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Variation in market access decisions for cell and gene therapies across the United States, Canada, and Europe

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ABSTRACT

Transformative cell and gene therapies have now launched worldwide, and many potentially curative cell and gene therapies are in development, offering the prospect of significant health gains for patients. Access to these therapies depend on decisions made by health technology assessment (HTA) and payer organizations. We sought to describe the emerging cell and gene therapies market access landscape by analyzing 17 US commercial payer medical policies, and HTA reports from five European countries and Canada. We found that some US health plans applied coverage restrictions more often than others (four plans applied restrictions in all decisions, while four plans applied restrictions in <30% of decisions). The European and Canadian HTA bodies recommend access to fewer therapies than US health plans, reflecting a more stringent approach in the context of limited evidence and high scientific uncertainty that is commonly associated with these treatments. Our findings suggest that patient access to approved cell and gene therapies is restricted in all regions studied, though the nature of these restrictions differs between US health plans and the European/Canada HTA recommendations. Payers, HTA groups, pharmaceutical companies, and other stakeholders should collaborate to more clearly define the "uncertainties" and develop market access policies that balance benefits of early access with ongoing data collection to close evidence gaps over time.

1. Introduction

Over the past several years, transformative cell and gene therapies have launched worldwide, and hundreds of potentially curative cell and gene therapies are in development, offering the potential of significant health gains for patients suffering from chronic or life-threatening conditions with limited existing treatment options. Regulators have accelerated the review and approval of these therapies, in some cases with relatively limited evidence, and most of these products have secured some degree of market access from payers. Yet, despite their potential value for patients and society, significant challenges and uncertainty related to value assessment, reimbursement, and payment models remain.

While potential patient benefits are recognized by payers, they are coupled with concerns over the limited evidence of benefits and safety available at the time of approval. Specific contributors to this uncertainty include the use of single-arm trials and historical cohorts for comparison [1], inappropriate comparators, questions about the durability of effect [2], and limited knowledge of effectiveness in larger patient cohorts. Indeed, these concerns have been described previously and were summarized in a sys-

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tematic overview of market access conditions for cell therapies in France, which found that a greater number of publications criticized uncertainty around the magnitude and duration of effect of regenerative therapies and precision medicines (54% of products in these categories in more than 60% of heath technology assessments [HTAs] in the set) compared with rare disease and non-precision oncology agents [3]. In addition, concerns over per patient and aggregate cost of these treatments are widely expressed, including worries about the cumulative financial impact on health care budgets of multiple gene therapies [1,4] and overall affordability [1.5,6].

Patient access to these therapies ultimately depends on decisions made by HTA and payer organizations. Payers in some countries have begun experimenting with mechanisms to mitigate both the high uncertainty at the time of product launch as well as concerns about affordability using managed entry agreements (e.g., outcomes-based agreements, installment payments) [5,7,8]. A clear understanding of HTA and payers' experience in reimbursing available cell and gene therapies will inform ongoing discussions and ultimately help to define optimal approaches for assessment and reimbursement of the numerous cell and gene therapies expected to reach the market in the next 5–10 years. The comparison of US policies with those in other countries offers some useful insights into the nuances of policies, and how they might be adjusted to ensure that market access decisions reflect the underlying evidence.

This article describes the market access landscape of emerging cell and gene therapies by analyzing commercial payer medical policies from 17 US payers and HTA reports from 6 other countries (EU5 [France, Germany, Spain, Italy, the United Kingdom (UK)], and Canada). We also summarized and compared HTA recommendations and reimbursement policies and practices for currently approved gene and cell therapies. Examining HTA and payer policies also documents patterns of restrictions on coverage and allows us to probe the rationales underlying those restrictions. Understanding the market access landscape provides insights about activities necessary to ensure that patients have timely access to therapies that are likely to provide clinical benefits. More specifically, insights into payer/HTA approaches could inform clinical development strategies, study design decisions, and commercialization approaches. In addition, regular, early meetings between HTA agencies and manufacturers provide an opportunity to manage expectations around evidence and to address pre- and post-market data collection.

2. Methods

2.1. US commercial payer medical policies

We used the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database to examine how US commercial health plans cover cell and gene therapies [9]. SPEC includes specialty product (drugs, biologics, and cell and gene therapies) coverage decisions issued by 17 of the 20 largest US commercial health plans (in terms of premiums earned) — information that represents the majority of the country's largest payers in terms of covered lives (~60% of commercially covered lives). Of the three excluded plans, two focus exclusively on public payers (Medicare or Medicaid populations), and the third does not make its coverage decisions publicly available [10]. SPEC includes six national and 11 regional commercial health care payers. The database details how the included health plans cover specialty products for their enrollees (including any restrictions or conditions on coverage), and the evidence that the plans cite in their coverage policies.

SPEC includes coverage decisions for four cellular therapies (tisagenlecleucel, axicabtagene ciloleucel, sipuleucel-T, and talimogene laherparepvec [t-vec]) and two gene therapies (onasemnogene abeparvovec and voretigene neparvovec-rzyl). Coverage decisions included in this analysis were current as of April 2020.

We compared health plan coverage policies with the Food and Drug Administration (FDA)-approved label. We categorized any coverage or reimbursement restrictions that plans applied in their decisions as

- Patient subgroup restrictions (a requirement for patients to meet certain clinical criteria beyond the parameters of the FDA label indication [e.g., severity or duration of symptoms]),
- Step therapy protocols (a requirement for patients to first fail an alternative therapy), or
- Site-of-care restrictions (a requirement for the treatment to be administered in a particular facility).

We also reported whether the coverage policy included a requirement for a certain type of physician (e.g., an oncologist) to prescribe the product. Specific rationale for clinical restrictions or information on non-clinical restrictions, such as price reductions and managed entry agreements, are not included in the SPEC database. This information was available in HTA reports from EU5 and Canada, as described below.

2.2. HTA reports from EU5 and Canada

A search was conducted in December 2019 to identify cell and gene therapies approved in Europe [11] and Canada [12]. Available HTA reports for these therapies were extracted from EU5 (France, Italy, Spain, the UK [England/Scotland], Germany) and Canada HTA websites: 1) France: French health authority (HAS), 2) Germany: Federal Joint Committee (G-BA) and Institute for Quality and Efficiency in Health Care (IQWIG), 3) UK England: the National Institute for Health and Care Excellence (NICE), Scotland: the Scottish Medicines Consortium (SMC), 4) Italy: the Italian Medicines Agency (AIFA), 5) Spain: Agencia de Evaluación de Tecnologias Sanitarias (AETS), 6) Canada: Canadian Agency for Drugs and Technologies in Health (CADTH).

For each HTA report, clinical restrictions were categorized as defined above for US medical policies. When available, we also extracted information on the rationale for positive coverage recommendations, any restrictions, non-coverage advice, and non-clinical restrictions such as price reductions and managed entry agreements. Restrictions for European and Canadian HTA reports were defined relative to the EMA or Health Canada marketing authorizations, respectively.

3. Results

3.1. US commercial payer medical policies

The included health plans issued 109 coverage policies for the six cell and gene therapies noted in the Methods section. Overall, these plans applied coverage restrictions in 64% (70/110) of their decisions (Fig. 1). Plans most generously covered t-vec, with 67% (8/12) covering the product in accordance with the FDA label. Health plans were most restrictive with coverage of voretigene neparvovec-rzyl and onasemnogene abeparvovec, applying restrictions in 100% of coverage decisions (17/17 and 16/16, respectively).

Some health plans applied coverage restrictions in their decisions more often than others. Four plans applied restrictions in 100% of their decisions, while four plans applied restrictions in <30% of their decisions.

Of restricted coverage decisions ($n = 70$), plans applied patient subgroup restrictions and site of care restrictions in 89% and 17% of decisions, respectively. No plans applied step therapy protocols in

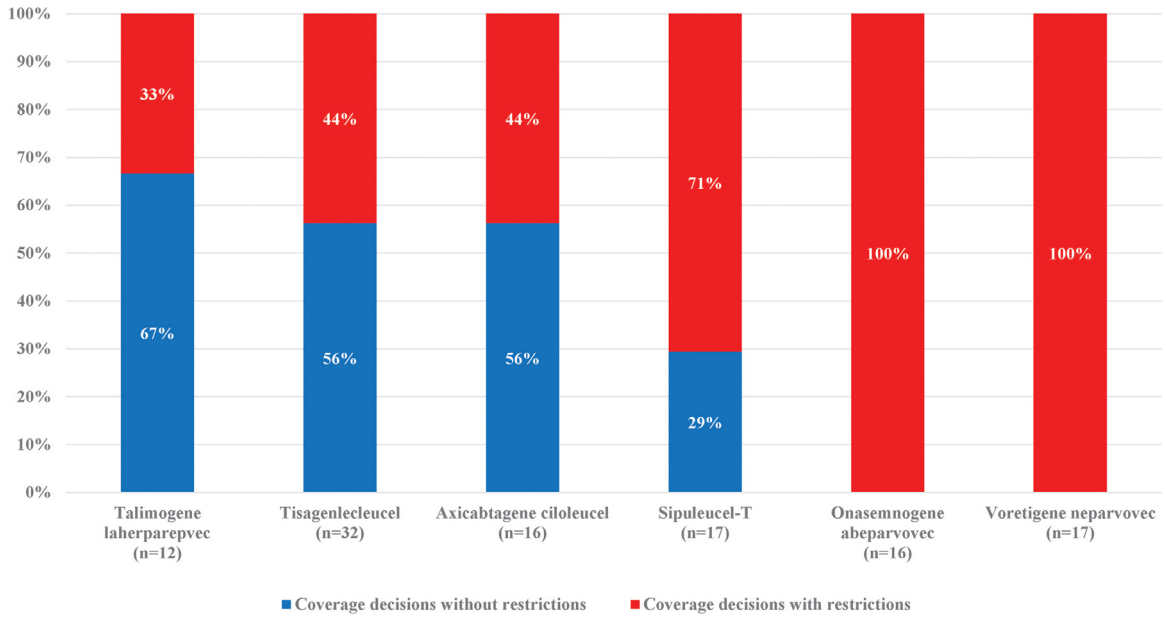

Fig. 1. Coverage restrictions: US commercial health plans # of coverage policies in parentheses — maximum of 17 policies.

their decisions. Health plans included prescriber requirements in 28% (31/110) of decisions. Health plans applied patient subgroup restrictions more consistently in their coverage decisions for some products than others. For instance, in their decisions for axicabtagene ciloleucel, six plans applied the same patient subgroup restriction by limiting access only to patients with an Eastern Cooperative Oncology Group performance status (a measure of patients' general well-being and activities of daily life) of ≤1. In contrast, in their decisions for onasemnogene abeparvovec, 15 plans required that patients have a particular number of copies of the *SMN2* gene (an indirect indicator of disease severity), but details of the requirement varied: one plan required two copies of the *SMN2* gene; two plans required one or two copies; one plan required two or three copies; and 11 plans required three or fewer copies. As noted in the Methods section, the SPEC database does not include information on non-clinical restrictions such as price reductions or managed entry agreements. Medical policies by US payers provide little detail about the specific rationale for clinical restrictions in these policies, and it is therefore not possible to make a direct link between the review of scientific evidence and the clinical restrictions included in these medical policies. General comments about the limitations of clinical studies are mentioned in some medical policies, but not explicitly tied to the clinical restrictions in those policies.

3.2. EU5 and Canada HTA reports

By December 2019, 10 cell and gene therapies had been granted a centralized marketing authorization (MA) in the European Union; three MAs were later withdrawn by the applicant for commercial reasons. Thirty-five HTA opinions were identified from the HTA agencies' official websites. Of the 10 products and 11 indications, G-BA reviewed 10 indications, HAS and NICE 8, AIFA 5, and other HTA agencies <5. HTA reports from Canada were available for the two tisagenlecleucel indications. Tisagenlecleucel and axicabtagene ciloleucel were reviewed by most agencies, while other products were reviewed by <50% of HTA agencies.

After the cutoff date for this review, onasemnogene abeparvovec was approved in Europe, but no HTA report was available at the time of manuscript preparation. In addition, the G-BA has recently issued a review of betibeglogene autotemcel (autologous CD34+ cells encoding $\beta^{A\text{-}T87Q}$-globin gene). Results were updated accordingly.

3.2.1. Clinical reimbursement restrictions

Coverage restrictions based on clinical or patient criteria were issued in only three cases in Europe (Fig. 2). T-vec received EMA authorization for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC, and IVM1a) with no bone, brain, lung, or other visceral disease. In England, it is reimbursed only for patients for whom immunotherapy was not suitable.

Darvadstrocel (an allogenic stem cell therapy for treatment of complex perianal fistulas associated with Crohn's disease) was approved in Europe for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. In France, it is reimbursed for the subpopulation with complex, uncomplicated perianal fistulas, in combination with biologic therapy only in patients with quiescent or non-active Crohn's disease, with complex but not complicated perianal fistulas, and following an inadequate response (non-closure of fistula openings) to at least one biologic therapy in the previous 6 months.

Betibeglogene autotemcel received EMA approval for the treatment of patients aged ≥12 years with transfusion-dependent β-thalassemia who do not have a $\beta 0/\beta 0$ genotype, and for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen-matched related HSC donor is not available. In France, the population is limited to patients aged between 12 and 35 years.

Most cell and gene therapies are administered in specialized centers only. For example, the two CAR-T cell therapies — axicabtagene ciloleucel and tisagenlecleucel — are restricted to specialized referral centers in the different countries. The autologous CD34+ for severe combined immunodeficiency related to adenosine deaminase deficiency (Strimvelis®) has only one approved manufacturer because of its 6-hour shelf life. This treatment is currently only available at Hospital San Raffaele Telethon Institute for Gene Therapy in Milan. Patients need to travel to this hospital for treatment

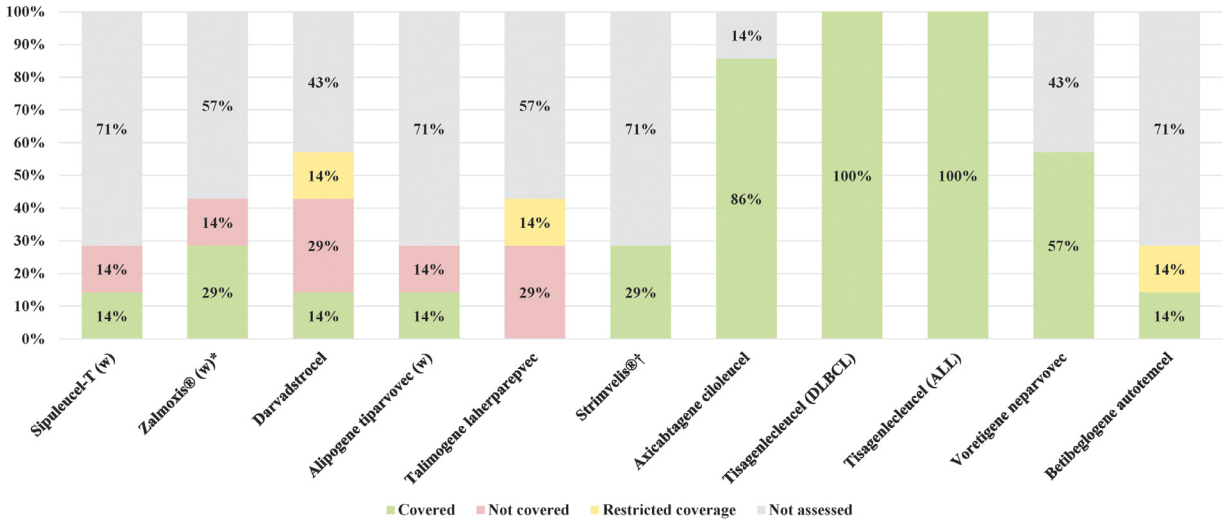

Fig. 2. Coverage restrictions based on clinical or patient criteria: EU5 and Canada. *W* = marketing authorization withdrawn.
*Allogeneic T cells. †Autologous CD34+ cells transduced to express adenosine deaminase deficiency.

with Strimvelis®. In France, administration of Luxturna® is authorized in just one center to date.

3.2.2. Non-clinical reimbursement restrictions

In the EU5 and Canada, non-clinical restrictions, specifically price reductions and managed access agreements, were identified in several countries (Table 1). In England, among the seven cell and gene therapies for which HTA reports were available, NICE has recommended reimbursement of two cell and gene therapies with negotiated price reductions called patient access schemes, and two CAR-T cell therapies (tisagenlecleucel and axicabtagene ciloleucel) were funded through the Cancer Drugs Fund, with requirements for additional data collection and future review of the incremental cost-effectiveness ratio in light of newly collected data. In Italy, AIFA has recommended four cell and gene therapies with managed entry agreements. In Canada, a price reduction has been negotiated for tisagenlecleucel and voretigene neparvovec.

3.2.3. Rationale

HTA reports often provide a rationale for decisions to limit access, with scientific uncertainty typically listed as the key reason. Single-arm study, short duration, and indirect comparison were reported as major sources of effectiveness uncertainty in 30–70% of reports. These HTA reports do not generally provide a specific explanation about the link between individual types of uncertainty and the specific clinical or non-clinical restrictions recommended.

4. Discussion

US health plans have applied restrictions in approximately 67% of their cell and gene therapy coverage policies. This suggests that US plans are substantially more restrictive in their coverage of cell and gene therapies compared with other orphan products, for which coverage is restricted in about 30% of health plan policies [13]. Given their high price, it is perhaps not surprising that health plans apply restrictions to the coverage of cell and gene therapies. Previous studies have shown that US health plans apply coverage restrictions more often to therapies with higher annual costs [9]. It is notable, however, that the frequency of coverage restrictions varied across US payers. We found that some health plans applied coverage restrictions more often than others, and that when health plans did apply restrictions, they did so inconsistently.

This variation is important because US residents who are enrolled in different health plans will not have equal access to these therapies, even when the clinical circumstances are identical. For instance, an SMA patient with three copies of the *SMN2* gene would be ineligible for treatment with onasemnogene abeparvovec if they were enrolled in three health plans in our sample, but would be eligible if enrolled in the other plans. This variation is also important for physicians, as it means that they must tailor individual treatment decisions not only to their patients' clinical presentation, but also to their insurance coverage. However, because most commercial health plans are provided through employers, individual consumers may have limited ability to select health plans that cover these therapies.

Medical policy reports from US payers do not provide a detailed explanation of the evidentiary basis of the restrictions in these policies, unlike the situation with HTA reports from the EU5 and Canada. It is therefore not possible to understand the scientific rationale for most coverage restrictions in US payer policies, which leaves questions unanswered about the reasons for diverging from the scientific basis reflected in the clinical indications approved by the FDA.

It is possible that the variation in these restrictions reflects the uncertainty regarding clinical benefits of these products, or that the restrictions reflect concerns about the cost of these therapies. The US policies do not describe which of those concerns, or possibly others, are the basis for the coverage restrictions. In general, factors that support access and reasons for restricted access are available in many but not all ex-US HTA reports. HTA agencies should explain their specific considerations for arriving at final recommendations. This has been common practice in US Medicare coverage decisions for approximately 20 years [14].

This study suggests that EU5 and Canadian HTA bodies recommend access to fewer cell and gene therapies than US health plans, which may reflect a more stringent approach in the context of limited evidence and high scientific uncertainty that is commonly associated with this class of therapies. In contrast, when coverage is recommended, it is typically consistent with the criteria included in regulatory approvals, with only a few exceptions where HTA bodies applied restrictions beyond the regulatory label. The EU5 and Canadian HTA bodies make market access recommendations reflecting scientific evidence that is appraised according to explicit HTA decision analytic frameworks [15]. Specifically, most HTA agencies continue to rely heavily on evidence from higher quality studies, such as randomized controlled trials, in their assessments of benefits, risks, and value [16].

Table 1
EU5 and Canada Non-clinical Reimbursement Restrictions.

	France	Italy	Spain	England/Scotland	Germany	Canada
Sipuleucel-T	Not assessed	Not assessed	Not assessed	Not covered/not assessed	Covered	Not assessed
Zalmoxis®* (withdrawn)	Not covered	Not assessed	Not assessed	Not assessed	Covered	Not assessed
Darvadstrocel	Restricted indication	Not covered	Not assessed	Not covered	Covered	Not assessed
Alipogene tiparvovec (withdrawn)	Not covered	Not assessed	Not assessed	Not assessed	Covered	Not assessed
Talimogene laherparepvec	Not assessed	Not assessed	Not covered	Restricted indication + PAS/not assessed	Covered (no added benefit)	Not assessed
Strimvelis®†	Not assessed	Covered with MEA	Not assessed	Covered/not assessed	Not assessed	Not assessed
Axicabtagene ciloleucel	Covered	Covered with MEA	Covered with MEA	Covered with MEA/covered with PAS	Covered	Not assessed
Tisagenlecleucel (DLBCL)	Covered	Covered with MEA	Covered with MEA	Covered with MEA/covered with PAS	Covered	Covered with price reduction
Tisagenlecleucel (ALL)	Covered	Covered with MEA	Covered with MEA	Covered with MEA/covered with PAS	Covered	Covered with price reduction
Voretigene neparvovec	Covered	Covered	Not assessed	Covered with PAS	Covered	Covered with price reduction
Betibeglogene autotemcel	Restricted indication	Not assessed	Not assessed	Not assessed	Covered	Not assessed

ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; MEA, managed entry agreement; PAS, patient access scheme.
* Allogeneic T cells, †Autologous CD34+ cells transduced to express adenosine deaminase deficiency.

As noted, the evidence available for cell and gene therapy products at the time of approval is often less robust than for the classes of therapies with which HTA agencies are familiar. For example, in France, HAS will only accept subgroup analyses that have been pre-specified, and considers secondary endpoints only if the statistical analysis adjusts for multiple testing. In both France and Germany, HAS and G-BA often reject indirect treatment comparisons despite existing European guidelines that support their use [17]. Similarly, HAS and G-BA consider single-arm trials with historical controls to represent low-grade evidence, and inadequate to demonstrate superiority over current standard of care. While UK HTA bodies are, in general, more receptive to indirect comparison and historical controls, their recommendations still reflect the view that such study designs result in high uncertainty regarding benefits and risks, and make cost-effectiveness findings more uncertain. This uncertainty is reflected in the variety of novel payment mechanisms, such as requirements to collect additional data and price discounts.

While HTA groups and payers have clearly expressed concerns with the high degree of scientific uncertainty at the time of regulatory approval, strategies to address these concerns are still developing. Given that restrictions in coverage policies and HTA recommendations are often influenced by residual uncertainty at the time of product approval, mechanisms to promote the generation of additional evidence to reduce uncertainty could be considered as an alternative to restrictions.

Outside the US, there is increasing experimentation with managed entry agreements as a mechanism to promote further evidence generation. However, there is not yet a significant body of experience to determine the impact of these approaches on patient outcomes and/or financial consequences. Managed entry agreements are used with greater frequency, but usually involve substantial price concessions in addition to data collection commitments.

Some experience from EU countries not included in this study provides additional examples of experimentation with payment models for cell and gene therapies. For example, in Sweden, Tandvårds- och läkemedelsförmånsverket (the national pricing and reimbursement authority) and the NT-council, (representative for the regions and the health care providers) have started working on ways to implement innovative payment models for cell and gene therapies. The purpose is to explore if innovative payment models can overcome both the uncertainty barrier and the budget barrier [18].

Outcomes-based agreements are being explored in the US as an approach to pay the full value-based price at the time of launch, with manufacturers at risk of paying rebates if longer-term outcome expectations are not met. These have not yet spread widely to US payers because of challenges related to the operational burden as well as limited availability of meaningful outcome measures to which these agreements should be linked.

Efforts are also underway to develop the infrastructure that can efficiently gather high-quality, long-term, real-world data on these interventions [19]. New approaches to longitudinal data collection have the potential to reassure payers and regulators about long-term benefits and risks; however, these therapies may be replaced by newer alternatives within five years, raising doubts about the practical utility of these data.

Finally, uncertainty at the time of product launch and the high cost of these products have led public payers in many countries to negotiate price discounts as an element of market access agreement. Because these agreements between drug companies and payers are confidential, we do not know if these agreements differ by jurisdiction, or if the magnitude of the price reduction is linked to any other managed entry agreements or novel payment mechanisms.

5. Limitations

Our analysis includes all currently approved cell and gene therapies. However, the limited number of such therapies approved in Europe and Canada, and the relatively small number of HTA reports available, make it difficult to draw more concrete conclusions. The therapies reviewed represent a heterogeneous group, ranging from highly effective to those with limited additional benefit. In some cases, a well-established, conventional therapy is available, while in others there may be no existing treatment alternative. Despite these sources of variability, the type of evidence limitations observed in this report are likely to persist going forward, with future therapies being supported by single-arm studies, short-term trials, surrogate endpoints, and other limitations that have been well documented in the HTA literature.

The comparisons between the US payer policies and HTA reports from the EU5 and Canada are hampered by differences between payer policies and HTA reports. The US health plan policies state directly what the payers will cover, and under what circumstances, while in the HTA reports from Europe and Canada, actual patient access will sometimes depend on how closely local payers follow the recommendations from the national HTA body. This connection is strong in France, Germany, and the UK, and less so in Canada, Spain, and Italy, where there are regional payers with active policy-making functions. Therefore, it is possible that in some cases, additional restrictions may be imposed by local payers, going beyond the official HTA recommendation.

The analysis of US payer medical policies has several limitations. First, these findings may not be generalizable to other commercial health plans, or to public health care payers. Second, not all health plans issued a coverage policy for each cell and gene therapy in our sample. Third, we did not account for differences in the included health plans. For instance, some plans are larger than others, and some are national while others are regional. Fourth, we did not account for how often patients successfully appeal denied coverage. Finally, we did not evaluate whether market access policies for cell/gene therapies differed in specific ways compared with policies for orphan therapies that are not cell/gene therapies.

6. Conclusions

Patients' access to cell and gene therapies varies across health plans in the US as well as member states in Europe and Canada. Our findings suggest that US commercial health plans use their coverage policies as a tool to carefully manage the utilization of these therapies. In Europe, several countries made no decisions regarding access for several gene therapies, and they remain unavailable in those countries.

These data and observations suggest that patient access to cell and gene therapies following regulatory approval is restricted in all geographic regions studied, although the nature of these restrictions differs between the US health plans and the EU5/Canada HTA recommendations. The primary underlying reasons for access restrictions in all regions appear to be scientific uncertainty at the time of approval, limited evidence, and the high cost of these therapies.

Access to cell and gene therapies remains very heterogeneous for different payers and countries, despite all decision makers using the same studies and evidence in their policy development processes. These differences are linked to the variable perspectives on policy development in the setting of higher than traditional scientific uncertainty. In some jurisdictions, this is being addressed with risk-sharing arrangements and other forms of managed entry agreements.

It would be valuable to engage the HTA and payer communities in continued discussions about how best to reduce uncertainty over time, while allowing patient access to promising, innovative therapies, and avoiding barriers to access that are linked to the geographic location of the organization that is paying for the patient's care. Within the limitations that inherently arise from the numerous, variable contextual factors affecting access decisions, payers, HTA groups, drug companies, and other stakeholders should work together to define the "uncertainties" more clearly, and collaboratively develop market access policy mechanisms that balance the benefits of early access with ongoing data collection that provides missing evidence over time.

Disclosures of conflicts of interest

Sean Tunis has received honoraria from Novartis Gene Therapies, Inc., for conduct of this study and participation in the Forum for Gene Therapy Health Ecomonics (ForGHE) advisory board. He has also received payment for participation on a Biomarin advisory board and participated in a scientific advisory board meeting for UCB Pharma. **Eve Hanna** is a consultant at Creativ-Ceutical, a company offering consulting services for pharmaceutical companies. **Peter J. Neumann** reports advisory boards or consulting from AbbVie, Amgen, Novartis Gene Therapies, Inc., Bayer, Congressional Budget Office, Vertex, Veritech, Janssen, Merck, Novartis, Novo Nordisk, Precision Health Economics, and funding from The CEA Registry Sponsors by various pharmaceutical and medical device companies. He also reports grants from Amgen, Lundbeck, Bill and Melinda Gates Foundation, NPC, Alzheimer's Association, NIH. **Mondher Toumi** is Professor of Public Health at Aix Marseille University and consultant at Creativ-Ceutical, a service provider in life sciences. Creativ-Ceutical has contracts with a broad range of pharmaceutical companies, several of which are being engaged in research, development, and commercialization in the field of gene therapies. **Omar Dabbous** is an employee of Novartis Gene Therapies, Inc. **Michael Drummond** has received consulting fees from Novartis Gene Therapies, Inc. **Frank-Ulrich Fricke** has received honoraria for ad board participation and consulting services from Novartis Gene Therapies, Inc./Novartis, Biomarin, Takeda, and other companies with an interest in gene therapy. **Sean D. Sullivan** has received research support and served as a consultant to Novartis Gene Therapies, Inc. **Daniel C. Malone** is a consultant to Novartis and Novartis Gene Therapies, Inc. He has also served as a consultant for Sarepta, Pharmacyclics, Currax, and Seres, and on advisory boards for Biomarin and Novartis. **Ulf Persson** has not received any economic contribution to disclose. IHE, The Swedish Institute for Health Economics have received economic contributions for consultancy services from Bluebird Bio and from Novartis Gene Therapies for attending the ForGHE advisory board. **James D. Chambers** reports personal fees from Astellas Pharma, personal fees from Lundbeck, outside the submitted work; and The Center for the Evaluation of Value and Risk (CEVR) receives funding from a variety of sources, including government agencies, foundations, and pharmaceutical and device companies. Some of the companies that CEVR receives funding from manufacture cell and gene therapies.

CRediT authorship contribution statement

Sean Tunis: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Eve Hanna:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Peter J. Neumann:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Mondher Toumi:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **Omar Dabbous:** Conceptualization, Funding acquisition, Methodology, Resources, Validation, Visualization, Writing –

review & editing. **Michael Drummond:** Conceptualization, Writing – review & editing. **Frank-Ulrich Fricke:** Validation, Visualization, Writing – review & editing. **Sean D. Sullivan:** Investigation, Methodology, Writing – review & editing. **Daniel C. Malone:** Validation, Visualization, Writing – review & editing. **Ulf Persson:** Validation, Visualization, Writing – review & editing. **James D. Chambers:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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