Health technology assessment of gene therapies for inherited genetic disorders in the US and Europe

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Introduction

- The US Food and Drug Administration (FDA) describe gene therapy as the administration of genetic material to modify or manipulate gene expression or to alter the biological properties of living cells[1]. This can be achieved by replacement, inactivation, addition, or modification of genes.
- Three gene therapies for inherited genetic disorders have received regulatory approval. The FDA approved voretigene neparvovec (VN)[2] and the European Medicines Agency (EMA) approved Strimvelis[3] and alipogene tiparvovec (AT)[4]. Several gene therapies for oncology are also licensed, including talimogene laherparepvec (FDA and EMA), axicabtagene ciloleucel (FDA), and tisagenlecleucel (FDA)[1,5].
- For inherited genetic disorders, providing a functional copy of the mutated gene offers the prospect of a long-term or permanent cure following a one-off treatment. However, rare diseases pose challenges for health technology assessment (HTA) of gene therapies, including small population sizes for clinical trials and high acquisition costs required to recoup R&D costs.
- HTA organizations commonly have specialized guidance to assess drugs for rare diseases, including those for inherited genetic disorders. Key criteria for the Institute for Clinical and Economic Review (ICER; US), the National Institute for Health and Care Excellence Highly Specialized Technology Programme (NICE HSTP; England), the National Authority for Health (HAS; France), and the Federal Joint Committee (G-BA; Germany) are described in **Table 1**[6-9].

Table 1: Criteria for assessment of drugs for rare diseases

HTA body	Key assessment criteria
ICER	• Clinical data rated according to Evidence Rating Matrix. • Social benefits considered. • BI threshold of $915 million/ year. • Willingness-to-pay CE threshold of $50,000-500,000/ QALY.
NICE HSTP	• Clinical benefit for patients and carers, if relevant. • Commercial discussions if BI >£20 ($27) million/ year. • CE threshold of £100,000 ($135,345)/ QALY, with incremental QALY weighting (1, 1-3, and 3) for incremental QALY gains (≤10, 10 to 30, and >30, respectively). • Innovation considered; MAA may be requested.
HAS	• SMR (substantial, moderate, mild, or insufficient) and ASMR (I to V [major, important, moderate, minor, or no clinical improvement]) assessed if BI threshold exceeded. • BI threshold of €30 ($35) million)/ year. • Accelerated procedure for innovative therapy. • Follow-up research may be requested.
G-BA	• Additional medical benefit considered proven at MA if BI <€50 ($60) million/ year. • EAMB assessed (major, considerable, minor, not quantifiable, no additional benefit, or less benefit). • Follow-up data may be requested.

ASMR, additional medical benefit; BI, budget impact; CE, cost-effectiveness; EAMB, extent of additional medical benefit; MA, market authorization; MAA, managed access arrangement; QALY, quality-adjusted life year; SMR, medical benefit.

Objectives

- Identify HTAs of gene therapies for inherited genetic disorders in the US and key European markets (UK, France, and Germany).
- Review the HTA outcomes and key considerations.
- Understand the HTA challenges and opportunities facing upcoming gene therapies for inherited genetic disorders.

Methods

- Searches were conducted on 2nd May 2018 for HTA reports of licensed gene therapies for inherited genetic disorders across:
  - ICER (https://icer-review.org/);
  - NICE (https://www.nice.org.uk/);
  - HAS (https://www.has-sante.fr/portail/);
  - G-BA (https://www.g-ba.de/).

Results

- A single HTA of VN was conducted by ICER[10]. Strimvelis was assessed by NICE HSTP[11]. Two HTAs of AT were conducted; one by HAS[12] and the other by the G-BA[13]. HTA conclusions are presented in **Table 2**.

Table 2: HTA conclusions of licensed gene therapies for inherited genetic disorders

Drug		Voretigene neparvovec (Spark Therapeutics)	Strimvelis (GlaxoSmithKlein)	Alipogene tiparvovec (uniQure)	
Indication		*RPE65*-mediated inherited retinal disease	Adenosine deaminase deficiency-severe combined immunodeficiency (ADA-SCID)	Familial lipoprotein lipase deficiency (LPLD) with severe/ multiple pancreatitis attacks despite dietary fat restrictions	
Regulatory approval	FDA	Approved (Dec. 2017)	Not assessed	Not assessed	
	EMA	Not assessed	Approved (Jun. 2016)	Approved (Nov. 2012, withdrawn 2017)	
HTA organization		ICER (final report Feb. 2018)	NICE HSTP (final guidance Feb. 2018)	HAS (Nov. 2015)	G-BA (May 2015)
HTA conclusions/ outcomes		Considered to provide small to substantial net benefit over SOC, "incremental or better" level of certainty (ICER Evidence Rating Matrix[14]: B+).	Recommended for ADA-SCID when no suitable HLA-matched related stem cell donor available.	Not recommended. SMR: insufficient; ASMR: N/A	Recommended (valid until 31st Dec. 2017); EAMB: not quantifiable.

Abbreviations: ASMR, additional medical benefit EAMB, extent of medical benefit; HLA, human leukocyte antigen; N/A, not applicable; SMR, medical benefit; SOC, standard of care.

- **Table 3** describes key factors considered for each HTA.
- ICER considered clinical trial data to support a significant benefit associated with VN therapy, despite uncertainties around the small treated population and long-term benefits.
  - High costs produced incremental cost-effectiveness ratios above common willingness-to-pay thresholds (e.g. $150,000/ QALY) in most scenarios.
  - Discounts of 75-82% (health care perspective) and 50-57% (modified societal perspective) were required for VN treatment at age 15 to achieve incremental cost-effectiveness ratios of $100,00-$150,000/ QALY.
  - Other key factors were expected improvements in patient and carer quality of life (QoL) and societal benefits, such as rejoining work or school.
- Key drivers of the NICE HSTP recommendation for Strimvelis included evidence of clinical effectiveness despite uncertainty because of the rarity of the disease and small patient numbers, and benefits to patient and carer QoL.
  - The scenario producing the highest plausible incremental cost-effectiveness ratio of £120,506 [$163,098]/ QALY was associated with QALY gains of 14.0. NICE HSTP committee considered that a weighting of 1.4 could be applied to the QALY gains and Strimvelis was considered cost-effective for all plausible scenarios.
- HAS did not recommend reimbursement of AT because of concerns about tolerability and long-term efficacy, combined with insufficient evidence of benefit.
- The G-BA assessed clinical benefit and treatment costs for AT. The extent of additional medical benefit was not quantifiable at the time of HTA, but AT was accepted for reimbursement with limited validity pending more data.

Table 3: Factors that were key considerations in the outcome of HTAs of gene therapies for inherited genetic disorders.

Key considerations	Voretigene neparvovec	Strimvelis	Alipogene tiparvovec	
	ICER[10]	NICE HSTP[11]	HAS[12]	G-BA[13]
Trial data	✓	✓	✓	✓
Patient QoL	✓	✓	-	-
Carer QoL	✓	✓	-	-
Societal benefits	✓	-	-	-
QALY gains (preferred estimate)	- (1.3)	✓ (14.0-19.6)	- (not assessed)	- (not assessed)
Unmet need	✓	-	✓	-
Budget impact (estimate)	- ($301,950,000/ yr)	- (£2.35 [$3.2] million/ 5-yrs)	- (not reported)	- (not reported)
Treatment cost (cost/ patient)	✓ ($854,876)	- (£505,000 [$710,350])	- (not reported)	✓ (€1,318,432 [$1,576,680])
Target pop. size (patients/ year)	- (350)	- (1)	- (not reported)	- (17-35)
Innovation	✓	✓	-	-
Cost-effectiveness analysis (cost/ QALY gained)	✓ ($135,331-$643,813)	✓ (<£120,506 [$163,350])	- (not assessed)	- (not assessed)

Abbreviations: QALY, quality-adjusted life year; QoL, quality of life; Yr, year.

✓ Key consideration; - Not a key consideration

Conclusions

- Uncertainty around clinical data from small populations and extremely high drug costs are key HTA challenges facing gene therapies.
- However, their one-time use combined with potential long-term/ lifetime benefits provides the opportunity to demonstrate value for money.
- The high cost of gene therapies make them unlikely to meet commonly-used cost-effectiveness thresholds. However, US decision-makers may give special weighting to other benefits for ultra-rare diseases, leading to funding at higher prices, while the NICE HST QALY weighting allows treatments with significant QALY gains to fall within the £100,000/ QALY threshold.
- Given their importance in HTAs of VN and Strimvelis, consideration should be given to societal and caregiver benefits in value propositions and HTA submissions of gene therapies for inherited genetic disorders.
- The importance of balancing cost recuperation with patient accessibility is exemplified by AT, which was withdrawn from European markets by the manufacturer due to limited uptake.
- As further high-cost gene therapies are commercialized, management of combined budget impact may become increasingly important.

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