# Cost-effective, but unaffordable: how can we pay for cell and gene therapies?

prof. dr. Steven Simoens

# Pricing and reimbursement of innovative medicines

# A health economic perspective



If society pursues the objective of maximising population health subject to limited resources, equity and solidarity principles, health economics provides instruments to price and reimburse innovative treatments which offer a therapeutic benefit at an acceptable cost and fill unmet medical needs

# Health economic instruments

## Economic evaluation

Economic evaluation calculates additional costs and health gain of cell and gene therapy as compared to alternative

*Assesses cost-effectiveness of cell and gene therapy*



## Budget impact analysis

Budget impact analysis calculates impact on health expenditure from adopting a new cell and gene therapy

*Assesses affordability of cell and gene therapy*



# Pricing of innovative medicines




= *supply-side approach*

Costs of:

- R&D
- Production
- Marketing
- Sales
- Profit margin

= *demand-side approach*

Price equals willingness to pay for incremental value of innovative medicine as compared to alternative

Garrison et al. Value-Based Pricing for Emerging Gene Therapies: The Economic Case for a Higher Cost-Effectiveness Threshold. J Manag Care Spec Pharm. 2019 Jul;25(7):793-799.

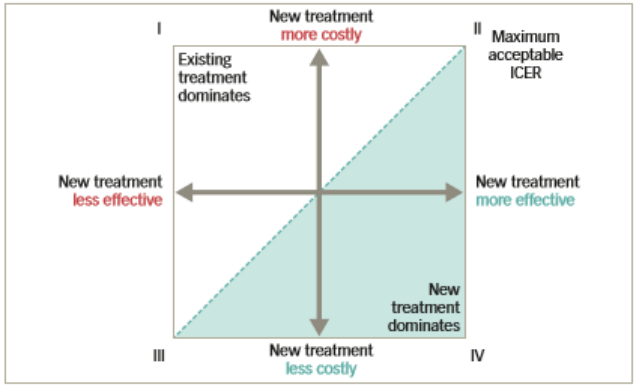
# Cost-plus pricing

Since 2000, multiple empirical studies have estimated how much it costs to research and develop an innovative medicine

Although there are differences in methodology, parameter values, samples and time periods between studies, R&D costs per innovative medicine (accounting for cost of failures) range from US$944m to US$2,826m (in 2019 prices)

# Value-based pricing

Figure 2: Cost-effectiveness plane diagram to assess the ICER and whether the additional health gained from using a certain drug outweighs any additional cost to the healthcare system resulting from its use




*ICER = incremental cost-effectiveness ratio.*

Table 1: World Health Organization cost-effectiveness threshold for selected European countries

| Country | WHO cost-effectiveness threshold (US$)[38] | |
|---|---|---|
| | GDP per capita in 2016 | 3 x GDP per capita in 2016 |
| Belgium | 44,881 | 134,643 |
| Denmark | 46,603 | 139,809 |
| France | 42,384 | 127,152 |
| Germany | 48,190 | 144,570 |
| Italy | 36,313 | 108,939 |
| Norway | 69,296 | 207,888 |
| Portugal | 28,515 | 85,545 |
| Spain | 36,451 | 109,353 |
| Sweden | 49,678 | 149,034 |
| The Netherlands | 50,846 | 152,538 |
| UK | 42,514 | 127,542 |

*GDP is the total market value of all final goods and services produced in a country in a given year. GDP per capita is calculated by dividing GDP by midyear population. To make meaningful comparison between countries, GDP per capita PPP data were used, by adjusting for differences in prices in different countries. The WHO cost-effectiveness threshold of 3 x GDP per capita per life year/QALY gained was calculated from GDP per capita per life year/QALY gained using 2016 projected GDP per capita data from the International Monetary Fund.[38] GDP = gross domestic product; PPP = purchasing power parity; QALY = quality-adjusted life year; WHO = World Health Organization.*

Simoens S et al. *European Oncology & Haematology* 2017;13 (2),108-113

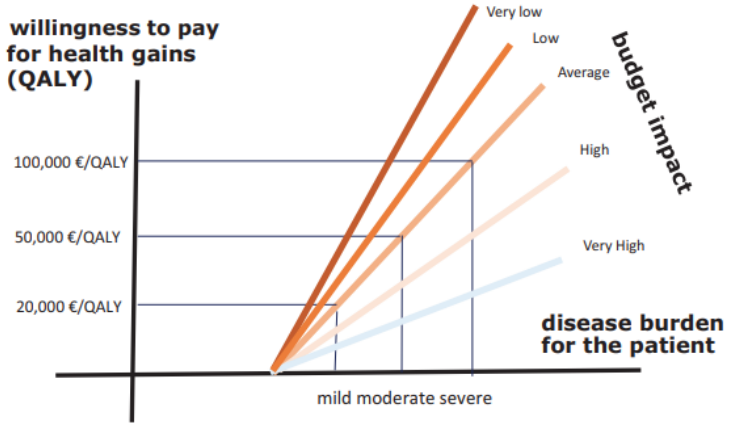
# How do we (price and) reimburse innovative medicines in Belgium?

Study of class 1 medicines (2010-2017):

- Higher probability of negative reimbursement decision if cost-effectiveness > €31,000 / QALY
- Higher probability of positive reimbursement decision until budget impact of €3.5 million

Van Dyck W., et al. Access decision-making in the Belgian Commission for Reimbursement of Medicines 2010-2017: investigating the readiness for value-based pricing. Vlerick Policy Paper Series no. 8 (October 2018).

# Cost-effective, but unaffordable

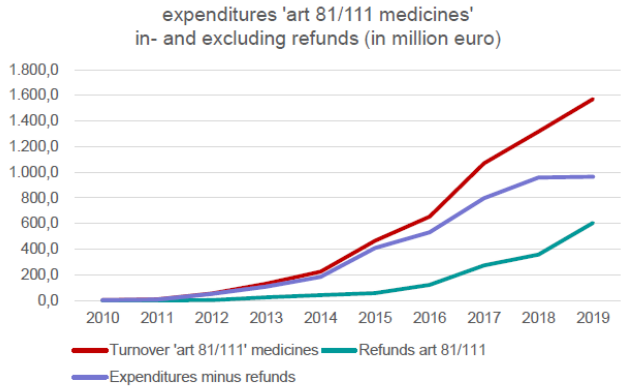


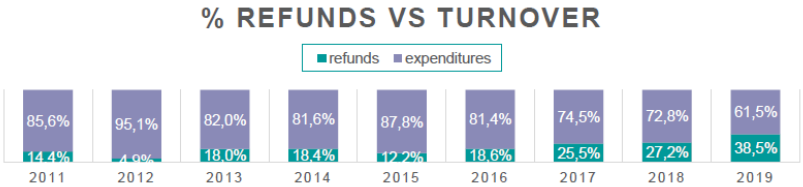

Adjust cost-effectiveness threshold in function of budget impact (and other criteria):

- maximum willingness to pay per unit of health gain should be higher for medicines with lower budget impact and targeting more severe disease
- appraisal of a medicine with high budget impact for less severe disease should be subject to lower cost-effectiveness threshold

Annemans L. A proposal for value informed, affordable ("via") prices for innovative medicines. Journal of Medical Economics 2019,22:11,1235-1239.

# Do managed entry agreements provide the answer?




Directie Farmaceutisch Beleid – Dienst voor Geneeskundige Verzorging RIZIV. Monitoring Of Reimbursement Significant Expenses MORSE Rapport 2020 (gegevens 2019). https://www.inami.fgov.be/SiteCollectionDocuments/MORSE%20_apport_gegevens_tot_2019.pdf

# Do managed entry agreements raise list prices?

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SPECIAL ISSUE PAPER

WILEY Health Economics

## The impact of managed entry agreements on pharmaceutical prices

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**Abstract**

Managed entry agreements (MEAs) have been used for several years, with the aim of curbing the growth of pharmaceutical expenditure and enhancing patient access to innovation. Yet, much remains to be understood about their economic implications. This paper studies the impact of MEAs on list prices, that is, prices before the deduction of any discount. Using a theoretical model, we show that, under most price setting regimes, the introduction of an MEA leads to a higher list price. This is confirmed by our empirical analysis of a sample of 156 medicines in six countries, providing a conservative estimate of the increase in price due to the MEA of 5.9%. A relevant policy implication is that payers may overestimate the financial gains that can be achieved through this tool.

KEYWORDS

managed entry agreements, pharmaceutical prices, risk-sharing agreements

# Pricing and reimbursement of cell and gene therapies

# Reimbursement of cell and gene therapies varies across Europe

**Payer decisions regarding gene therapies approved in Europe, the US and Canada**

| Product | Europe | | | | | | US | | Canada | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MA date | Payer decisions (EU big 5) | | | | | MA date | Payer | MA date | Payer |
| | | France | Germany | UK | Italy | Spain | | | | |
| ~~Glybera®~~ | ~~2012~~ | ~~NR~~ | ~~R~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ |
| Imlygic® | 2015 | NA | NR | R | R | NA | 2015 | R | NA | NA |
| Strimvelis® | 2016 | NA | NA | R | R | NA | NA | NA | NA | NA |
| Kymriah® | 2018 | R | R | R | R | R | 2017 | R | 2018 | R[a,b] |
| Yescarta® | 2018 | R | R | R | R | R | 2017 | R | 2019 | E[a] |
| Luxturna® | 2018 | R | R | R | NA | NA | 2017 | R | NA | NA |
| Zynteglo® | 2019 | NA | R | NA | NA | NA | NA | NA | NA | NA |
| ~~Zalmoxis®~~ | ~~2016~~ | ~~NR~~ | ~~R~~ | ~~NA~~ | ~~R~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ | ~~NA~~ |
| Zolgensma® | 2020 | NA | E | NA | NA | NA | 2019 | R | NA | NA |

Abbreviations: E, reimbursement expected; MA, marketing authorization; NA, not applicable as application for marketing authorization or reimbursement has not been submitted or a decision has not yet been reached; NR, not reimbursed; R, reimbursed

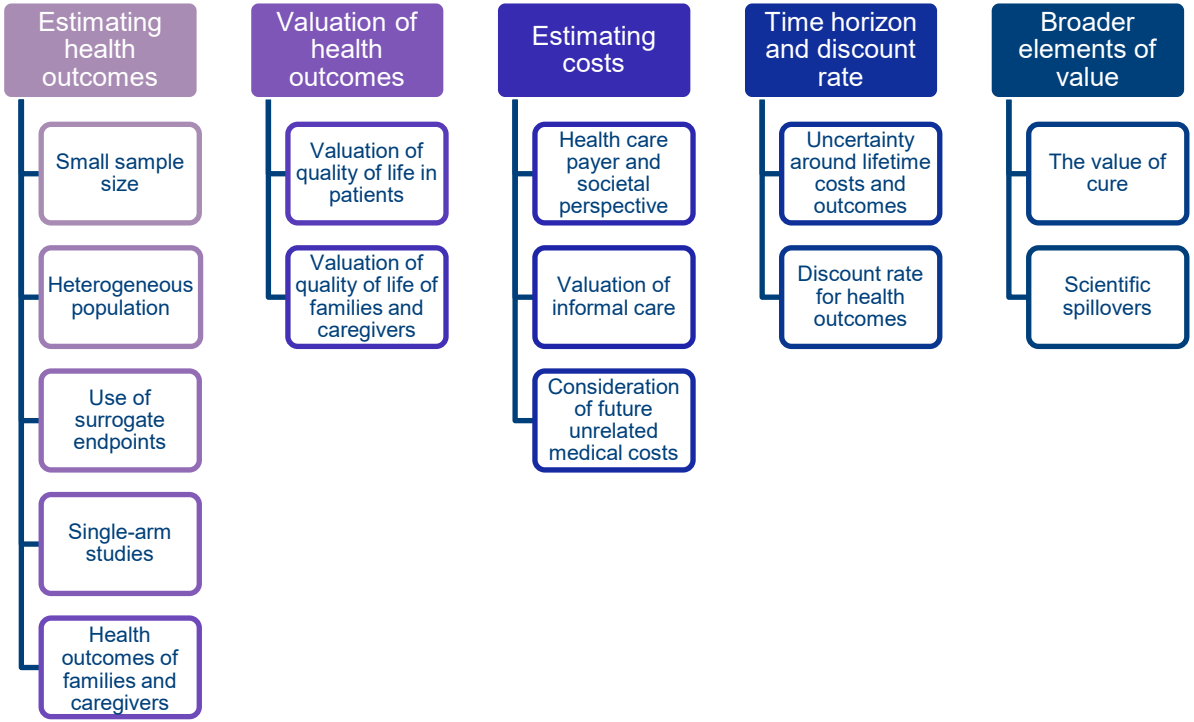
Legend: Green, countries where product is reimbursed; Red, countries where reimbursement of product was refused; Blue, decisions are no longer effective as product is withdrawn from the market; Yellow, recommended by HTA body but not reimbursed by any payer.

a. Recommended by national HTA body on the condition of a substantial price reduction

b. Reimbursed in Ontario and Quebec

van Overbeeke et al. Market access of gene therapies across Europe, the US and Canada: challenges, trends and solutions. Drug Discovery Today 2021;26(2):399-415.

# Cost-effectiveness of cell and gene therapies




Aballéa et al. Health economic evaluation of gene replacement therapies: methodological issues and recommendations. Journal of Market Access and Health Policy 2020, vol. 8, no. 1, 1822666.

# Cost-effectiveness of cell and gene therapies

| Year | Country | CGT | Comparator | Indication | Cost-effectiveness |
|---|---|---|---|---|---|
| 2017 | UK | CAR-T | Standard of care | Acute lymphoblastic leukaemia | £49,995/QALY |
| 2019 | USA | CAR-T | Standard of care | Relapsed/refractory B-cell acute lymphoblastic leukaemia | $64,600/QALY |
| 2018 | SCO | Yescarta® | Best supportive care | Relapsed or refractory diffuse large B cell lymphoma and primary mediastinal large B cell lymphoma | £57,943/QALY |
| 2019 | SCO | Kymriah® | Salvage chemotherapy | Relapsed or refractory diffuse large B-cell lymphoma | £49,975/QALY |
| 2018 | USA | Kymriah® | Clofarabine | Childhood B-cell acute lymphoblastic leukaemia | $45,871/QALY |
| 2018 | USA | Kymriah® | Clofarabine | Paediatric patients with relapsed or refractory leukaemia | $46,000/QALY |
| 2018 | USA | Kymriah® | Blinatumomab-clofarabine | Relapsed or refractory paediatric B-cell acute lymphoblastic leukaemia | $61,000/QALY |
| 2018 | USA | Yescarta® | Salvage chemotherapy | Relapsed or refractory large B-cell lymphoma | $55,128/QALY |

Lloyd-Williams and Hughes. A systematic review of economic evaluations of advanced therapy medicinal products. Br J Clin Pharmacol. 2020;1–16.

# Cost-effectiveness of cell and gene therapies

At which price is Kymriah® cost-effective using a $100,000 per quality-adjusted life year gained threshold in the United States?

- Value-based price of $505,999 vs clofarabine monotherapy; $557,141 vs clofarabine combination therapy; $491,442 vs blinatumomab; $488,470 vs other salvage chemotherapies; $663,965 vs allogeneic stem cell transplant
- Actual price of $475,000

Hao Y, Eldjerou LK, Yang H, Qi C, Globe D. Cost-effectiveness analysis of CTL019 for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia in the United States. Blood. 2017;130 suppl. 1:609.

# Budget impact of cell and gene therapies

Does price tag of cell and gene therapies (estimates range from $500,000 to $1 million or more per treatment) raise issues for affordability and payment?

As compared to alternative therapies for diseases for which cell and gene therapies are available or in development:

- Lifetime costs of prophylactic or periodic factor administration for hemophilia A are $5-10 million
- Costs of heart transplant, the only curative therapy currently available for end-stage heart failure, are $1,670,000

High upfront drug acquisition costs vs long-term cost offsets (and health gains)

Orkin and Reilly. Paying for future success in gene therapy. Science. 2016;352(6289):1059-61.
Ali. The heart of market access: opportunities and challenges for cell and gene therapy development for orphan and prevalent cardiovascular diseases. Cell & Gene Therapy Insights 2020; 6(7), 1141-1153.

# Budget impact of cell and gene therapies

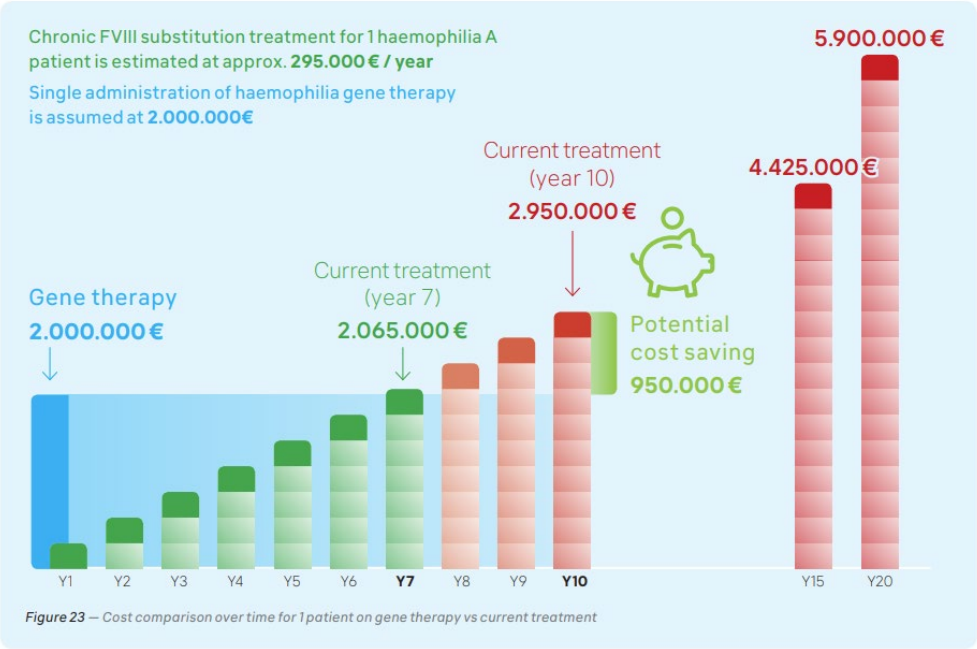



*Figure 23 — Cost comparison over time for 1 patient on gene therapy vs current treatment*

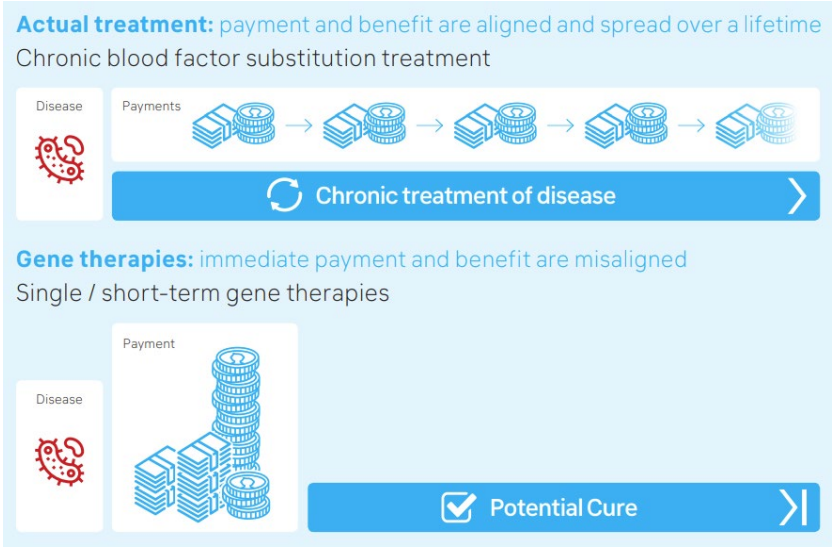
Cost of gene therapy approximately equals cost of chronic FVIII substitution treatment during 7 years

If gene therapy is assumed to be effective for 10 years, gene therapy saves €950,000 per patient over this period

Maes et al. Innovative solutions for paradigm changing new therapies – Policy report based on multi-stakeholder round tables. 2019.
https://www.inovigate.com/media/filer_public/e8/9c/e89ca2b0-1dcf-48fb-9afc-9e911ddcef84/innovative_funding_solutions_-_short_version_without_appendix_vs09.pdf

# Cell and gene therapies: challenges for affordability and payment

## One-time cost is not aligned with long-term health benefits




Maes et al. Innovative solutions for paradigm changing new therapies – Policy report based on multi-stakeholder round tables. 2019.
https://www.inovigate.com/media/filer_public/e8/9c/e89ca2b0-1dcf-48fb-9afc-9e911ddcef84/innovative_funding_solutions_-_short_version_without_appendix_vs09.pdf

# Outcome-based managed entry agreement

= contractual agreement between manufacturer and payer which ties reimbursement to effectiveness of cell and gene therapy in real world

**TABLE 3**

**Outcome-based payment scheme categories and definitions.**

| Scheme category | Definition |
|---|---|
| Cost sharing arrangements | Price reduction for initial treatment cycles until it is clear whether a patient is responding to the medicine |
| Payment-by-results | Innovators reimburse the payer in full in instances where the patient does not respond to the treatment |
| Risk sharing | Innovators reimburse a proportion of the cost of the medicine for non-responders |
| Outcomes guarantees/ pay-for-performance | Innovators provides rebates, refunds or price adjustments if the medicine fails to meet pre-agreed outcome targets at the individual patient level |
| Coverage with evidence development | Access to a drug is initially provided on the condition that further population-level evidence is gathered. Based on this further evidence the payer then makes a decision whether to continue funding the treatment or not |
| Conditional treatment continuation | Payment for the continued use of a given drug is based on intermediate endpoints at the individual patient level |

Hague and Price. Challenges and proposed solutions to value assessment and reimbursement of CAR-T therapies in Europe. Cell & Gene Therapy Insights 2020; 6(7), 1013-1028.

# Challenges for implementing outcome-based agreement with spread payments

**Payment structure**

- Payment amounts
- Duration of payments
- Compliance with accounting rules
- Flexible agreement that accounts for competitive environment

**Outcome correction**

- Individual-level or population-based

**Set up of data collection**

- Study design
- Selection of outcomes
- Data infrastructure and administrative burden
- Data quality, protection and analysis

**Governance structure**

- Role, responsibilities, interests and incentives of stakeholders (payer, manufacturer, health care provider)
- Ownership of data
- Funding arrangements of the agreement
- Decision-making rules to adjust payments based on outcomes

Michelsen S, Nachi S, Van Dyck W, Simoens S, Huys I. Barriers and Opportunities for Implementation of Outcome-Based Spread Payments for High-Cost, One-Shot Curative Therapies. Front Pharmacol. 2020;11:594446.

# Outcome-based agreement with spread payments for cell and gene therapies in BE

**Kymriah® (tisagenlecleucel) for adults with r/r DLBCL**

- Pay-for-performance: *treatment response and patient condition at 6, 12, 18, 20 months*
- Spread payments: *at administration (€296,800), 12 months (€21,200), 20 months (€21,200)*

**Yescarta® (axicabtagene ciloleucel) for adults with r/r DLBCL**

- Pay-for-performance: *treatment response and patient condition at 6, 12, 18, 20 months*
- Spread payments: *at administration (€304,220), 12 months (€21,200), 20 months (€21,200)*

National Institute for Health and Disability Insurance. Search engine reimbursable medicines. 2019; https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch

# Assessment of cell and gene therapies by cross-country collaborations

## BeNeLuxAI

- Horizon scanning
- Health technology assessment (HTA)
- Information sharing
- Pricing and reimbursement

*Joint HTA, pricing and reimbursement of Spinraza® for spinal muscular atrophy in Belgium and the Netherlands*

*Is conducting joint HTA of Zolgensma® for spinal muscular atrophy*

https://beneluxa.org/

## FINOSE

- Health technology assessment (HTA)

*Joint HTA of Zynteglo® for transfusion-dependent ß-thalassaemia in Finland, Norway and Sweden*

https://www.fimea.fi/documents/160140/1454401/FINOSE+joint+assessment+report+Zynteglo+FINAL.pdf/1a1d3dc5-db79-48c8-6622-cff9b04ce088?t=1589197458993

# Take home messages

- Cell and gene therapies can be cost-effective
- Payers struggle with high prices and uncertainties associated with these products
- There is a role for outcome-based managed entry agreements with staggered payments
- How to reconcile cost-effectiveness with affordability?

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