Evaluating High-cost Gene Therapies for Non-cancer Conditions: Insights From NICE's Standard Appraisal Process

HTA132

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Background

- Gene therapies offer significant clinical potential, yet these treatments pose substantial reimbursement challenges of high prices and uncertain long-term results.
- The National Institute for Health and Care Excellence (NICE) has typically appraised these therapies via either:
  - The highly specialised technology (HST) route which employs higher cost-effectiveness thresholds and lower evidence requirements for technologies that are innovations for an ultra-rare and debilitating condition and are likely to offer substantial additional benefit over the inadequate existing established clinical management
  - The single technology appraisal (STA) route and the Cancer Drugs Fund (CDF) for cancers not meeting HST criteria
- However, NICE has recently recommended gene therapies for non-cancer conditions via standard STA, despite list prices being >£1.6 million.

Objectives

- **To assess the factors considered during NICE's appraisals of gene therapies for non-cancer conditions via standard STA and to determine whether the Innovative Medicines Fund (IMF) was employed to enable NICE's recommendations for high-cost, non-cancer therapies that do not meet the criteria for HST**

Methods

- A targeted review was conducted of NICE STA guidance on gene therapies for non-cancer conditions published up to June 2025.

Results

- As of June 2025, NICE had appraised three gene therapies for non-cancer conditions through the STA route: Hemgenix for the treatment of moderately severe or severe haemophilia B and Casgevy for the treatment of transfusion-dependent beta-thalassaemia (TDT) and severe sickle cell disease (SCD; **Table 1**).[1-3]
- In the three appraisals, Hemgenix and Casgevy (TDT and SCD) were not recommended for routine use by NICE, but were recommended for managed access via the IMF with confidential discounts, allowing patients to access these treatments under specific conditions and monitoring.[1-3]

Table 1. Overview of NICE STA appraisals for gene therapies for non-cancer conditions

	Hemgenix[1]	Casgevy[2]	Casgevy[3]
NICE STA	TA989	TA1003	TA1044
Indication	Moderately severe or severe haemophilia B	TDT	SCD
List price	£2,600,000/dose	£1,651,000/course of treatment	£1,651,000/course of treatment
Initial appraisal	July 2023	N/A	March 2024
Final appraisal	July 2024	August 2024	February 2025
Recommendation	Managed access via IMF[a]	Managed access via IMF[a]	Managed access via IMF[a]

Abbreviations: IMF = Innovative Medicines Fund; N/A = not applicable; NICE = National Institute for Health and Care Excellence; SCD = severe sickle cell disease; STA = single technology appraisal; TDT = transfusion-dependent beta-thalassaemia
[a] Collection of additional data within 5 years through the ongoing clinical trial programme and clinical practice

Outcomes across NICE STA appraisals

Cost-effectiveness estimates

- The committee noted uncertainties in cost-effectiveness estimates for all three indications, due to limited long-term data, modelling uncertainties, and incremental cost-effectiveness ratio (ICER) estimates exceeding preferred thresholds (**Table 2**)
- **Hemgenix**: The committee noted the treatment has the potential to be cost effective compared with congenital factor X (FIX) prophylaxis (with several scenarios falling in the acceptable range). However, the cost-effectiveness estimates were highly uncertain due to uncertainty around indirect treatment comparison (ITC) results and durability extrapolation (lack of long-term data).[1]
- **Casgevy** (TDT and SDC): In both appraisals, the ICERs were considered above the preferred cost-effectiveness range (>£20,000 per quality-adjusted life-year [QALY]) in a pessimistic scenario and below the range in an optimistic scenario; uncertainty around most of the committee-preferred modelling assumptions (e.g., model structure, mortality rate, non-reference case discount rate criteria, etc.) was noted.[2]

Disclosures

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Results (cont.)

Outcomes across NICE STA appraisals

Clinical evidence

- The NICE STA of clinical evidence indicated that, although clinical trial data for Hemgenix (haemophilia B) and Casgevy (TDT and SCD) suggested clinical effectiveness, uncertainties remained due to the lack of direct comparisons, small sample sizes, and questions about the long-term treatment effect (**Table 2**).[1-3]

Equality considerations

- Equality considerations, including health inequalities related to ethnic background, as well as the innovative nature and complex technology of Casgevy, led NICE to accept higher uncertainties and consider higher cost-effectiveness estimates than usual (up to £35,000 per QALY for SCD), while no such adjustments were made for Hemgenix.[1-3]

Table 2. Overview of outcomes assessed by NICE

	Hemgenix[1]	Casgevy (TDT)[2]	Casgevy (SCD)[3]
Unmet need	○ Solution to reduce the burden of prophylaxis treatment	☑ High unmet need for an effective treatment that improves outcomes for patients and QoL for patients and families/carers	☑ High unmet need for an effective, well-tolerated treatment as current treatments offer only temporary relief and do not address the underlying cause of SCD
Clinical evidence	● Single-arm trial, uncertainties regarding the ITC	● Single-arm trial, uncertainties regarding the ITC	● Single-arm trial
Long-term durability	⊗ Insufficient long-term data (up to 36 months of follow-up presented at consultation)	⊗ Insufficient long-term data (n=42/59 with ≥16 months of follow-up)	⊗ Insufficient long-term data (up to 2 years with an average of 20.1 months of follow-up)
Cost-effectiveness estimates	● Potential for cost effectiveness, but uncertainties regarding long-term durability may result in ICERs exceeding acceptable thresholds	● Potential for cost effectiveness, but uncertainties regarding long-term durability, QoL and outcomes in people treated with SoC may result in ICERs exceeding acceptable thresholds	● Potential for cost effectiveness, but uncertainties regarding long-term durability, QoL and outcomes in people treated with SoC may result in ICERs exceeding acceptable thresholds
Equality considerations	○	☑ Higher uncertainty accepted due to existing health inequalities and technology's innovation and complexity	☑ Outcomes uncertainty and higher ICERs were accepted due to existing health inequalities for people with SCD

Legend: ☑ Positive effect in appraisal; ⊗ Negative effect in appraisal; ● Potentially negative effect in appraisal; ○ Not considered in appraisal
Abbreviations: ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; QoL = quality of life; SCD = severe sickle cell disease; SoC = standard of care; TDT = transfusion-dependent beta-thalassaemia

Managed access granted after previous rejection:

- Both Hemgenix and Casgevy (for SCD) were initially not recommended by NICE before eventually being recommended for managed access via the IMF.
  - **Hemgenix:** Due to uncertainties, the treatment was not recommended for routine use; the lack of a managed access proposal during the initial submission to NICE led to no recommendation for managed access.[4]
  - **Casgevy for SCD:** Due to the initial managed access proposal not addressing many of NICE's identified uncertainties and the treatment potentially not being cost-effective at the suggested price, managed access was not recommended at first.[5]

Conclusions

- **High-cost gene therapies can be recommended by NICE via standard STA under managed access even after an initial negative recommendation, if there is plausible cost-effectiveness potential and new evidence could feasibly be collected to address enough uncertainties.**
- **The innovative nature of the technology and existing health inequalities in the target patient populations allowed higher-than-usual cost-effectiveness estimates to be considered/**
- **Further analysis of the appraisal process is limited due to lack of transparency in reporting cost-effectiveness estimates and discounting agreements.**

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