SHOULD GENE THERAPIES BE EXEMPT FROM HTA SCRUTINY?

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Developing and Paying for Gene Therapies – Can We Resolve the Conflicts?

Bill Dreitlein, PharmD, BCPS, Institute for Clinical and Economic Review, Boston, MA, USA; **Adrian Towse, MA, MPhil**, Office of Health Economics, London, United Kingdom; **John B. Watkins, PharmD, MPH**, Premera Blue Cross, Mountlake Terrace, WA, USA; **Clark Paramore, MSPH**, BlueBird Bio, Cambridge, MA, USA

Table 1: Conflicts for innovators and payers created by gene therapies

Innovator Challenge	Payer Challenge
Innovators seek fair compensation corresponding with the level of risk required to develop gene therapies	Concerns about affordability and fear of bankrupting the healthcare system
Safety and efficacy are supported by relatively short-term data	Concerns about the certainty of safety and durability or response (Is it truly a cure?)
Developing gene therapies for rare conditions requires trials that utilize small sample sizes, single-arm trials, novel trial designs, and surrogate endpoints	Payers want robust evidence to inform decision making

Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, Palmer S. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. *Health Technol Assess* 2017;**21**(7).

- Use of surrogate endpoints
- Use of historical controls
- Detailing mandated further clinical studies
- Quantifying decision uncertainty
- MEAs: risk sharing, payment plans, discounts, …

FDA Approves Zolgensma, 1st Gene Therapy to Treat SMA in Children Up to Age 2

MAY 24, 2019 BY JOSE MARQUES LOPES, PHD IN NEWS.

Zolgensma, a first gene therapy for spinal muscular atrophy — and first for any chronic neurologic disease — is now an approved and potential "one-time" intravenous treatment for pre-symptomatic newborns through 2-year-olds with any type of SMA, the U.S. Food and Drug Administration (FDA) announced today, issuing an historic decision.

With this news, Novartis' Zolgensma (onasemnogene abeparvovec-xioi) became the first gene therapy for SMA and its second disease-modifying treatment after Spinraza (nusinersen, by Biogen), whose approval came just days before Christmas in 2016.

Zolgensma is now the second FDA-sanctioned gene therapy for a hereditary disease, after Luxturna (voretigene neparvovec-rzyl, by Spark Therapeutics), approved to treat children and adults with inherited retinal dystrophy in December 2017.

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Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value

Table ES11. Results for Spinraza versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	$1,112,000	$590,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

Table ES12. Results for Zolgensma versus BSC in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$2,000,000*	$1,657,000	$3,657,000	12.23	18.17	$243,000	$182,000
BSC	$0	$789,000	$789,000	0.46	2.40	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

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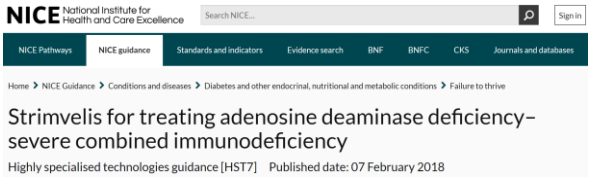
Table ES13. Results for Zolgensma versus Spinraza in Infantile-Onset (Type I) SMA: Health Care Sector Perspective

	Drug Treatment Costs	Non-Treatment Health Care Costs	Total Costs	QALYs	LYs	Incremental Results	
						Cost/QALY Gained	Cost/LY Gained
Zolgensma	$3,630,000*	$1,671,000	$5,301,000	13.46	19.76	$139,000	$117,000
Spinraza	$2,231,000	$1,653,000	$3,884,000	3.24	7.64	--	--

BSC: best supportive care, LY: life-year, QALY: quality-adjusted life year

*Includes the Zolgensma costs (placeholder price of $2 million) and additional Spinraza costs.

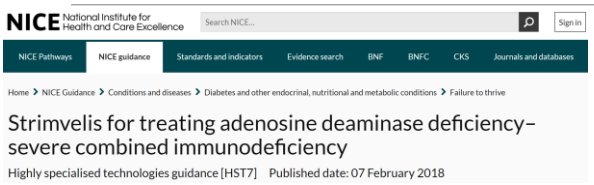
ARE GENE THERAPIES ALWAYS NOT COST-EFFECTIVE?



- Company: incidence at 3 diagnoses/year, Patient group: 6-10
- €594,000 per case

improvement. The committee noted that, when compared with an HSCT from a haploidentical donor, the ICERs for Strimvelis were consistently substantially lower than £100,000 per QALY gained. The committee also noted that there were several health-related benefits and wider benefits of Strimvelis treatment that were not captured in the economic analysis, and recognised that Strimvelis is an innovative technology. The committee concluded that, although Strimvelis was a high-cost technology and uncertainties remained in the clinical evidence, it is likely to provide important clinical benefits for people with ADA–SCID at a cost that is manageable and value for money in the context of a highly specialised service.

ARE GENE THERAPIES ALWAYS NOT COST-EFFECTIVE?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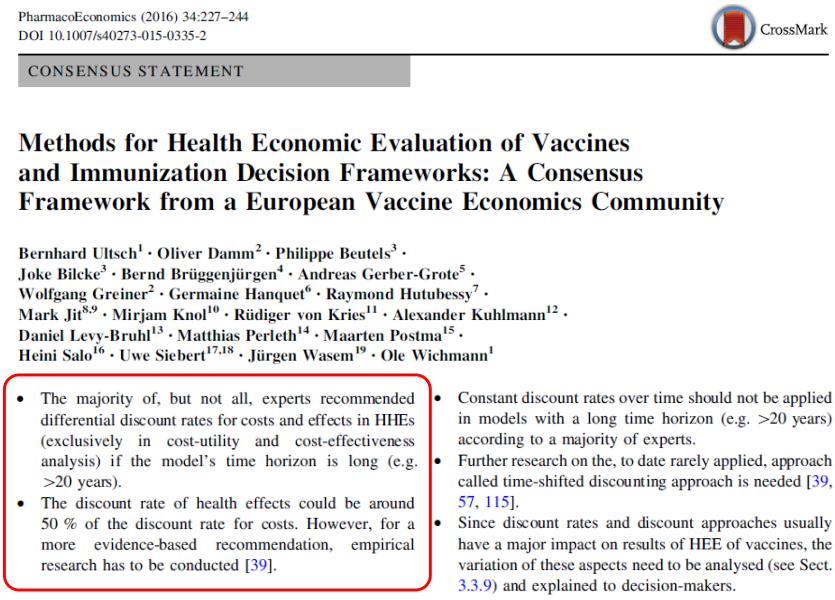
Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency

Highly specialised technologies guidance [HST7] Published date: 07 February 2018

- Discounting has major effect on CE of interventions with LT-effects
- Bit comparable to investing in an infant vaccination program

Discounting rate for costs and health effects

4.28 The committee was aware that NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) specify that the reference case discounting rate is 3.5%. However, it also states that a non-reference-case rate of 1.5% may be used when treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives, if it is highly likely that there will be long-term benefits, and if the treatment does not commit the NHS to significant irrecoverable costs. The committee heard from the company that it considered a discount rate of 1.5% to be most appropriate because Strimvelis restores people who would otherwise die or have a very severely impaired life to full or near-full health, and


PharmacoEconomics (2016) 34:227–244
DOI 10.1007/s40273-015-0335-2

CrossMark

CONSENSUS STATEMENT

Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community

Bernhard Ultsch[1] · Oliver Damm[2] · Philippe Beutels[3] · Joke Bilcke[3] · Bernd Brüggenjürgen[4] · Andreas Gerber-Grote[5] · Wolfgang Greiner[2] · Germaine Hanquet[6] · Raymond Hutubessy[7] · Mark Jit[8,9] · Mirjam Knol[10] · Rüdiger von Kries[11] · Alexander Kuhlmann[12] · Daniel Levy-Bruhl[13] · Matthias Perleth[14] · Maarten Postma[15] · Heini Salo[16] · Uwe Siebert[17,18] · Jürgen Wasem[19] · Ole Wichmann[1]

- The majority of, but not all, experts recommended differential discount rates for costs and effects in HHEs (exclusively in cost-utility and cost-effectiveness analysis) if the model's time horizon is long (e.g. >20 years).
- The discount rate of health effects could be around 50 % of the discount rate for costs. However, for a more evidence-based recommendation, empirical research has to be conducted [39].
- Constant discount rates over time should not be applied in models with a long time horizon (e.g. >20 years) according to a majority of experts.
- Further research on the, to date rarely applied, approach called time-shifted discounting approach is needed [39, 57, 115].
- Since discount rates and discount approaches usually have a major impact on results of HEE of vaccines, the variation of these aspects need to be analysed (see Sect. 3.3.9) and explained to decision-makers.

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EXPERT REVIEWS

Economic evaluation of vaccines: specificities and future challenges illustrated by recent European examples

Expert Rev. Vaccines 12(5), 555–565 (2013)

Maarten J Postma*[1], Tjalke A Westra[1], Sibilia Quilici[2] and Nathalie Largeron[2]

Table 3. Stepwise numerical discounting approaches analyzed in the literature and hypothetical algorithm.

UK Treasury [106]		Beutels *et al.* [1]		Bazelon and Smetters [41]		Hypothetical algorithm	
Time (years)	*Rate (%)*	*Time (years)*	*Rate (%)*	*Time (years)*	*Rate (%)*	*Time (years)*	*Rate (%)*
0–30	3.5	1–5	4	0–10	3.5	0–10	4
31–75	3.0	6–25	3	11–20	1.5	11–20	3.5
76–25	2.5	26–75	2	21 and beyond	0	21–30	3
126–200	2.0	76–300	1			31–40	2.5
201–300	1.5	300 and beyond	0			41–50	2
300 and beyond	1.0					51–60	1.5
						61–70	1
						71–80	0.5
						81 and beyond	0

Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]

Darius N. Lakdawalla, PhD[1,*], Jalpa A. Doshi, PhD[2], Louis P. Garrison Jr, PhD[3], Charles E. Phelps, PhD, MBA[4], Anirban Basu, PhD[5], Patricia M. Danzon, PhD[5]

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Elements of Value

Challenge: Map each element into an underlying economic framework for value assessment.

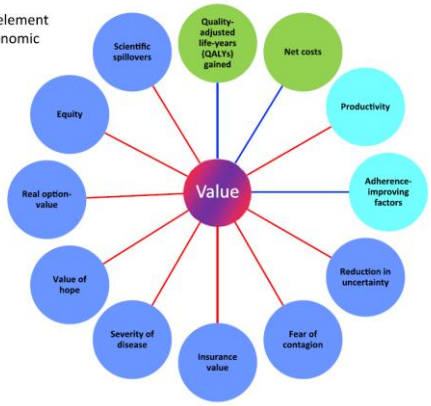

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Table 1 – Value elements inventory.

Elements of value	Type of element	Features of medical technologies in which element is relevant in value assessment	Consideration under health care perspective[§]	Consideration under societal perspective[§]
Net costs[*]	Core	All	Yes	Yes
QALYs gained[*]	Core	All	Yes	Yes
Productivity[†]	Common but inconsistently included	Relevant when treatment has an impact on productivity	No	Yes
Adherence-improving factors[†]	Common but inconsistently included	Relevant when features of the treatment itself improve adherence with the treatment	Yes	Yes
Value of reduction of uncertainty due to a new diagnostic[‡]	Novel	Relevant when the treatment is accompanied by a companion diagnostic test	Yes	Yes
Fear of contagion[‡]	Fear (novel)	Relevant when dealing with treatments for infectious diseases	Yes	Yes
Risk of contagion[‡]	Risk (common)			
Insurance value[‡]	Novel	Relevant when baseline health status is particularly poor	No	Yes
Severity of disease[‡]	Novel	Relevant when considering treatments for end-of-life care or high-severity conditions	No	Yes
Value of hope[‡]	Novel	Relevant when therapies have uncertain effects that cannot be predicted beforehand by a diagnostic test	No	Yes
Real option value[‡]	Novel	Relevant when technology extends the life of patient	No	Yes
Equity[‡]	Novel	All	No	Yes
Scientific spillovers[‡]	Novel	Relevant when technology identifies a new mechanism of action or mode of delivery	No	Yes

QALY, quality-adjusted life-year.
[*] Core elements of value.
[†] Common but inconsistently used elements of value.
[‡] Potential novel elements of value.
[§] Health care versus societal perspectives are as defined by the Second Panel on Cost-Effectiveness.

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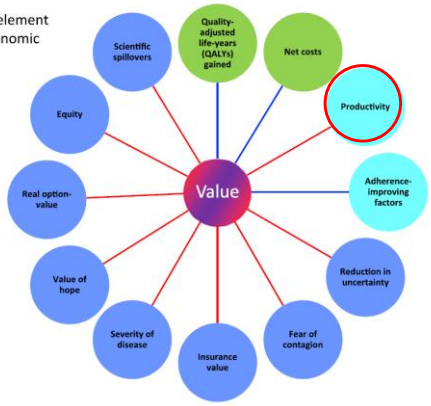

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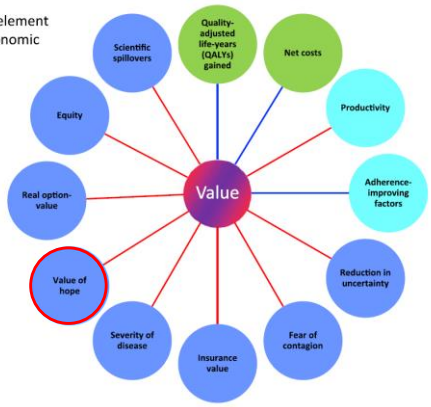

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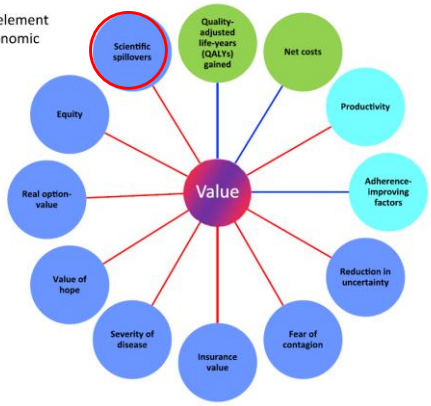

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GENE THERAPIES MAY FIT IN HTA AS

- Broad value framework can be implemented in societal perspective
- Adapt methodological aspects, such as discounting
- Expensive competitors enhance cost-effectiveness
- Managing budgets through investment funds, payment in arrears...

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Kymriah is a medicine for treating two types of blood cancer:

- B-cell acute lymphoblastic leukaemia (ALL), in children and young adults up to 25 years of age whose cancer did not respond to previous treatment, has come back two or more times, or has come back after a transplant of stem cells;
- Diffuse large B-cell lymphoma (DLBCL) in adults whose cancer has come back or did not respond after two or more previous treatments.

Kymriah is a type of advanced therapy medicine called a 'gene therapy product'. This is a type of medicine that works by delivering genes into the body.

The blood cancers that Kymriah is used to treat are rare, and Kymriah was designated an 'orphan medicine' (a medicine used in rare diseases) for B-cell ALL on 29 April 2014 and DLBCL on 14 October 2016.

Kymriah contains the active substance tisagenlecleucel (consisting of genetically modified white blood cells).

TISAGENLECLEUCEL

***Zorginstituut*'s conclusion**
For the indication acute B cell lymphoblastic leukaemia, tisagenlecleucel complies with established medical science and medical practice. Including it in the package for this indication will have limited budget impact. As a result, it is eligible for inclusion in the standard health care benefit package. We will conclude an orphan drug arrangement and, due to the high treatment costs per patient, we will evaluate its use once it has been included in the insured package.

As already mentioned, we will send our assessment of the use of tisagenlecleucel for the indication DLBCL early in 2019. We also note that various studies are currently examining the effectiveness of tisagenlecleucel on other indications. In other words, future expectations are that tisagenlecleucel will be used more broadly. The budget impact of this product can therefore grow considerably in the future. When we determine the cost-effectiveness of tisagenlecleucel for one of the future indications, we will take the product to the Insured Package Advisory Committee (ACP) for complete package advice.