Recalibrating health technology assessment methods for cell and gene therapies

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Abstract

Recently licensed cell and gene therapies have promising but highly uncertain clinical benefits. They are also entering the market at very high prices, with the latest entrants costing hundreds of thousands of dollars. The significant long-term uncertainty posed by these therapies has already complicated the use of conventional economic evaluation approaches such as cost-effectiveness analysis and cost-utility analysis, which are widely used for assessing the value of new health interventions. Cell and gene therapies also risk jeopardizing health care systems' financial sustainability. There is therefore a need to recalibrate the current health technology assessment methods used to measure and compensate the value of cell and gene therapies. In this paper, we outline a set of technical adaptations and methodological refinements to address key challenges in the appraisal of cell and gene therapies' value, including the assessment of efficiency and affordability. We also discuss the potential role of alternative financing mechanisms. Ultimately, uncertainties associated with cell and gene therapies can only be meaningfully addressed by improving the evidence base supporting their approval and adoption in health care systems.

Key points

- There are significant uncertainties associated with both the clinical benefits and economic costs of cell and gene therapies that complicate their appraisal using standard health technology assessment methods.
- We outline a set of methodological refinements to improve the assessment of efficiency (costs, benefits and cost-effectiveness) and affordability (budget impact) of cell and gene therapies, together with options for their financing.
- Recommendations range from relatively small adjustments such as adopting different time horizons and cost-effectiveness thresholds, to developing more advanced statistical techniques for survival modelling and applying multi-criteria decision analysis.

1. Introduction

Cell therapies, such as cellular immunotherapies and gene therapies, long discussed since the beginning of the century, have recently become a reality with a number of such products entering the market over the last few years. Despite their breakthrough nature, which is accompanied by escalating patient expectations and hype, their extremely high prices risk to overwhelm the already-stretched financial resources of health care systems. A debate is emerging about how these new therapies should be assessed and compensated by payers.

Central to the pricing discussion is the value that these therapies offer, mainly to patients and possibly payers. However, their evaluation is challenging because of substantial uncertainty with their outcomes. Current health technology evaluation methods can be traced back to the 1970s in the US (1), when such therapies did not exist; therefore, these methods might no longer be appropriate, as they have been traditionally used for, and validated through, more "mainstream" products with incremental health benefits at incremental prices.

A *gene therapy* can be defined as a "set of strategies that modify the expression of an individual's genes or that correct abnormal genes", involving the administration of a specific DNA (or RNA) (2). A *cell therapy* is defined as the "administration of live whole cells or maturation of a specific cell population in a patient for the treatment of a disease" (2). *Cellular immunotherapies* are a sub-type of cell therapies using "immune or other type of cells for the modulation of host immune system or direct elimination of pathogen/tumour" (3). *Regenerative medicine* is often used as an umbrella term to cover any type of cell-based therapies, but also molecules, devices, tissue or scaffold (matrix), that are "replacing or regenerating human cells or organs, for the purpose of restoring or establishing normal function" (3).

Typically indicated for serious, life-threatening diseases with high unmet needs, cellular immunotherapies and gene therapies represent new therapeutic options with innovative mechanisms of action. Because they target a disease at its cause, they can, at least in theory, reverse a diseased state back to a healthy one. According to some, these therapies possess characteristics of "cures" due to their promising benefits expected to accumulate over patients' lifetimes. However these benefits are far from certain. Some patients with genetic conditions normally expected to live their remaining years with exacerbating symptoms, and possibly dying prematurely, might have the prospects for healthier lives, but their benefits are assessed by projecting them in the future.

It is evident that these therapies differ substantially from the traditional small molecule chemicals and even, the now-mainstream, advanced large protein biologics. Cell therapies are the result of complicated procedures of laboratory cell manipulation, often involving only the patients' own cells. Therefore, ethical questions with regulatory implications also emerge, relating to whether it is accurate to classify these therapies as drugs, procedures, combinations of both or

even whether they "qualify as a drug" in the first place, as they can correspond to living substance drawn from a patient's own body (4).

These complex questions make cell and gene therapies a challenging subject for evaluation, highlighting the need to rethink our approach to measuring their value.

2. Regulatory frameworks and approvals

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have so far used their own classification and evaluation frameworks for cell and gene therapies, but the two agencies are increasingly collaborating (5). In the US, the FDA has published a number of guidance documents shaping a regulatory framework for regenerative medicine products, referring to human cells, tissues, and cellular and tissue-based products (HCT/Ps) intended for implantation, transplantation, infusion, or transfer into a human recipient (6, 7). In Europe, EMA classifies medicines for human use that are based on genes, tissues or cells as advanced therapy medicinal products (ATMPs), which are sub-divided into gene therapies, somatic cell therapies, tissue-engineered medicines, and combined ATMPs under the remit of a designated committee (7, 8).

In the US, the FDA sub-classification of advanced therapies covers two major groups of products, gene therapies and cellular therapies, with the regulatory terminology for ATMPs and their classification revealing some differences between the two regions, as for example in terms of human cells and tissue products(9). FDA's Office of Tissues and Advanced Therapies (OTAT) has licensed 17 cellular and gene based products for human use since April 2010 (Table 1). Half of these products are hematopoietic progenitor cell (HPC) cord blood therapies for use in unrelated donor hematopoietic progenitor cell transplantation (HPCT) procedures, supplied by medical blood centres; three products are (viral) gene therapies, three are immunotherapies and the rest are other types of cellular therapies (10), covering a wide range of therapeutic areas. The four latest gene therapies and cell immunotherapies, which are also the most expensive ones as discussed below, have also been approved by the EMA.

<Table 1>

3. Treatment costs of latest cell and gene therapies and their pricing debate

Back in 2010, when the first cellular immunotherapy hit the market (sipuleucel-T for asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer), budgetary concerns for payers were raised in the US, signaling what was to follow (11). After excluding the first set of therapies that entered the market between 2010 and 2016, mainly associated either

with moderate effectiveness (e.g. sipuleucel-T was withdrawn from the EU for commercial reasons having an overall survival of 25.8 months vs 21.7 for placebo)(12, 13), or indicated for non-severe diseases (e.g. laviv for moderate to severe nasolabial fold wrinkles), a trend has since emerged: all four latest therapies are associated with substantial prices in the range of hundreds of thousands of US dollars per patient.

Voretigene neparvovec (for treating a type of retinal dystrophy) and onasemnogene abeparvovec (for spinal muscular atrophy) represent the top two of the 10 most expensive treatments (14). It is acknowledged that part of advanced therapies' cost is due to the labour intensive manufacturing and shipping processes, including the set-up, maintenance and quality control procedures within the manufacturing laboratory. However, decentralized manufacturing within the hospital or clinic, combined with increased automation through consolidation of key processes as more sophisticated equipment are developed could substantially reduce aggregate cost of goods (15), with academic dose production for CAR-T cell therapies quoted to be as low as $6,000 (16) to $20,000 (17).

Recently, the Centers for Medicare & Medicaid Services (CMS) made a coverage determination for the FDA-approved CAR-T cell therapies for Medicare beneficiaries(18). Central to this decision was the FDA requirement for post-market surveillance programs involving the monitoring of potential risks in the relevant patient population but also the Cellular Immunotherapy Data Resource, a patient registry for patients receiving CAR-T therapies allowing long-term clinical data collection on outcomes and adverse events (18, 19).

The main justification for the high prices are associated with the significant development and commercialization costs of new, innovative therapies. As for-profit, public or private companies, sponsors need appropriate financial incentives to invest in such high-risk projects, particularly when the target patient group is relatively small, as in the case of many disorders treated with advanced therapies. As the industry-led narrative suggests, without "reasonable" profits, it would be hard to secure adequate financial resources needed for R&D investments and the commercialization of new innovative therapies. This narrative justifies high returns for high-risk, high-cost investments.

However this debate is futile given the non-disclosure of full R&D costs by manufacturers, without which there can be no constructive discussion about "reasonable" or "excessive" returns; however, recent estimates point towards substantially lower R&D cost requirements for new drugs compared to past figures (20).

Nevertheless, this R&D cost-based pricing model is already outdated. Most health care systems have been shifting towards a value-based assessment and pricing approach. Therefore, payer decisions are increasingly informed by the "value" of new therapies for patients and the health care system. This is the analytical perspective we adopt for the challenges and recommendations discussed below.

4. Economic evaluation challenges

Historically, many payers and Health Technology Assessment (HTA) agencies have guided the coverage and reimbursement, and indirectly the pricing, of new therapies on the principles of economic evaluation. Central to the conduct of economic evaluation is the estimation of costs and benefits for which the perspective, comparator, and time horizon of the analysis are key, all of which involve a number of challenges. Below we describe some of the key challenges associated with the assessment of cell and gene therapies' efficiency (in terms of costs, benefits and cost-effectiveness) and affordability (in terms of budget impact), together with some relevant HTA agencies' experience.

Costs estimation

First, economic costs are not always easy to capture, especially in rare diseases with unmet need. A typical health economic argument made by manufacturers in an effort to support high prices of "curative" products relates to the net cost component of the incremental cost effectiveness ratio (ICER), possibly corresponding to the resources (saved) following the new product's utilization, often forecasted over patients' lifetimes. The cost of a disease and its financial implications are usually estimated through the so-called "cost of illness" studies, aiming to measure all cost types arising due to a particular disease, ranging from direct costs to indirect productivity losses and even intangible dimensions such as psychosocial costs, for patients and possibly their carers (21, 22). Conventionally, total lifetime and annual costs per patient are estimated, with direct costs being broken down to medical related (i.e. hospital admissions, emergency visits, outpatient care) and non-medical related (i.e. transportation, social care services, caregiver's time), and indirect costs broken down in terms of productivity aspects (i.e. absenteeism, presenteism, early retirement), with a range of different patient reported outcome instruments being used for patient and carer outcomes. Such cost data though might be sparse, especially for diseases with small patient populations (23) which are often targeted by cell and gene therapies, and together with the existence of different costing methodologies can make the estimation of costs a complicated task. Depending on the perspective adopted, the health economic analysis typically includes health care related costs (and benefits) as in England, but might be more restrictive to capture only pharmaceutical related costs as in France or more encompassing expanding to cover wider societal costs from other segments of the economy as in Sweden. Given that economic evaluations are comparative in nature, what counts as cost is crucial for the estimated net cost.

Benefits estimation

Second, clinical benefits are generally even more challenging to estimate given their higher uncertainty, in contrast to therapies' costs which are usually paid upfront and are therefore

generally known, with important implications for ICER's calculation and reimbursement. Given the high severity of the corresponding disease indications, possibly with no available treatments, cell and gene therapies are very often licensed based on limited clinical evidence and as part of expedited regulatory pathways. Their pivotal clinical trials might only have a single experimental arm without any concurrent comparator, using restrictive eligibility criteria that lead to a small number of enrolled patients, while lasting for a short duration of just a few months. For the case of rare diseases with small patient populations, patient recruitment might be challenging, whereas for severe life-threatening diseases, patients might be reluctant to enter placebo-controlled trials when a promising experimental therapy exists, potentially increasing the chances for small, single-arm, uncontrolled studies (24). Notably, previous studies found no association between the rarity of disease and feasibility of undertaking randomized controlled trials; randomized controlled trials exist even for so-called "ultra-orphan" conditions (25, 26). Furthermore, even within clinical trials, whilst advanced therapies can show impressive responses and outcomes for several patients, some patients might have little or no benefit. Nevertheless, their results are often extrapolated over long time periods for patients and generalized to a wider patient population, giving rise to what is known as "efficacy-effectiveness gap", describing possible discrepancies between and evidence on efficacy and effectiveness (27). For example, it was recently illustrated for voretigene neparvovec (Luxturna) that current evidence fails to support a curative benefit for most patients, with large heterogeneity in response rate and possible shorter than expected duration of benefits (28). Another set of challenges in the estimation of clinical benefits relates to the incorporation of novel or additional aspects of value that are not captured as part of the quality-adjusted life-year (QALY) or economic evaluation, including their trade-offs (24, 29-31).

Typically, the above clinical related issues and uncertainties will give rise to other uncertainties in cost-effectiveness as part of decision analytic modeling, which could be mainly classified as structural (i.e. relating to the construction and interpretation of the model), parameter (i.e. relating to the true value of a parameter), methodological (i.e. relating to the choice of analytic methods) and patient population (i.e. heterogeneity) uncertainties (32, 33). In terms of structural uncertainties, essentially referring to all the scientific judgments and assumptions inherent in the model, these could be further divided based on their source according to the relevance of comparators, events, statistical estimation methods, and clinical uncertainty (34).

Budgetary considerations

Beyond the challenges associated with assessing an intervention's *efficiency,* i.e. value-for-money*, affordability* represents another concern relating to "what is the budget impact for covering the intervention across the relevant patient population", a question usually considered once an intervention's efficiency has been found to be acceptable.

However a gap exists between efficiency and affordability concerns, including the limited ability of economic evaluation to serve payers' needs, as illustrated by past experience with Hepatitis C breakthrough treatments. Starting with Sofosbuvir (Sovaldi) and then followed by other next generation direct-acting antiviral agents showing sustained virologic responses and nearly universal durability (i.e. being equivalent to cures), these treatments demonstrated high cost-effectiveness for the system while at the same time being unaffordable (35, 36). This showcased the incapacity to align these breakthrough products' economic evaluation results with payers' needs.

Such affordability concerns are set to grow in the future, given that hundreds of cell and gene therapies are currently in clinical development (37). Examples include therapies based on the CRISPR technology as a "gene-editing" tool, which, in theory, can correct genetic diseases by "splicing" the defective gene and replacing it with a corrected version. Although their expected prices are still highly uncertain given that they only recently moved into proof-of-concept human trials, if they prove to be effective their prices could range in hundreds of thousands. Currently, just below 10 human interventional clinical trials are listed to be recruiting patients in the US for studying the safety and efficacy of CRISPR edited T cells or Human Hematopoietic Stem and Progenitor cells for a range of cancer indications, eye diseases and sickle cell disease (38), with another 10 human CRISPR clinical trials enrolling patients in China (39).

HTA agencies' experience

A detailed look at NICE's recent appraisal of tisagenlecleucel (Kymriah) for the treatment of relapsed or refractory B-cell ALL (40) reveals the complexity faced by HTA agencies. At the core of the Evidence Review Group's critique of the manufacturer's submission was the high uncertainty around the long-term benefits of the technology given data censoring and very small numbers of patients at risk beyond 18 and 36 months (41). Because the majority of benefits gained were accrued over the model extrapolation period, small changes in survival predictions had a significant impact on the estimated ICER. Another source of uncertainty was the technology's novel mechanism of action as the extrapolation of clinical trial data over the long-term was not supported based on current evidence in which long-term treatment-effect persistence remains unknown. A number of additional uncertainties were raised, such as the representativeness of patients in clinical trials, and the choice of appropriate comparator. In recognition of the inadequate evidence base and the immature data, the NICE committee decided to resolve cost-effectiveness uncertainties through the commissioning of the technology via the dedicated Cancer Drugs Fund (CDF) allowing the collection of further evidence as part of a managed access agreement (42). However, as pointed out below, the use of real world data can be biased by residual confounding given that key patient characteristics affecting the

outcome are unmeasured, and therefore might not provide an adequate response for establishing which drugs are relatively effective (43).

Due to these therapies' very high prices and their large numbers under clinical development (37), they have been perceived by some as a threat to payers' sustainability. In the case of England's NICE, it had been suggested that these therapies might present a challenge to its appraisal methods because of the challenging combination of their high price and promising benefits (despite weak evidence); however following a 2016 pilot it was concluded that the agency's current methods and decision framework would still be applicable to such therapies (44).

More recently, the Institute for Economic and Clinical Review in the US identified four key areas of technical issues that could justify the need to use alternative methodologies or amendments for the evaluation of such technologies (31). These areas relate to different types of uncertainty at the time of launch and their risk of high unrecoverable costs, time divergence between short-term spending and future health benefits, existence of additional dimensions of value not captured in economic evaluation, and affordability and fair sharing of economic savings created.

5. Recommendations

Although most of the above issues in HTA evaluation and funding are not new and have already been encountered in the past with other technologies (as noted above, e.g. extrapolation of long term outcomes from short term studies in cancer drugs, affordability of cost-effective Hep C cures), the recent arrival of cell and gene therapies have highlighted their implications, pushing against the boundaries of available methodological and budgetary capacity. Below we discuss methodological recommendations towards the resolution of such challenges, which can be broadly categorized under the stages of efficiency assessment, affordability assessment and financing mechanisms design.

Potential solutions for estimating more accurate costs, benefits and ICERs, range from relatively simple technical fixes to more holistic reforms at system level, as shown in Table 2. In regards to perspective selection, the Second Panel on Cost-Effectiveness in Health and Medicine recommends that, for purposes of comparability and completeness, cost effectiveness analyses should provide two reference case analyses, i.e. sets of results based on standardized methods: a societal perspective for capturing broader benefits and a health care perspective which will be more relevant for health care decision making contexts (45).

Efficiency assessment

In terms of costs estimation, in cases that an existing treatment is available and therefore supposed to be replaced from the new intervention, the price of the comparator should be carefully reviewed and if judged to be poor value-for-money then be appropriately justified. Otherwise, overpriced comparators could artificially "facelift" the value of the new product (46), as in the case of onasemnogene abeparvovec (Zolgensma) where the comparator nusinersen (Spinraza) was arguably over-priced. In case that no treatment is available, possible drug related side effects and their cost should be accounted for, as in the case of tisagenlecleucel (Kymriah) (47). In terms of methodological advancements and evidence collection, international research collaborations could be leveraged for developing updated good practice guidelines towards the converge of common costing methodologies, possibly in combination with the generation of unified, cross-country, cost datasets (48).

In terms of benefits estimation, traditional methods for handling uncertainty in economic evaluation have included the use of sensitivity analysis for structural uncertainties, in combination with scenario analysis for patient population uncertainties, and value of information analysis for parameter uncertainties (32, 49). For example, in dealing with parameter uncertainties as part of data extrapolation, a standard analytical approach could involve a probabilistic sensitivity analysis based on a large number of Monte Carlo simulations allowing several variables to vary simultaneously across a plausible range of distributions (50), followed by a value of information analysis to determine future data collection activities (24).

Given that the label indication of curative therapies is projected over patients' lifetime, a relatively simple corrective adaptation could be the application of multiple time frames to assess the estimated benefits and ICERs over different time horizons, while possibly placing a higher weight over shorter horizons, to reduce uncertainty accumulating over the long term. This could be combined with probabilistic sensitivity analysis to explore the impact of changes in various modeling assumptions on the estimated results, and over different time horizons of varying importance. Such products could then undergo price reductions to push their ICERs under the respective cost-effectiveness thresholds. For the more accurate extrapolation of benefits, new advanced statistical techniques for the more accurate fit of survival data could be explored (51-54). For example, in terms of modeling the survival outcome of new immune-oncology drugs, flexible methods such as restricted cubic splines have shown to provide better fit of trial data compared to traditional parametric techniques (51). Cure models that measure survival separately for cured versus non-cured patients have been recommended as an alternative statistical tool for analyzing survival in therapeutic contexts of cured patients (55), with an application in advanced melanoma supporting the use of cure modeling for incorporation of patient heterogeneity into economic evaluation and improving accuracy in the estimation of overall survival, QALYs and ICERs (52).

Quantitative decision analysis modeling approaches such as Multiple Criteria Decision Analysis (MCDA) could also be used for the assessment of therapies' consequences both in terms of benefits and risks. MCDA could enable the incorporation of multiple value aspects, their trade-offs and aggregation into a single metric while allowing to incorporate uncertainty through the use of probabilities on benefits and risks (56, 57). Such an approach could be used to integrate estimated results of different outcomes from various analytical techniques thus enabling the synthesis of evidence from different sources (58), especially for cases where aspects of value are not captured in economic evaluation (59, 60). This would be in alignment with the Second Panel on Cost-Effectiveness in terms of quantifying and valuing all effects if a health care sector reference case significantly differs from a societal reference case (45), and also with the recommendations by Drummond and colleagues about completing an amended impact inventory for gene therapies outlining important non-health consequences (e.g. effects on family caregivers, education costs, and economic productivity (24). MCDA could also be particularly useful for appraising the relevance and extending the completeness of the evidence base in cases of limited data based on expert judgment. However the use of MCDA is often poorly applied in practice and improved heath care applications would be needed, including the advancement of robust methodologies and practical tools for better study quality (61), and in any case it would not be a panacea for all efficiency assessment challenges, especially not in relation to dealing with uncertainty and generating additional evidence.

In terms of evidence collection outside conventional randomized clinical trials (RCTs), generation of real world data (RWD) aiming to reflect effectiveness at community level, such as through patient registries, has received a lot of attention (62). Similarly, the so-called "pragmatic trials" aim to provide data for adoption in clinical practice, as opposed to the conventional explanatory trials with strict protocols (63). However, evidence suggests that replacing randomized trials with observational studies would be a false solution as it is difficult to derive reliable relative effectiveness estimates due to residual confounding, and only randomization can result in groups of patients that are balanced with respect to both known and unknown risk factors and, therefore, with respect to their risks of any type of health outcome (64). Instead, timely RCTs within routinely collected data sources at the point of care, adopting multi-arm, multistage adaptive trial designs, have been proposed to address various clinical uncertainties in evidence review for the purpose of Cancer Drugs Fund (CDF) in the UK (e.g. immature survival data, lack of relevant comparators, and inconsistencies in trial population) (43); however such trial designs might be more challenging for rare disorders and would require manufacturers to compete into a single trial. If the use of observational studies is necessary, for example as part of establishing a historical, i.e. retrospective, cohort study for single-arm trials, attention should be paid to minimizing bias, exploring heterogeneity in the patient population, understanding confounding factors affecting study outcomes and considering the generalizability of clinical data

(24). Improving the analysis and interpretation of non-randomized studies could be useful towards informing a more accurate estimation of treatment effects for use in economic evaluation but possibly not adequate (65-67), and other advanced statistical techniques could also be explored for this purpose.

Some of the above technical recommendations are illustrated in the amendments introduced by the Institute for Clinical and Economic Review in its value framework for valuing single and short-term therapies (31). In terms of assessing uncertainty, proposals include more advanced analytical techniques such as cure proportion models that might better fit survival data in combination with scenario analyses, use of optimistic and conservative benefit scenarios in conjunction with the base case, inclusion of a threshold analysis for determining the durability of beneficial effect, and an explicit consideration of uncertainties and controversies related to economic evaluation.

Beyond the estimation of benefits and costs, given that extremely high product prices could still prove to offer good value-for-money even if they are unsustainable for the health care system in the long-term, ICER thresholds could require some adjustment. Examples of adjustments could take the form of a "sliding ICER scale" with clear rules based on product performance, "re-pricing cost offsets" if comparators are not cost-effective by discounting cost savings, applying a "QALY-cap" by capping the price at the maximum willingness to pay per QALY gained, and applying "shared savings" by splitting a proportion of the savings achieved with the payers (68).

If MCDA approaches are adopted, existing ICER "cost per outcome" thresholds could be used as benchmarks to map out a multi-attribute value threshold proportionally to the attributes' relative weight assigned in the model (69). Given that the opportunity costs should in theory be constant within the health care system and across diseases, the estimation of such a value threshold should be comprehensive enough to reflect value trade-offs among all technologies, which might require the consideration of public preferences via large-scale elicitation studies.

<Table 2>

Affordability assessment

Following the estimation of more accurate ICERs, a better-grounded negotiation process between the payer and the manufacturer could take place. Affordability issues could be discussed based on the more realistic or "adjusted" ICERs, better reflecting expected benefits with less uncertainty because of shorter time horizons in the analysis.

Trying to formally incorporate affordability concerns during the evaluation of these therapies' efficiency, could be a more balanced way forward. Examples include the use of explicit budget impact thresholds by the Institute for Clinical and Economic Review in the US beyond which short-term affordability and access challenges are highlighted (70), or the use of budget impact test by NICE in England that can trigger commercial discussions with NHS England for technologies that cost above £20million per year (71).

However even after such adaptations, some therapies could still be judged to be unaffordable even if cost-effective. One policy option in this scenario could be to expand the specific budget for such innovative technologies, though we consider such an option to be problematic as it might not be sustainable. An alternative option would be to simply solve the budgetary issue by reducing the ICER threshold for all technologies (72).

With the use of MCDA, the value resulting from an improved budget impact could be explicitly taken into account and weighted relative to the value resulting from therapies' other components (benefits and risks, clinical and non-clinical). This in turn could integrate affordability and efficiency value concerns. In the case of a defined budget, treatment purchasing costs could also be used to derive cost-value ratios as part of a portfolio optimization exercise (73), therefore naturally incorporating opportunity costs through the selection of each therapy while trying to maximize benefits within the budget.

Financing mechanisms design

Finally, once the evaluation is completed in terms of ICER and budget impact, a number of innovative payment methods could be applied for curative therapies, with outcome-based payments perceived by payers as one of the most promising (74). Also known as performance-based agreements, or health-based managed entry agreements, they correspond to formal schemes between payers and manufacturers for sharing the financial risk due to the uncertainty in health outcomes (75, 76). Their timelines are typically linked to further evidence collection, and any reward to manufacturers takes place following the delivery of the agreed milestone(s), such as the validation of an expected health benefit. An alternative type of managed entry would be financial-schemes, or financial-based (managed entry) agreements, focusing on the financial implications of technologies' utilization by using different formulas of discounts, rebates, dose caps and price-volume agreements. These schemes could be used both to lower the financing challenges for payers but also for handling uncertainty relating to therapies' costs, benefits, and ICERs. In any case, the clinical and economic advantages of specific agreements and whether they have yielded the desired results remains uncertain, due to lack of transparency and their confidential nature (77). Overall, innovative schemes could be explored for facilitating timely patient access, as it has also been acknowledged by NICE (44). Payment by installments involving amortization over time, such as life leasing, credit or loan mechanism and reinsurance

for payers, would form alternative financing methods for situations characterized by high, possibly prohibitive, budget impact (74), which could be combined with the use of performance-based agreements (78).

However, evidence from the US suggests that the power of outcomes-based contracts to reduce spending on high-cost drugs is questionable so far, mainly because their use is usually restricted to only a few products while having limited meaningful metrics to evaluate their impact (79). Besides measurement challenges, other barriers to their use include high implementation costs and lack of suitable data infrastructure (80).

In any case, demanding upfront payments, when expected health benefits (of high uncertainty) are expected to materialize in the long term may not be justifiable. Manufacturers heavily investing in R&D should try to gain the trust of health payers by bringing them on their side through evidence-based arguments rather than lobbying pressures for which hundreds millions of dollars per year are spent on average for the US federal government alone (81). Not demanding from payers to bear the risk alone upfront would be a fair starting point for both parties and new constructive models of engagement should be explored, as part of which there should be more focus on what happens if technologies do not live up to their promise, for example by heavily discounting the price for future uncertainty or rewarding only when certain milestones are reached.

6. Conclusion

Current health technology assessment methods require adaptations to accommodate the significant uncertainty associated with new cell and gene therapies. We propose a number of technical adaptations and methodological refinements to address challenges in the estimation of costs, benefits and ICERs, all of which we believe are feasible. Our recommendations range from relatively minor changes such as using different time horizons and cost-effectiveness thresholds, to more major changes to the current health technology assessment framework by using more advanced statistical techniques and multi-criteria decision analysis. Going forward, any hurdles encountered with the assessment of these therapies and their payment should not translate to financial burden for patients. Ultimately, uncertainties associated with cell and gene therapies can only be meaningfully addressed by improving the evidence base supporting their approval and adoption in health care systems.

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Table 1: Approved cellular and gene based products by the FDA's OTAT

Brand name	Generic name	Classification	Manufacturer	Date of FDA approval	Indication	List price per patient*
ZOLGENSMA	onasemnogene abeparvovec	adeno-associated viral vector-based gene therapy	AveXis	24-May-19	spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene (less than 2 years old)	$2,125,000 (2018)[a]
None	HPC**, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	MD Anderson Cord Blood Bank	21-Jun-18	unrelated donor HPCT*** procedures	N/A
LUXTURNA	voretigene neparvovec	adeno-associated viral vector-based gene therapy	Spark Therapeutics, Inc.	19-Dec-17	confirmed biallelic RPE65 mutation-associated retinal dystrophy	$850,000/ $425,000 per eye (2018)[b]
YESCARTA	axicabtagene ciloleucel	genetically modified autologous T cell immunotherapy	Kite Pharma	18-Oct-17	relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy (adults)	$373,000 (2017)[c]
KYMRIAH	tisagenlecleucel	genetically modified autologous T cell immunotherapy	Novartis	30-Aug-17	B-cell precursor acute lymphoblasticleukemia (ALL) refractory or in second or later relapse (up to 25 years old); relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy (adults)	$475,000 (2017)[d]

MACI	Autologous Cultured Chondrocytes on a Porcine Collagen Membrane	autologous cellularized scaffold product	Vericel Corporation	13-Dec-16	single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement (adults)	N/A
CLEVECORD	HPC, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	Cleveland Cord Blood Center	01-Sep-16	unrelated donor HPCT procedures	N/A
None	HPC, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	Bloodworks	28-Jan-16	unrelated donor HPCT procedures	N/A
IMLYGIC	talimogene laherparepvec	genetically modified herpes virus gene therapy	Amgen Inc.	27-Oct-15	local treatment of melanoma recurrent after initial surgery	$65,000 (2015)[e]
None	HPC, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	LifeSouth Community Blood Centers, Inc.	13-Jun-13	unrelated donor HPCT procedures	N/A
ALLOCORD	HPC Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	SSM Cardinal Glennon Children's Medical Center	30-May-13	unrelated donor HPCT procedures	N/A
DUCORD	HPC, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	Duke University School of Medicine	04-Oct-12	unrelated donor HPCT procedures	N/A
None	HPC, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	Clinimmune Labs, University of	24-May-12	unrelated donor HPCT procedures	N/A

			Colorado Cord Blood Bank			
GINTUIT	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	allogeneic cellularized scaffold product	Organogenesis Incorporated	09-Mar-12	mucogingival conditions (adults)	N/A
HEMACORD	HPC, Cord Blood	allogeneic cord blood hematopoietic progenitor cell therapy	New York Blood Center, Inc	10-Oct-11	unrelated donor HPCT procedures	N/A
AZFICEL-T	laviv	autologous cellular (fibroblasts) product	Fibrocell Technologies, Inc.	21-Jun-11	moderate to severe nasolabial fold wrinkles (adults)	$19,900 (2012)[f]
PROVENGE	sipuleucel-T	autologous cellular immunotherapy	Dendreon Corporation	29-Apr-10	asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer	$93,000 (2010)[g]

Source: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
Notes: * full course; ** hematopoietic progenitor cell; *** hematopoietic progenitor cell transplantation
a: https://www.wsj.com/articles/at-2-million-new-novartis-drug-is-priciest-ever-11558731506
b: https://www.reuters.com/article/us-spark-icer/sparks-price-for-luxturna-blindness-gene-therapy-too-high-icer-idUSKBN1F1298
c: https://www.reuters.com/article/us-gilead-sciences-fda/fda-approves-gilead-cancer-gene-therapy-price-set-at-373000-idUSKBN1CN35H
d: https://www.bloomberg.com/news/articles/2017-08-31/novartis-kymriah-cancer-drug-475-000-but-read-the-fine-print
e: https://www.amgen.com/media/news-releases/2015/10/fda-approves-imlygic-talimogene-laherparepvec-as-first-oncolytic-viral-therapy-in-the-us/
f: https://www.businesswire.com/news/home/20130424006764/en/Fibrocell-Science-Pursues-Premium-Aesthetic-Market-Position
g: https://www.nature.com/articles/nbt0910-882a

Table 2: Proposed recommendations for different challenge types arising with cell and gene therapies.

Payer stages	Challenge types	Proposed solutions
Assessment of efficiency	Costs estimation	Appropriate adjustment/ justification of (inefficient) comparator's cost
		Consideration of costs associated with drug related side effects
		Adoption of common costing methodologies and unified cross-country cost datasets
	Benefits estimation	Application of multiple time horizons with different weights
		Probabilistic sensitivity analysis for model inputs and time horizons
		Development of advanced modeling techniques for more accurate data fit
		MCDA for assessing therapies' consequences, trade-offs and aggregation
	ICER adjustment	Sliding ICER scale with clear rules
		Re-pricing cost offsets of non cost-effective comparators by discounting savings
		QALY-cap equal to max WTP per QALY
		Shared-savings between manufacturers and health systems
		MCDA for mapping out a multi-attribute value threshold
Assessment of affordability	Balancing with efficiency	Explicit budget impact thresholds for highlighting access challenges
		Explicit budget impact thresholds triggering negotiation with manufacturers
		Expand budget for innovative therapies/ decrease ICER threshold for all technologies
		MCDA for explicit consideration of budget impact and portfolio optimization
Financing mechanisms	Financial risk due to uncertainty	Performance based agreements for uncertainty in health outcomes
		Financial based agreements for uncertainty in utilization
	Prohibitive budget impact	Payment by installments, credit/ loan mechanism and reinsurance for payers