What Holds Gene Therapies Back?

A Review of NICE Critiques Across Health Technology Appraisals

HTA358

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1 BACKGROUND

- **Gene therapies (GTx)** have emerged as potentially transformative treatments for **severe, life-threatening** and **often rare** diseases.[1]
- Sustained benefit, or potentially a **cure**, after a **single administration** distinguishes GTx from conventional long-term treatments.[1]
- However, **high upfront costs**, limited clinical datasets, and uncertain **durability of effect** challenge health technology assessment (HTA) decisions and reimbursement.[1]

GAP: Which evidence limitations recur across NICE appraisals of GTx, and what should future submissions prioritize?

2 OBJECTIVES

We reviewed **Evidence Assessment Group (EAG)** critiques reported in **National Institute for Health and Care Excellence (NICE)** technology appraisals (TAs) of GTx.

The aim is to inform manufacturers preparing future GTx submissions seeking **NICE approval**.

REVIEW
EAG critiques in NICE appraisals

IDENTIFY
Recurring clinical and economic evidence critiques

HIGHLIGHT
Priority areas for future submissions

3 METHODS

- NICE website was searched to identify **TA guidance, company submissions, EAG reports** and final appraisal documents (where available) were retrieved for each GTx as shown in **Figure 1**.
- EAG critiques were reviewed and **categorized thematically** to identify recurring methodological and evidentiary challenges across appraisals.

Figure 1: Project Methodology Overview

1. Desk search
GTx approved in 2021–2026 identified

→

2. NICE website search
Corresponding TAs and documents retrieved

→

3. Structured extraction
Eligible TAs extracted with a set framework

→

4. Thematic categorization
Critiques grouped into recurring challenges

Extracted per TA:

- **PICOS and clinical evidence**
- **Economic evidence critiques**
- **Patient & caregiver outcomes**
- **NICE decision and funding**

4 RESULTS

10 TAs 10 GTx 11 indications

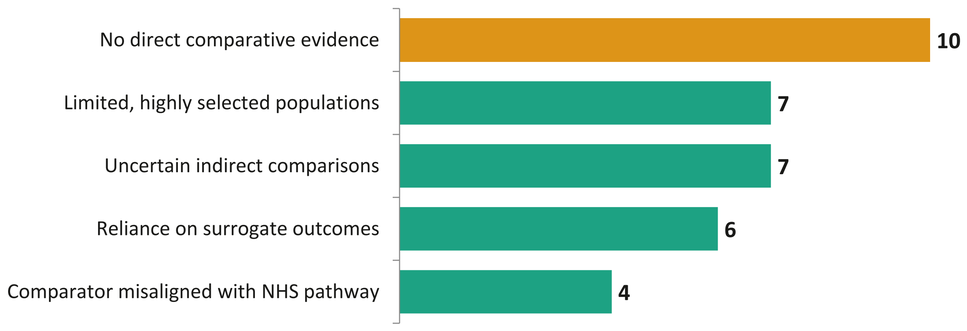
(5 Oncology, 3 Hematology, 3 Rare genetic neurological studies are included for analysis)

NICE decisions across 11 indications: none rejected

7 full recommendations and funding
4 conditional and funding uncertainty

- Of the 37 FDA-approved cell and gene therapies, 23 lacked NICE TAs, 1 had a terminated appraisal, and 3 were excluded due to timeline criteria, leaving 10 GTx for inclusion (11 indications).
- Without concurrent control groups, comparisons relied on **historical controls, external datasets or indirect evidence**, adding potential for bias and residual confounding.
- Cost-effectiveness results were **highly sensitive to long-term outcome assumptions**, given substantial upfront acquisition costs and immature clinical evidence.
- **Funding barriers for 7 GTx** were addressed through managed-access arrangements, commercial agreements or other pricing schemes.

Figure 2: PICOS-related EAG critiques (number of TAs, of 10)



Direct comparative evidence was absent in all 10 appraisals.

Table 1: EAG critiques by evidence domain

Domain	Reported	Key EAG critiques
Population	**9 TAs**	Limited generalisability to NHS practice: younger, fitter patients enrolled; older or frailer people, women and those with comorbidities under-represented
Clinical evidence	**8 TAs**	Single-arm or non-randomised studies, small samples, short or incomplete follow-up; uncertain replication in routine practice
Economic	**Frequent**	Extrapolation of survival and benefit beyond trials, duration or waning of treatment effect, healthcare resource use
Patient & caregiver	**Consistent**	Considerable burden and unmet need, but direct, systematically collected PRO data often limited
Funding	NA	MAAs, CAAs, PAS, CDF, IMF, RSA or funding uncertainty

Population and clinical evidence critiques affected most appraisals.

5 DISCUSSION

- Uncertainty arose from **immature, non-comparative and narrowly generalizable** clinical evidence, which carried into economic evaluations.
- Yet **no indication was rejected**: managed access and pricing schemes helped address funding barriers.

Table 2: EAG critiques and priority for future submissions

Recurring EAG critique	→ Priority for future submissions
Single-arm, non-comparative trials	**Generate robust comparative evidence**
Highly selected trial populations	**Recruit populations reflecting NHS practice**
Short follow-up; surrogate outcomes	**Extend follow-up; validate surrogate endpoints**
Uncertain long-term benefit in models	**Model durability and survival transparently, with alternative scenarios**
Limited PRO data	**Systematically collect patient and caregiver outcomes**

6 CONCLUSION

- NICE appraisals of GTx frequently highlighted **uncertainties in clinical and economic evidence**.
- Strengthening **comparative, long-term and patient-reported evidence** may improve future reimbursement decisions.
- **Early evidence planning and appropriate managed access** may reduce decision uncertainty and support timely patient access.

> While NICE has supported gene therapies, more comparative, long-term, and patient-reported evidence is needed to strengthen future assessments.

REFERENCES & ABBREVIATIONS

1. Berry D, Hickey C, Kahlman L, et al. Ensuring patient access to gene therapies for rare diseases: Navigating reimbursement and coverage challenges**.** Molecular Therapy Methods & Clinical Development, 2025; 33.
2. National Institute for Health and Care Excellence. Technology appraisal guidance. Available at: www.nice.org.uk/guidance.

CAAs: Commercial Access Agreements, CDF: Cancer Drugs Fund, EAG: Evidence Assessment Group, FDA: Food & Drug Administration, GTx: gene therapy, , IMF: Innovative Medicines Fund, MAAs: Managed Access Agreements, NHS: National Health Service, NICE: National Institute for Health and Care Excellence, PICOS: population, intervention, comparator, outcomes, study design, PRO: patient-reported outcome, PAS: Patient Access Schemes, RSA: Risk-sharing Agreements, TA: technology appraisal.

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