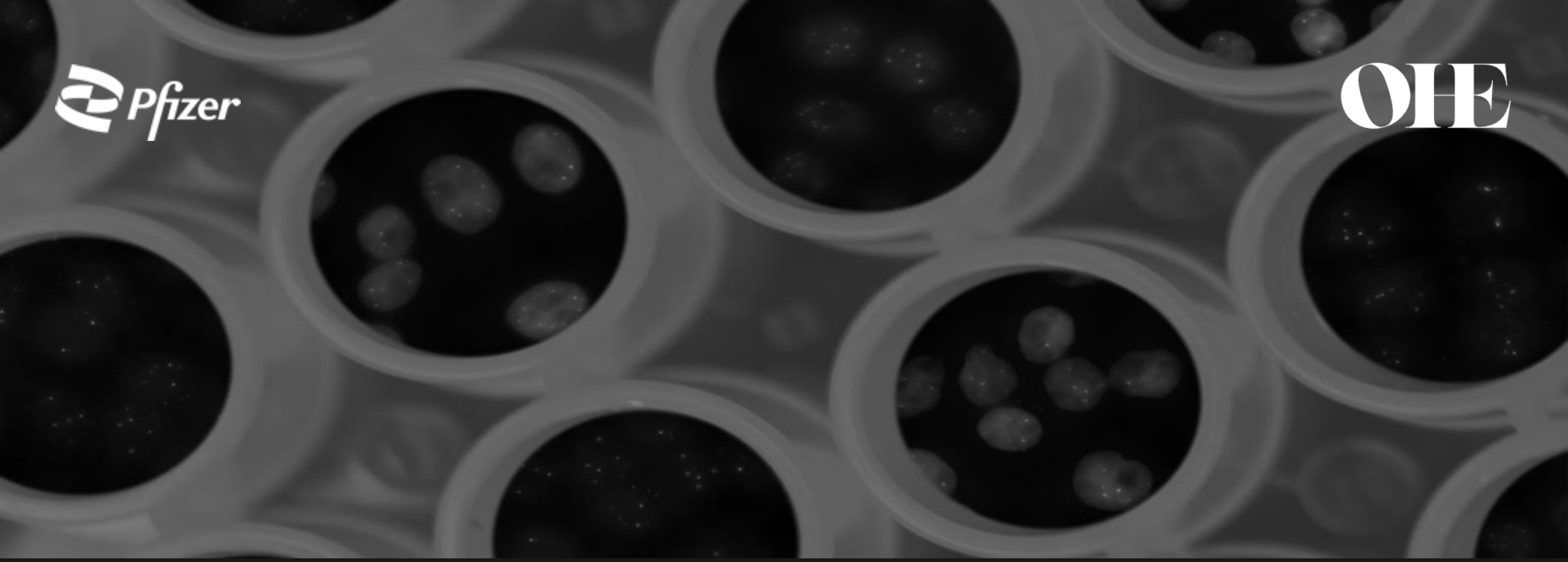
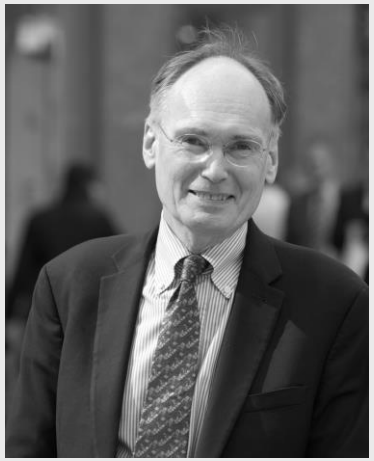


ISPOR EDUCATIONAL SYPOSIUM. 8TH NOVEMBER 2022

Gene Therapies: Where High Promise Meets High Uncertainty, How Should HTA Methodologies Appropriately Value and Enable Access?

chair



PROF ADRIAN TOWSE
Director Emeritus and Senior Research Fellow
OHE

DR AMANDA COLE
Senior Principal Economist
OHE

JOSIE GODFREY
Director
JG Zebra Consulting

DR RUTH KIM
Value & Evidence Team Leader Rare Disease and Internal Medicine
Pfizer

DR ORIOL SOLA-MORALES
Chair & Founder
HiTT Foundation

Agenda

AGENDA	
Welcome	Prof Adrian Towse
Overview of the challenges of HTA of gene therapies and the actionable recommendations to improve access	Dr Amanda Cole
Patient perspective: Why the need for solutions? Building evidence for HTA: Practical example from Project HERCULES	Josie Godfrey
Industry perspective: What is the role for developers in overcoming the challenges?	Dr Ruth Kim
Payer perspective: What can we change about the way we evaluate and pay for these medicines to facilitate access?	Dr Oriol Solà-Morales
Audience Q & A	All
Closing Remarks	Prof Adrian Towse

Overview of challenges & potential solutions

Dr Amanda Cole, Senior Principal Economist, OHE

Project objectives

Generate expert **consensus** on:

01

Challenges

The **limitations of current HTA methods** for the assessment of gene therapies: issues arising

02

HTA solutions

Deriving the **principles of the HTA solutions** that can best address the challenges identified for gene therapies

03

Policy recommendations

Implementing the solution: practical recommendations for changes to HTA methods and processes.

OHE

Our findings are detailed in our report published in June 2022.

Focus: HTA methodology

https://www.ohe.org/publications/health-technology-assessment-gene-therapies-are-our-methods-fit-purpose

“Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use”

Source: FDA, 2020. What is Gene Therapy? *FDA*. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

Gene therapy: the benefits

It is broadly accepted that gene therapies have the potential to transform lives and provide further benefits for society and the health system.

These may include:

- The potential to correct underlying genetic defects, offering the potential for transformational health gains rather than simply managing symptoms.
- A single dose/short duration treatment regime to confer lifelong improvement rather than a lifetime of ongoing treatment, thereby dramatically reducing costs associated with years of chronic care management.
- Increased carer and family quality of life

- Several gene therapies have been developed and recommended by HTA agencies in indications such as spinal muscular atrophy (SMA) and inherited retinal dystrophy.
- However, these therapies still present unique challenges during HTA, and the factors driving their value to patients and society are also unique.
- Additionally, gene therapies are often indicated for rare diseases and so face the same challenges as other orphan medicines
- **How should HTA evolve to enable the potential opportunities associated with gene therapies to be realised?**

Challenges of HTA of Gene Therapies

INITIAL ASSESSMENT OF CLINICAL EFFECTIVENESS

- **Generalisability** of clinical trial results
- **Trial design**: alternatives to RCTs
- Appropriate **outcome measures**
- Differing HTA body/payer **evidence requirements** increase the difficulty of designing trials

ASSESSMENT OF COSTS

- One/short duration treatments mean high **irrecoverable costs**
- Does / should **budget impact** affect the value-for-money rule used for reimbursement?
- Patient **portability** (insurance policyholders)

UNCERTAINTY REGARDING LONG-TERM OUTCOMES

- **Short-term follow up** (requires modelling)
- Uncertainty over whether **benefits sustained**
- Uncertainty regarding adverse events & **safety concerns**
- Need for appropriate HTA methods to handle uncertainty
- **Discount rates**

INCORPORATING ADDITIONAL ELEMENTS OF VALUE

- Are potentially **one-time treatments/life-changing therapies** valued more by society?
- Importance of **severity weighting**
- **Spillover effects** on family members/carers and society
- **Other elements,** including equity, insurance value, option value, etc.

Actionable Recommendations

- … To better capture the value of gene therapies
  - Incorporate methods to recognise the potential *lifetime benefits* of gene therapies by including a lifetime perspective in modelling accompanied by sensitivity analysis including of the discount rate.
  - Operationalise *additional elements of value* as part of the decision-making process within HTA, on the basis of continued research.
- … To address uncertainty in outcomes
  - Develop transparent standards for the *inclusion of RWE and surrogate endpoints* in HTA.
  - Include *outcomes-based arrangements or other value-based arrangements* as part of or following HTA to mitigate uncertainty in long term outcomes whilst enabling patient access.
  - *Expand data collection* through registries and international collaboration.
  - Enable *early multi-stakeholder dialogue*, including patient representatives, to align on feasible and appropriate HTA evidence packages.

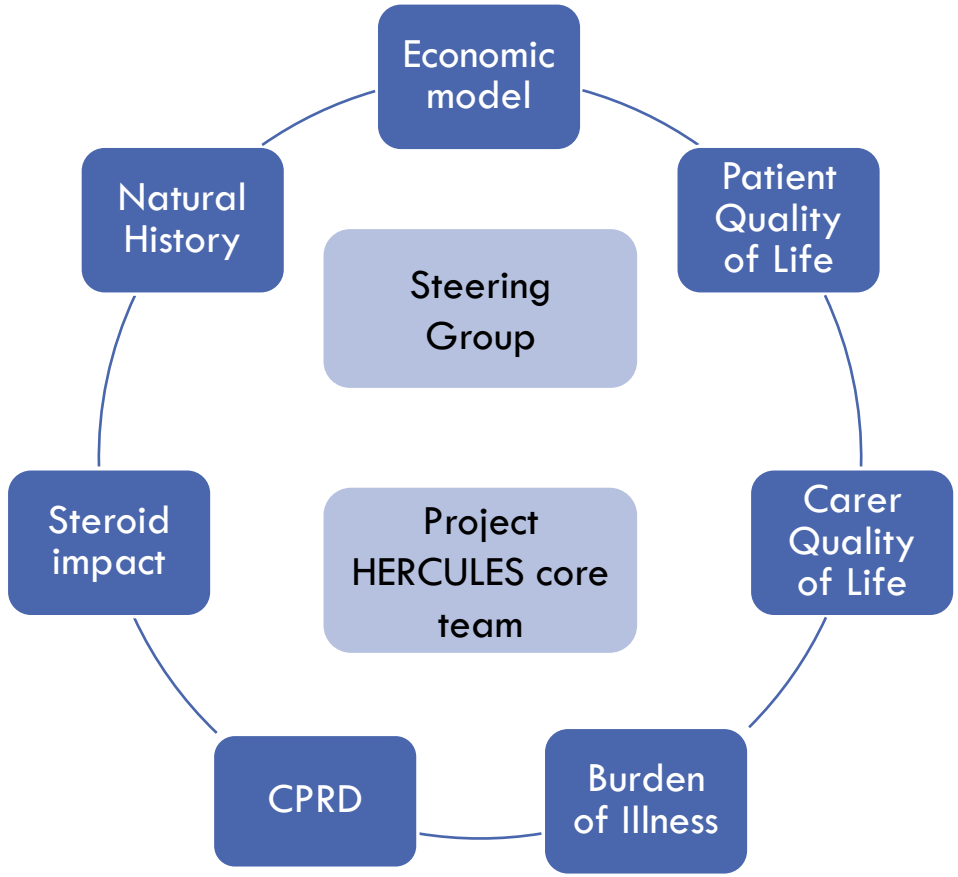
Patient perspective: Building evidence for HTA

Josie Godfrey, Director, JG Zebra Consulting

How does Project HERCULES work?

JGZEBRA CONSULTING

- Strong patient leadership
- Patients at the centre of each workstream
- Iterative approach
- Communications and engagement throughout



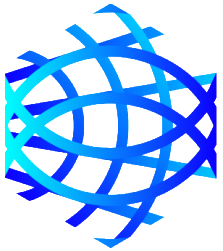
Independent expert advice

Publications, communications and engagement

Unique global collaboration

- Work together to **build the evidence base** for DMD required by Health Technology Assessment bodies.

- To **generate, align and share high quality disease-level tools and data** to enable more transparent and consistent reimbursement decisions.



Duchenne
UK

HERCULES

JGZEBRA CONSULTING

Key findings

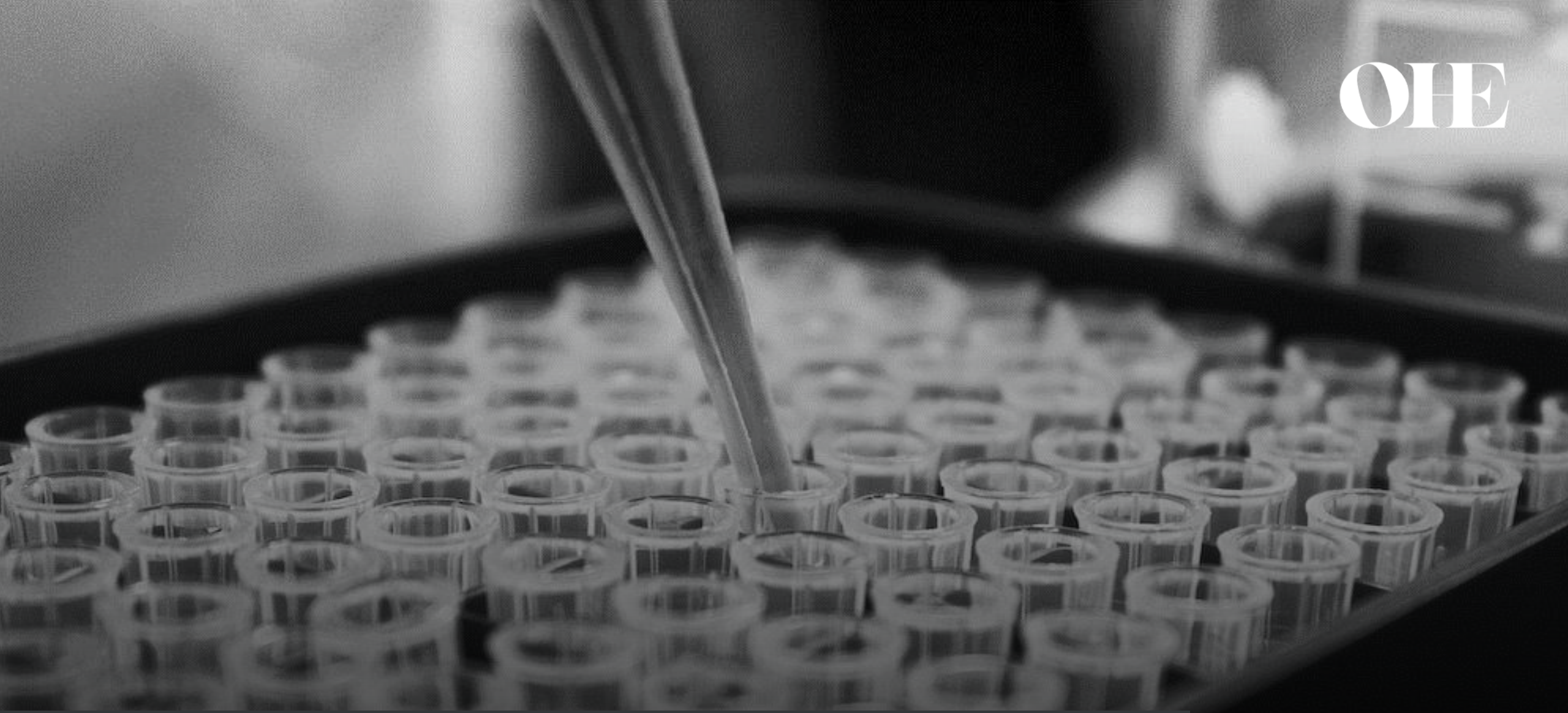
Patient and clinician led disease model

- Quality of life and cost impacts of losing ability to weight bear
- ‘New” disease state – transfer stage between ambulatory and non ambulatory states

We need to better measure what is important to patients and families – *it can’t count if we don’t count it!*

Family/caregiver quality of life and burden of illness is poorly measured

- Looking to develop a measure of carer quality of life that could include other paediatric progressive life-limiting conditions



Industry Perspective

Dr Ruth Kim, Value & Evidence Team Leader, Rare Disease and Internal Medicine, Pfizer, Inc

Recall…

Challenges of HTA of Gene Therapies

OHE

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Pfizer

Challenges to valuing Gene Therapies

INITIAL ASSESSMENT OF CLINICAL EFFECTIVENESS

- Standardized or validated Endpoints
- Surrogate Endpoints?
- Relevance at Approval?

ASSESSMENT OF COSTS

- Patient's life-time, productivity and societal cost
- Budget impact and affordability
- Appropriateness of current ICER threshold?

UNCERTAINTY REGARDING LONG-TERM OUTCOMES

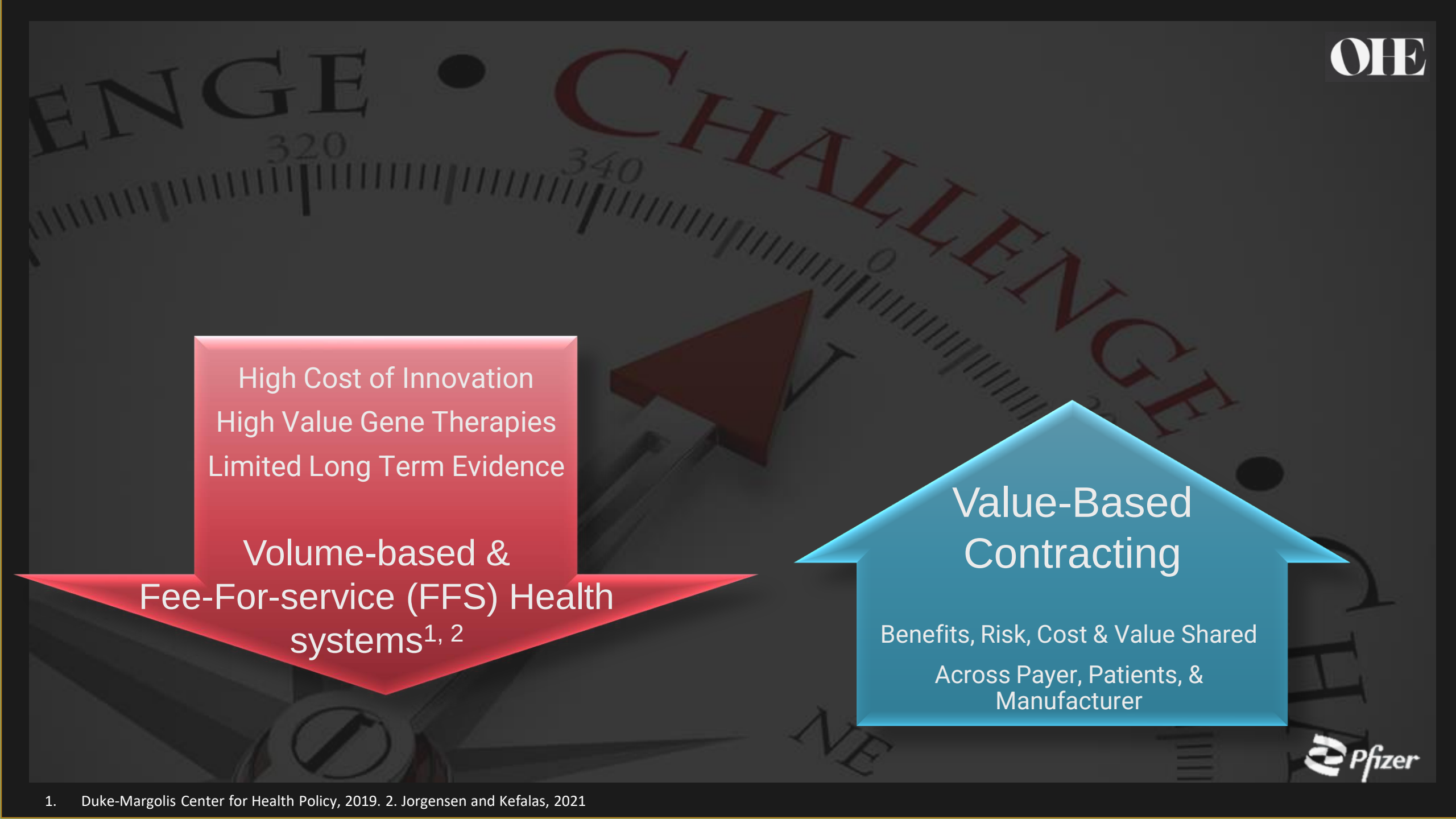
- Durability and sustainability of outcomes
- Life-time potential side effects
- Relevance at approval?

INCORPORATING ADDITIONAL ELEMENTS OF VALUE

such as…

- Quantifying values
- Value of Hope
- severity modifier

Nestler-Parr, S et al., 2018; Person, 2019



1. Duke-Margolis Center for Health Policy, 2019. 2. Jorgensen and Kefalas, 2021

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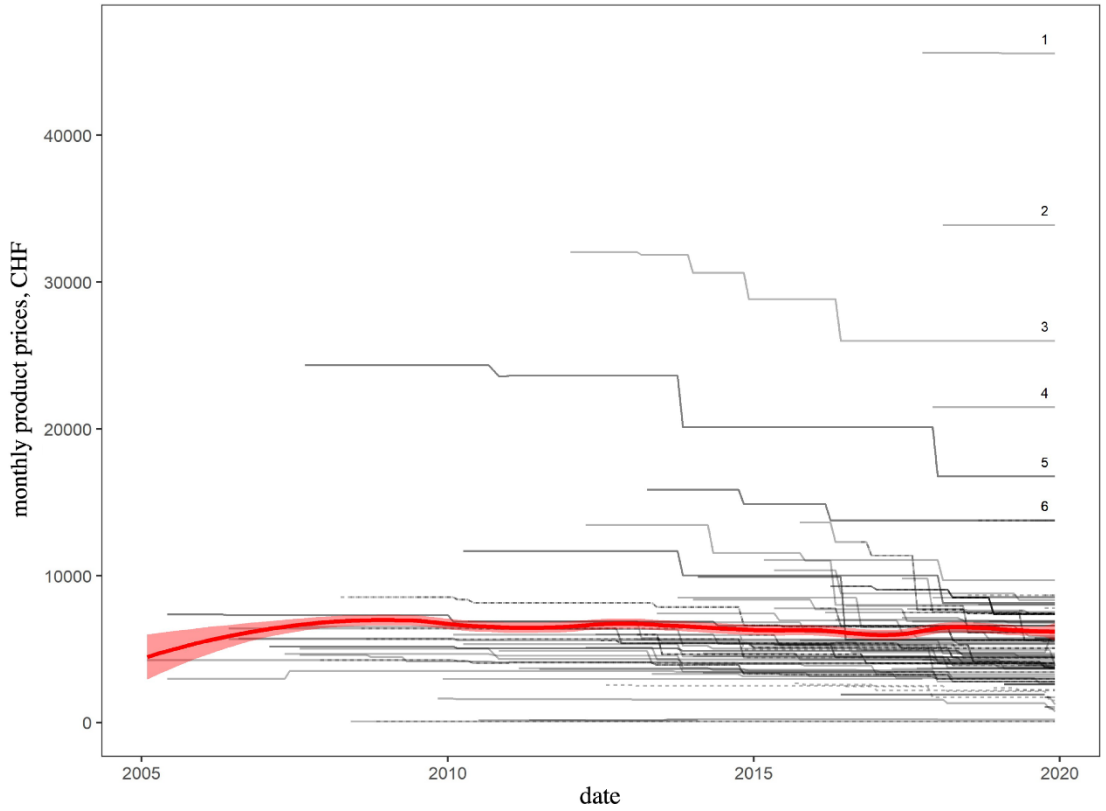
Fundació HiTT

Payer Perspective

Dr Oriol Solà-Morales, Chair & Founder, HiTT Foundation

Pfizer

How are payers doing?



- Cost of Cancer Drugs is not increasing

https://doi.org/10.1371/journal.pone.0259936

Evidence vs Political Will

KYMRIAH® (tisagenlecleucel) vs. YESCARTA® (axicabtagene ciloleucel)

Table 6 Study C2201: Efficacy results in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

	Enrolled patients N=167	Infused patients N=115
Primary endpoint[1]	**N=147**	**N=99**
Overall response rate (ORR) (CR+PR)[2], n (%) 95% CI	**54 (36.7)** (28.9, 45.1)	**54 (54.5)** (44.2, 64.6)
CR, n (%)	41 (27.9)	41 (41.4)
PR, n (%)	13 (8.8)	13 (13.1)
Response at month 3	N=147	N=99
ORR (%)	40 (27.2)	40 (40.4)
CR (%)	34 (23.1)	34 (34.3)
Response at month 6	N=147	N=99
ORR (%)	34 (23.1)	34 (34.3)
CR (%)	31 (21.1)	31 (31.3)
Duration of response (DOR)[3]	**N=54**	**N=54**
Median (months) (95% CI)	Not reached (10.0, NE[5])	Not reached (10.0, NE[5])
% relapse free probability at 12 months	63.4	63.4
% relapse free probability at 18 months	63.4	63.4
% relapse free probability at 24 months	60.8	60.8
% relapse free probability at 30 months	60.8	60.8
Other secondary endpoints	**N=167**	**N=115**
Overall survival (OS)[4]		
% survival probability at 12 months	41.0	48.2
% survival probability at 24 months	33.3	40.4
% survival probability at 36 months	29.0	36.2
Median (months) (95% CI)	8.2 (5.8, 11.7)	11.1 (6.6, 23.9)

1 The primary endpoint was analysed on all patients whose Kymriah was manufactured at the Novartis US facility.
2 ORR is the proportion of patients with best overall response (BOR) of CR or PR based on the Lugano response criteria (Cheson 2014); non-infused patients were assigned BOR=Unknown (i.e. non-responders).
3 DOR was defined as time from achievement of CR or PR to relapse or death due to DLBCL, whichever occurs first.
4 OS was defined as time from date of Kymriah infusion to the date of death due to any cause (N=115) and time from date of enrolment to the date of death due to any cause for enrolled patients (N=167).
5 Not estimable.

A systematic review of meta-analyses assessing the validity of tumour response endpoints as surrogates for progression-free or overall survival in cancer

Katy Cooper, Paul Tappenden, Anna Cantrell & Kate Ennis

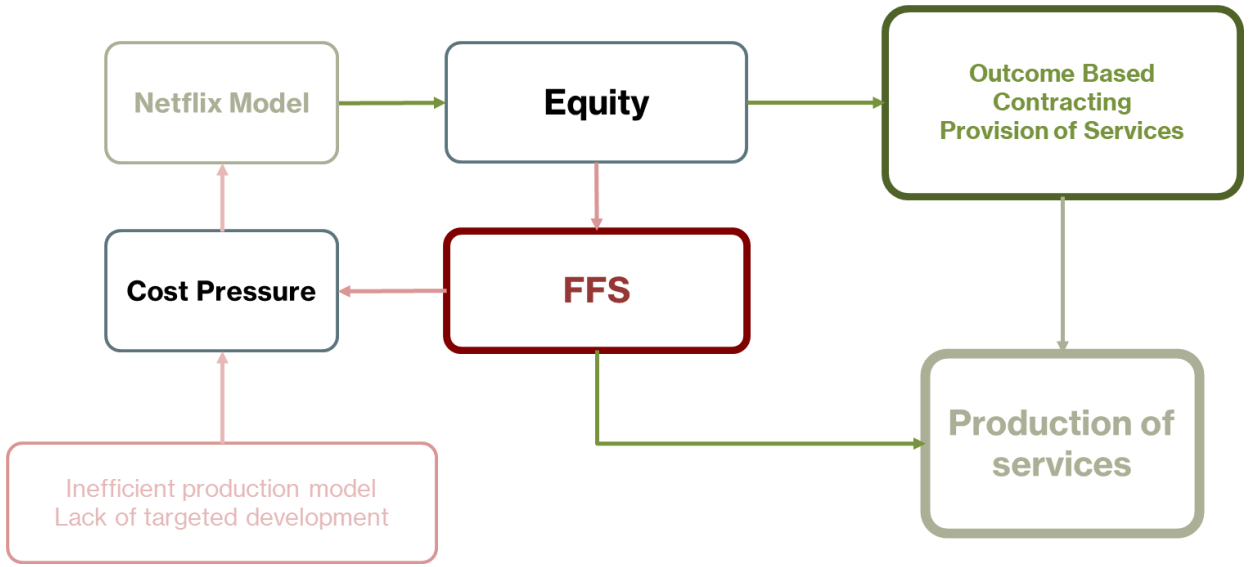
British Journal of Cancer **123**, 1686–1696 (2020) | Cite this article

2072 Accesses | **18** Citations | **14** Altmetric | Metrics

Results: The systematic review included 63 studies across 20 cancer types, most commonly non-small cell lung cancer (NSCLC), colorectal cancer (CRC) and breast cancer. The strength of association between ORR or CR and either PFS or OS varied widely between and within studies, with no clear pattern by cancer type. The association between ORR and OS appeared weaker and more variable than that between ORR and PFS, both for associations between absolute endpoints and associations between treatment effects.
Conclusions: This systematic review suggests that response-based endpoints, such as ORR and CR, may not be reliable surrogates for PFS or OS.

- Because there was political will ORR & CR were accepted

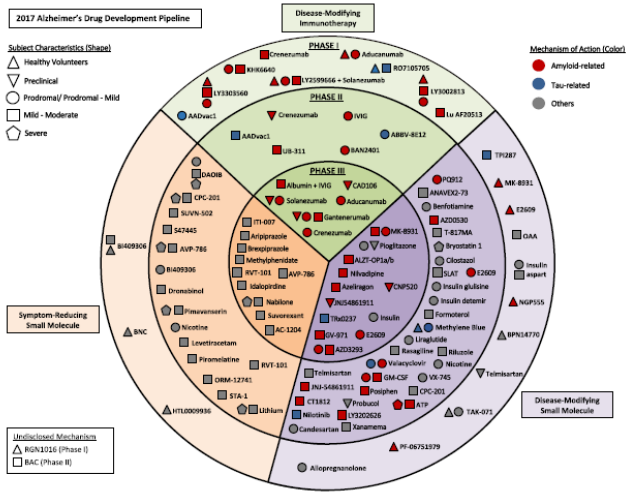
Outcome Based Healthcare



- We need to move away from a **FFS paradigm** to a Producer of Services Paradigm, where the GT (or other) are 'just' part of the solution

The Alzheimer paradox

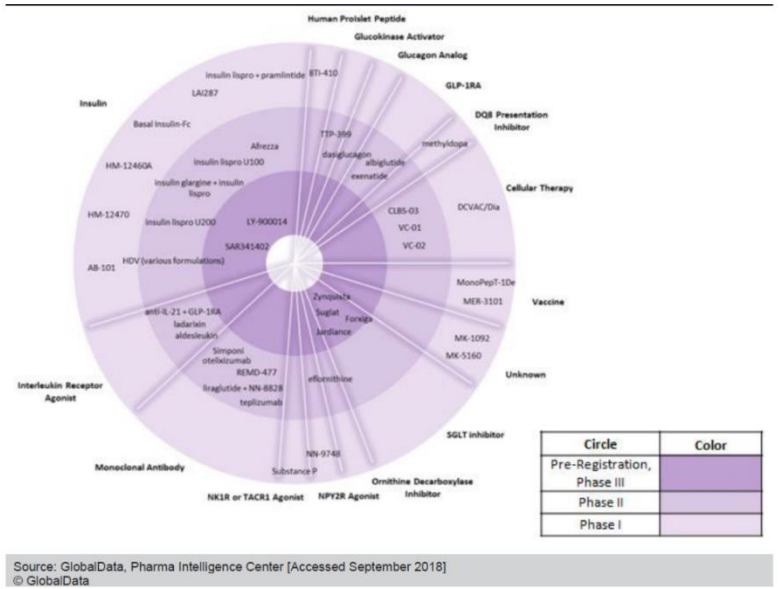
- The potential market is huge
- The potential price is huge
- The potential risk for no-approval is huge



Cummings_AlzDem17
Cummings_AlzDem22

The Diabetes paradox

- What if GT was able to bring a solution to diabetes?
- What if we could provide a solution that provides insulin?
- What if that solution was an mRNA solution?



	Program	Indication	Targets	Internal / Partnered	Discovery	Pre-clinical	IND	Phase I	Phase II
	Dual specific antibody targeting two cytokines	Atopic Dermatitis	IL-13 / TSLP	Internal					
	Conditional agonist/ antagonist for AID	AID	IL-2	Internal					
	Super engager for IO	IO	*Undisclosed*	Internal					
	Molecular exchanger for oncology	Oncology	*Undisclosed*	Internal					
	Designed agonist for autoimmune diseases	AID	*Undisclosed*	NEKTAR	*Undisclosed*				
	Multibodies for diabetes	Diabetes	*Undisclosed*	Lilly	*Undisclosed*				
	Conditional agonist/ antagonist for IO	IO	IL-2	aulos *ATP and Biolojic spinout*					

https://www.pharmaceutical-technology.com/comment/late-stage-type-2-diabetes-pipeline-dominated-drugs/ https://www.biolojic.com/pipeline-1

CAN GENE THERAPY (GT) PRICES REMAIN THE SAME? WHAT WE HAVE LEARNED FROM THE COVID-19 VACCINES

Sigurðardóttir, K., Solà-Morales, O |FHiTT, Barcelona, Spain

Virtual ISPOR Europe 2021 #ISPOREurope

intro & objectives

) have progressively been reaching the ast years, despite the often high per- associated. This high cost has in part been justified by the small target patient population and the high research and development cost associated with GTs. However, in the light of newly approved, low-cost gene therapies, with a vast addressable market, such as the Moderna Covid-19 mRNA vaccine, the question becomes, what impact will this have on the future of GT pricing. The **objective** of this study was to analyse the pricing of marketed gene therapies, and if there is a link between their price and their addressable market.

methods

We identified all EMA approved GTs in the United Kingdom up to the year 2021. We analysed the addressable market for each treatment, and where possible, found their list prices as cited by the NHS and/or NICE. Then we analysed the correlation between the prices and the addressable market.

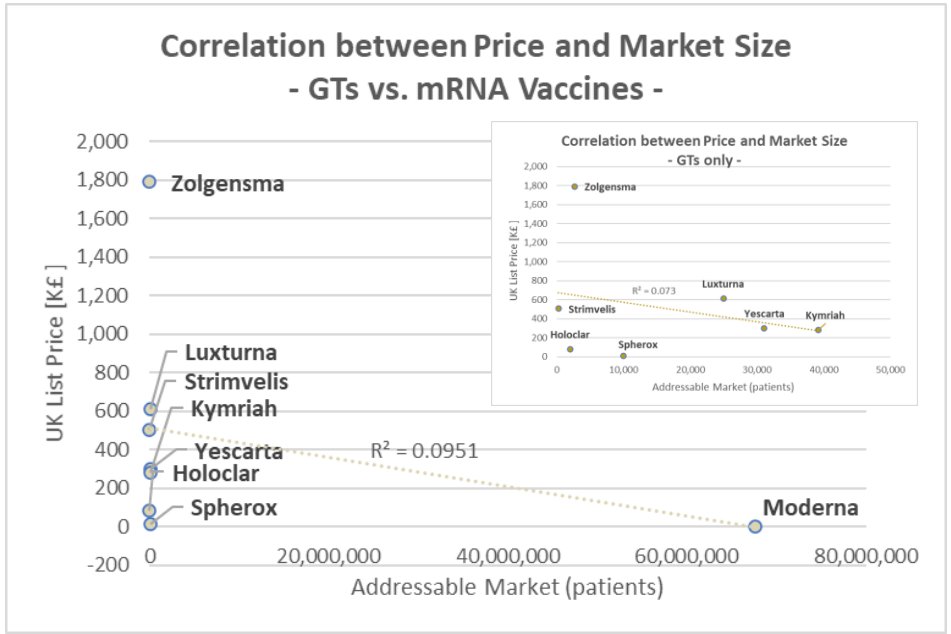
conclusions

Novel mRNA vaccines have set a new standard for the pricing of GTs, and it could be that the willingness to pay for the replication of that innovation is low, thus killing the 'hen of the golden eggs'.

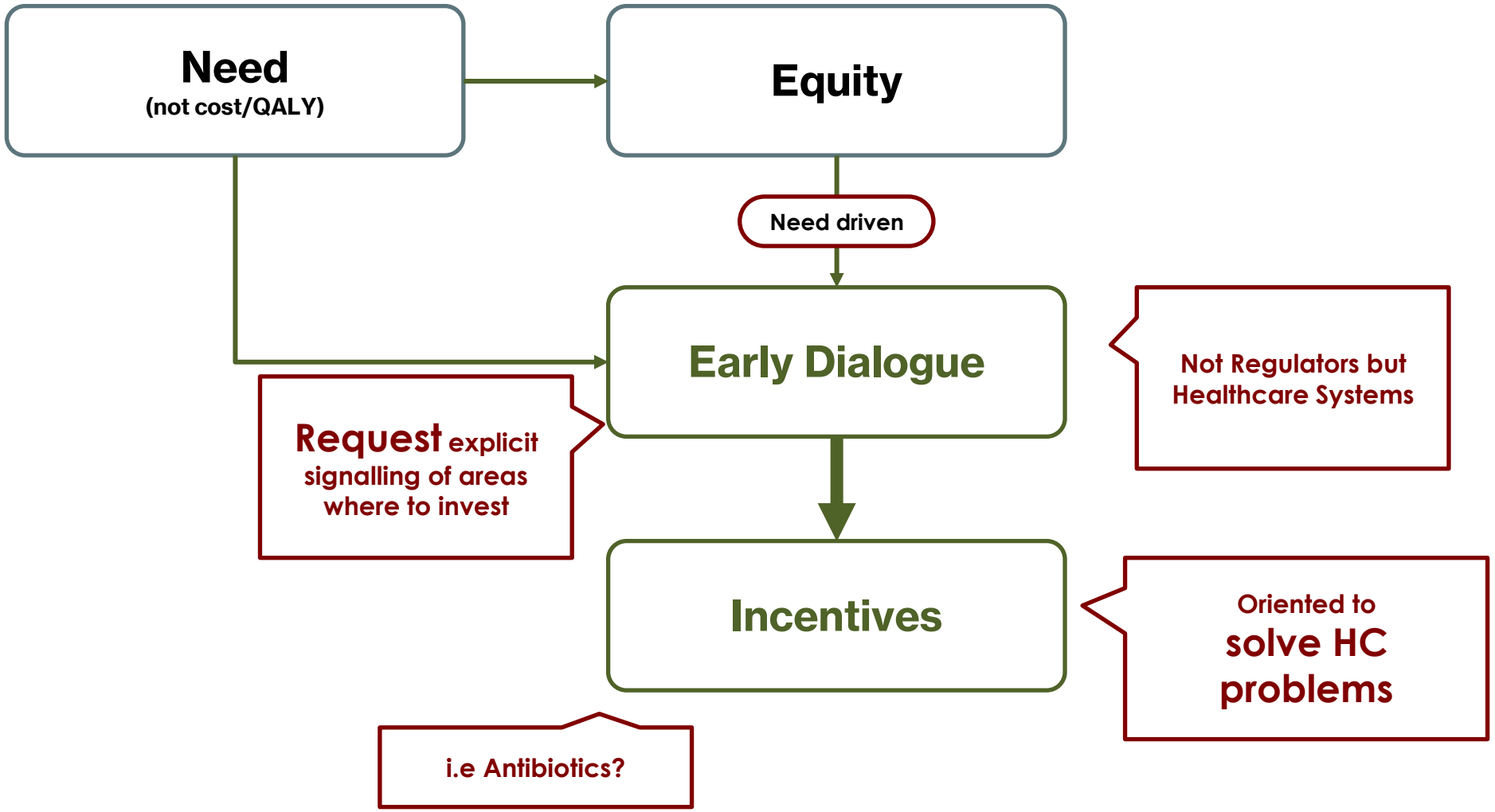
rationale

GT is there to replace a missing/malfunctioning gene. The advent of mRNA vaccines could substitute the current approach by 'obliging' the cell to produce the defective protein. Considering monogenic diseases, **one could regard that providing and delivering genetic material is a ´me-too´ intervention** now that mRNA vaccines have been effectively rolled out on a large scale and at an affordable cost.

Current mRNA vaccines have shown the technology can be cheap (in terms of per person cost). As the manufacturing cost is limited, then the only argument for higher treatment costs relates to the rarity of the target disease such as the increased costs of finding and following patients with rare diseases, increased development costs and cost of cash, etc.



Orient Development to NEED



Conclusion

- The so called patient centric care starts by the assessment of patient's **NEEDS**.
- And how those needs are interpreted by payers in relative terms

  (Epidemiology? QALY lost? QALY Gains? Effect size? NNT?)

- So moving from a Science Opportunity industry to a **NEED SOLUTION PROVIDER**

Fundació **HiTT**

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Audience Q&A

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