is small enough for individual follow-up to be manageable once a registry is in place. However, one downside of a small population is that take-up is difficult to forecast, with large fluctuations from year to year possible. Consequently, price-volume agreements and expenditure caps are difficult to apply credibly.

We therefore propose a phased approach for the implementation of CGTs in Qatar.

1. A small number of specialist centers for the administration of CGTs should be designated. Their technical capabilities to deliver these innovative therapies should be evaluated and, where not available, a credible path toward their implementation should be outlined. A national outcomes registry also needs to be in place prior to wide CGT implementation.

2. A cumulative multiyear budget impact assessment based on a range of scenarios should be carried out in conjunction with the budget holder.

3. While the registry matures, access could be granted on case-by-case basis through warranties or staged payments administered by the manufacturer.

4. Qatar's negotiating position should be strengthened by the project to establish a national health technology assessment (HTA) unit that the Ministry of Public Health launched in 2025 under the Qatar National Health Strategy 2024–2030. The HTA unit will be able to appraise CGTs and inform price negotiations on the basis of an explicit value assessment, thereby partly offsetting the limited leverage of a small market.[95]

5. Explicit rules should govern treatment abroad, expatriate coverage and long-term follow-up. Expenditure caps and price-volume agreements could be revisited once treated volumes justify them.

SECTION 7. CONCLUSIONS AND RECOMMENDATIONS

High-income countries (HICs), upper-middle-income countries (UMICs), low-income, and lower-middle-income countries face markedly different challenges in providing patient access to cell and gene therapies (CGTs). Therefore, different types of countries should pursue different strategies. HICs generally possess the resources to meet the high prices these therapies command. Even so, the ability to pay does not establish value for money. As coverage expands, payment models and the obligations they create should be considered within a medium-term expenditure framework, particularly where financial obligations extend across budget periods. HIC payers should concentrate on securing value for money and affordability by combining payment models according to the challenge each therapy presents and the features of their own system, (as set out in the decision framework in Section 5).

UMICs are unlikely to command the same resources for CGTs as HICs. Where the necessary clinical and logistical prerequisites are met, however, they may be able to reimburse a subset of these therapies. Doing so entails sharper trade-offs than those faced by HICs, and a correspondingly greater emphasis on value for money and affordability. UMICs may draw on the payment models identified for large and small upper-middle-income payers in Section 5. But these countries may apply considerably more stringent value-for-money and affordability tests, so that the larger health gains achievable through more cost-effective treatments are not displaced. This may also require appraisal and coverage criteria to reflect local budget constraints and the institutional capacity to implement the chosen payment models. In settings without explicit cost-effectiveness thresholds, transparent and consistently applied decision criteria are particularly important.

LMICs are likely to lack several of the prerequisites for reliably implementing CGTs – ranging from infrastructure to a suitably trained workforce. As Step 1 of the decision framework in Section 5 indicates, where these prerequisites are absent, the choice of payment model is premature. Affordability is a further major concern, and one that conventional payment models are unlikely to resolve. Alternative access routes, such as voluntary licensing, technology transfer or hospital exemptions, may offer a partial solution over the longer term, although the institutional and technical conditions required to implement them are still developing in many settings. In the nearer term, strengthening health system capacity and investing in interventions that deliver larger population health gains are likely to represent higher priorities for many LMICs than widespread adoption of high-cost CGTs.

Across all settings, implementing the models preferred in Section 5 depends on two enablers, which we put forward as priority recommendations.

- Payers should invest in outcome registries linked directly to their contracting and reimbursement functions. These registries should be supported by clear data governance arrangements, including responsibilities for data management, procedures for outcome verification and handling missing data, and appropriate safeguards for patient information. Without such registries, outcomes-based

payments cannot be actioned because pre-specified endpoints cannot be tracked for each patient, and payment cannot be withheld or reclaimed when outcomes are not achieved.

- Payers should build the epidemiological and legal expertise that price-volume agreements require: the former to accurately estimate eligible populations and set credible volume thresholds; the latter to define how volumes are verified and rebates enforced. Where this capacity is lacking, it should be developed in dedicated negotiation units or pooled through cross-stakeholder collaborations.

APPENDIX

Table A1. Cell and gene therapies receiving first regulatory authorization between 2016 and 2025

Brand name	International nonproprietary name (INN)	Disease area	Country of first approval	Year of first approval	One-course AND curative/disease altering
Strimvelis	Autologous CD34+ cells transduced with retroviral vector encoding ADA	Immunology	EU	2016	Yes
Zalmoxis	Allogeneic T cells transduced with retroviral vector (HSV-TK Mut2)	Hemato-oncology	EU	2016	No
Invossa-K	Tonogenchoncel-L	Musculoskeletal	South Korea	2017	No
Kymriah	tisagenlecleucel	Hemato-oncology	US	2017	Yes
Luxturna	voretigene neparvovec	Ophthalmology	US	2017	Yes
Yescarta	axicabtagene ciloleucel	Hemato-oncology	US	2017	Yes
Alofisel	darvadstrocel	Gastroenterology	EU	2018	No
Stemirac	Autologous bone-marrow-derived MSCS	Neurology	Japan	2018	No
Collategene	beperminogene perplasmid	Cardiovascular	Japan	2019	No
Zolgensma	onasemnogene abeparvovec	Neurology	US	2019	Yes
Zynteglo	betibeglogene autotemcel	Hematology	EU	2019	Yes
Libmeldy	atidarsagene autotemcel	Neurology	EU	2020	Yes

Brand name	International nonproprietary name (INN)	Disease area	Country of first approval	Year of first approval	One-course AND curative/disease altering
Tecartus	brexucabtagene autoleucel	Hemato-oncology	US	2020	Yes
Abecma	idecabtagene vicleucel	Hemato-oncology	US	2021	Yes
Breyanzi	lisocabtagene maraleucel	Hemato-oncology	US	2021	Yes
Carteyva	relmacabtagene autoleucel	Hemato-oncology	China	2021	Yes
Delytact	teserpaturev	Oncology (solid/other)	Japan	2021	No
Rethymic	Allogeneic processed thymus tissue	Immunology	US	2021	Yes
Skysona	elivaldogene autotemcel	Neurology	EU	2021	Yes
Adstiladrin	nadofaragene firadenovec	Oncology (solid/other)	US	2022	No
Carvykti	ciltacabtagene autoleucel	Hemato-oncology	US	2022	Yes
Ebvallo	tabelecleucel	Hemato-oncology	EU	2022	No
Hemgenix	etranacogene dezaparvovec	Hematology	US	2022	Yes
Roctavian	valoctocogene roxaparvovec	Hematology	EU	2022	Yes
Upstaza	eladocagene exuparvovec	Neurology	EU	2022	Yes
Casgevy	exagamglogene autotemcel	Hematology	UK	2023	Yes
Elevidys	delandistrogene moxeparvovec	Neurology	US	2023	Yes
Fucaso	equecabtagene autoleucel	Hemato-oncology	China	2023	Yes
Lantidra	donislecel	Endocrinology	US	2023	No

Brand name	International nonproprietary name (INN)	Disease area	Country of first approval	Year of first approval	One-course AND curative/disease altering
Lyfgenia	lovotibeglogene autotemcel	Hematology	US	2023	Yes
NexCAR19	actalycabtagene autoleucel	Hemato-oncology	India	2023	Yes
Omisirge	omidubicel	Hematology	US	2023	Yes
Vyjuvek	beremagene geperpavec	Dermatology	US	2023	No
Yuanruida	inaticabtagene autoleucel	Hemato-oncology	China	2023	Yes
Akuugo	vandefitemcel	Neurology	Japan	2024	Yes
Amtagvi	lifileucel	Oncology (solid/other)	US	2024	Yes
Aucatzyl	obecabtagene autoleucel	Hemato-oncology	US	2024	Yes
Beqvez	fidanacogene elaparvovec	Hematology	Canada	2024	Yes
Ryoncil	remestemcel-L	Immunology	US	2024	No
Tecelra	afamitresgene autoleucel	Oncology (solid/other)	US	2024	Yes
Zevor-cel	zevorcabtagene autoleucel	Hemato-oncology	China	2024	Yes
Encelto	revakinagene taroretcel	Ophthalmology	US	2025	Yes
HICARA / Hengkailai	ranicabtagene autoleucel	Hemato-oncology	China	2025	Yes
Itvisma**	onasemnogene abeparvovec-brve	Neurology	US	2025	Yes
Papzimeos	zopapogene imadenovec	Otolaryngology/ respiratory	US	2025	Yes
PuLiDeKai	priscabtagene autoleucel	Hemato-oncology	China	2025	Yes

Brand name	International nonproprietary name (INN)	Disease area	Country of first approval	Year of first approval	One-course AND curative/disease altering
Qartemi	varnimcabtagene autoleucel	Hemato-oncology	India	2025	Yes
Ruibosheng	amimestrocel	Immunology	China	2025	Yes
Waskyra	etuvetidigene autotemcel	Immunology	US	2025	Yes
Zemcelpro	dorocubicel	Hematology	EU	2025	Yes
Zevaskyn	prademagene zamikeracel	Dermatology	US	2025	Yes
XinJiuNing	dalnacogene ponparvovec	Hematology	China	2025	Yes

* Administered as repeated intratumoral doses, up to six doses.

** Same INN as Zolgensma, but different formulation and administration route.

Table A2. One-course potentially curative cell and gene therapies under European Medicines Agency review as of March 2026

This table summarizes candidate therapies identified through an assessment of medicines undergoing evaluation by the European Medicines Agency (EMA) in March 2026. The EMA was used as the sole source because equivalent information on products currently under review by the US Food and Drug Administration and Medicines and Healthcare products Regulatory Agency was not publicly accessible.

Therapies were selected only if they aligned with the study criteria for a potentially curative cell or gene therapy delivered as a single treatment course. Products intended for prevention, vaccination, diagnosis, or routine maintenance treatment were not considered, nor were biosimilars, generic medicines, regulatory variations, manufacturing updates, or changes to the method of administration.

Brand name	Disease area	Indication
Amtagvi (lifileucel)[1]	Oncology (solid/other)	Treatment of adults with unresectable or metastatic melanoma previously treated with PD-1 blocking antibody
Adstiladrin (nadofaragene firadenovec)*	Oncology (solid/other)	Treatment of adults with high-grade, BCG-unresponsive non-muscle invasive bladder cancer (NMIBC)
Papzimeos (zopapogene imadenovec)[1]	Respiratory	Treatment of adults with recurrent respiratory papillomatosis caused by HPV 6/11

* EMA. Medicines for human use under evaluation. 2026. https://www.ema.europa.eu/en/medicines/medicines-human-use-under-evaluation.

Table A3. Cell and gene therapies with recorded expenditure in our sample by year

These tables report the cell and gene therapies (CGTs) for which expenditure was recorded in the study sample, disaggregated by year. It is intended to show the therapies contributing to observed spending over time and reflects only those products for which expenditure was observed in the dataset.

1. Denmark (2019–2024)

Year	No. drugs	Drug names
2019	1	Kymriah
2020	1	Luxturna
2021	4	Holoclar, Kymriah, Luxturna, Zolgensma
2022	3	Kymriah, Luxturna, Zolgensma

Year	No. drugs	Drug names
2023	2	Carvykti, Zolgensma
2024	4	Hemgenix, Kymriah, Yescarta, Zolgensma

2. Italy (2019–2024)

Year	No. drugs	Drug names
2019	2	Holoclar, Kymriah
2020	3	Kymriah, Luxturna, Yescarta
2021	5	Holoclar, Kymriah, Luxturna, Yescarta, Zolgensma
2022	6	Holoclar, Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma
2023	6	Holoclar, Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma
2024	10	Abecma, Breyanzi, Kymriah, Libmeldy, Luxturna, Roctavian, Tecartus, Upstaza, Yescarta, Zolgensma

3. France (2020–2024)

Year	No. drugs	Drug names
2020	5	Kymriah, Luxturna. Tecartus, Yescarta, Zolgensma
2021	6	Abecma, Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma
2022	6	Abecma, Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma
2023	9	Abecma, Breyanzi, Carvykti, Ebvallo, Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma
2024	8	Abecma, Breyanzi, Ebvallo, Kymriah, Luxturna, Tecartus, Yescarta, Zolgensma

4. Belgium (2020–2024)

Year	No. drugs	Drug names
2020	1	Kymriah,
2021	4	Kymriah, Yescarta, Zolgensma, Luxturna
2022	4	Kymriah, Yescarta, Zolgensma, Luxturna
2023	5	Kymriah, Yescarta, Tecartus, Zolgensma, Luxturna
2024	6	Kymriah, Yescarta, Tecartus, Ebvallo, Zolgensma, Luxturna

Table A4. Cost of administration of cell and gene therapies in France

Economic evaluations by Haute Autorité de Santé (HAS), the French National Health Authority, have been used to collect information on specific costs associated with the administration of cell and gene therapies (CGTs). Economic evaluation is not produced for every new assessment in France, as it is generated by a budget impact test. Therefore, the administration costs reported here were obtained for a specific drug and indication for which an additional economic evaluation was undertaken. The figures refer only to the total administration cost of the drug as reported in that evaluation; they exclude long-term post-administration follow-up, and any costs arising from complications.

Drug name	Cost of administration	Indication	Reference
Kymriah[1]	€27,272	Follicular Lymphoma	HAS Economic and Public Health Evaluation Committee (CEESP) economic opinion, Kymriah
Yescarta[1]	€27,314	DLBCL	HAS CEESP economic opinion, Yescarta
Breyanzi[2]	€26,964	DLBCL	HAS CEESP economic opinion, Breyanzi
Luxturna[3]	€6,241	Retinal dystrophy	HAS CEESP efficiency opinion, Luxturna

[1] For Kymriah and Yescarta, administration costs include the Diagnosis-Related Group (DRG)/ *Groupe Homegène de Malades* (GHM)-based hospitalization cost plus the relevant CAR-T supplementary payment where applicable. For Kymriah, the figure was calculated as the updated hospital stay cost including transport (€11,218.69) plus the CAR-T flat-rate supplement (€15,000). For Yescarta, the reported hospitalization/administration cost (€27,047.90) already includes the DRG/GHM tariff and *Supplément Cellules T Chimériques* (CTC) supplement. *HAS CEESP economic opinion, Kymriah, Table 36, p. 53*; *HAS CEESP economic opinion, Yescarta, Table 13, pp. 41–42.*

[2] For Breyanzi, the average total cost of administration was based on the estimated administration cost of €17,024 plus a revised supplementary payment of €9,940 based on the 2023 tariff. The DRG tariff was added to the supplementary payment to ensure the comparability of figures. *HAS CEESP economic opinion, Breyanzi, Table 16, pp. 54–55.*

[3] The total average cost for the administration of Luxturna was calculated by summing up all the individual elements listed as individual items in the administration cost table of the report. The figures are in 2018 prices per patient/cycle, which includes two administrations. No supplementary payment was applied. *HAS CEESP efficiency opinion, Luxturna, Table 9, p. 37.*

ABBREVIATIONS

AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
APA	advance purchase agreement
ARI-0001	varnimcabtagene autoleucel
ASMR	Amélioration du Service Médical Rendu (Additional Clinical Benefit)
ATMP	advanced therapy medicinal product
CAR-T	chimeric antigen receptor T-cell
CDF	Cancer Drugs Fund (UK)
CED	coverage with evidence development
CEESP	Economic and Public Health Evaluation Committee (HAS)
CGT	cell and gene therapy
CMS	Centers for Medicare & Medicaid Services (US)
DRG	Diagnosis-Related Group
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GHM	Groupe Homogène de Malades
GMP	good manufacturing practice
HAS	Haute Autorité de Santé (French National Health Authority)
HCRP	high-cost risk pool
HDI	Human Development Index
HIB	health impact bond
HIC	high-income country
HTA	health technology assessment
ICER	Incremental Cost-Effectiveness Ratio
INN	international nonproprietary name
LMIC	low- and middle-income country
mRNA	messenger ribonucleic acid
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NMIBC	non-muscle invasive bladder cancer

OBP	outcomes-based payment
PVA	price-volume agreement
QALY	quality-adjusted life-year
R&D	research and development
SCD	sickle cell disease
UMIC	upper-middle-income country

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STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Claude Opus models 4.8, 5 and 5.5 were used to improve the flow and readability of this report. Figure 3 was generated using ChatGPT's GPT-5.5. However, the contents of Figure 3 were provided by the authors. The data extraction for Figures 4 and 5 was carried out manually from the cited sources by the authors.

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ENDNOTES

* The most reliable clinical evidence comes from double-blind randomized controlled trials. These compare the new treatment against a control group, with patients assigned by chance and, ideally, neither patients nor clinicians aware of who received what. The trials described here depart from that standard in three respects: (i) single-arm trials have no comparison group, so their results must be judged against external data rather than a concurrent control; (ii) open-label trials are unblinded, meaning patients and clinicians know who is receiving the treatment; and (iii) a surrogate endpoint is an indirect marker, such as a scan or laboratory measure, used in place of an outcome that matters directly to patients, such as living longer. Because a treatment can shift the marker without ultimately delivering that benefit, each of these features adds uncertainty relative to a blinded, randomized trial measuring patient-relevant outcomes.

† When a treatment is tested in only a handful of patients, the trial gives a far less precise estimate of how well it works: the results are compatible with a wide range of possible true effects, summarized by the confidence interval. Cost-effectiveness analysis combines that effect estimate with cost to calculate value for money, so the imprecision carries straight through to the headline result, the cost per quality-adjusted life-year (QALY). With small trials, that result is reported alongside a wide range of plausible values, and sensitivity analysis, which reruns the calculation under different assumptions, shows how wide that range is. The practical consequence is that a payer may be unable to tell whether a therapy is clearly good value or clearly poor value, because the evidence is consistent with both.

‡ A single-arm trial has no control group, so the treatment's benefit must be judged against an outside source, such as patients from earlier trials, disease registries, or records of how the condition normally progresses. Statistical techniques try to align these comparison patients with the treated ones on measurable characteristics, but they can only correct for differences that were recorded; if the groups differed in some unmeasured way, that hidden difference, rather than the treatment, may explain the apparent benefit. This is why such evidence is weaker than a randomized controlled trial, where assignment by chance makes the groups comparable by design.

§ Cell and gene therapies are intended to work for many years, but trials can only observe patients for a few years before the therapy is priced and funded. Cost-effectiveness analysis, however, projects costs and benefits over a patient's whole lifetime, so it must assume what happens after the trial ends, in particular, whether the treatment's effect lasts (is sustained) or fades over time (wanes). Because that assumption is unobserved, small changes to it can swing the estimated value for money substantially. This leaves payers to commit to a high upfront price without knowing whether the long-term benefit will materialize.

- Severity weighting applies where a disease causes significant health loss to patients, measured as shortfall. Shortfall is typically calculated both in absolute terms, meaning the QALYs patients would lose to the disease relative to the general population, and in proportional terms, as the share of remaining expected QALYs those losses represent. When either measure crosses a defined threshold, the QALYs gained from treatment are multiplied by a fixed weight greater than one, in effect raising the cost-effectiveness threshold.[32,34] The National Institute for Health and Care Excellence (NICE) in England, for instance, applies a weight of 1.2 or 1.7 to QALYs gained, depending on the magnitude of absolute and proportional shortfall; the Netherlands' National Health Care Institute (Zorginstituut) instead operates several severity-based reference thresholds, with higher willingness-to-pay applied to conditions of greater proportional shortfall.[34]

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