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Assessing evidence packages of CRISPR technologies: will they meet payer needs?

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Introduction and objectives

The emergence of therapies utilizing clustered regularly interspaced short palindromic repeats (CRISPR) technology (CRISPR therapy) holds promise to revolutionize the treatment landscape of numerous diseases. This includes diseases typically overlooked by traditional pharmaceutical interventions, such as the over 5,000 documented monogenic diseases, each stemming from a mutation in a single gene.[1] Whereas the cause of these often debilitating and rare indications has often been known for years, treatment options remain either non-existent or severely limited.[1]

To ensure that the potential of CRISPR therapies in addressing these neglected indications is reached, patient access will be of great importance. Therefore, it is crucial to anticipate and mitigate health technology assessment (HTA) challenges for CRISPR therapies.

The aim of the research was to provide an understanding of the HTA challenges that are to be expected for CRISPR therapies.

Methods

The research was conducted in three phases (Figure 1), based on reviews of:

1. The designs of the clinical trials evaluating CRISPR therapies
2. The appraisal of the first evaluated CRISPR therapy, exagamglogene autotemcel (exa-cel) for sickle-cell disease (SCD), by the National Institute for Health and Care Excellence (NICE) in the UK[2]
3. Previous health economic appraisals of gene therapies, paying specific attention to monogenic diseases, by NICE

Figure 1: Methodology

Design of clinical trials of CRISPR therapies

Aim
- Describe characteristics of the clinical trials of CRISPR-based interventions
- Assess how these trials are likely going to impact HTA and health economic modeling

Method
- Identify interventional clinical trials of CRISPR-based interventions from ClinicalTrials.gov (search term "CRISPR"; no limits on publication date; excluded non-interventional studies)
- Extract and synthesize the following main characteristics: trial design, trial phase, masking method, indication, patient population, (estimated) sample size

Review of the first NICE appraisal of a CRISPR therapy for SCD

Aim
- Identify challenges from the HTA submission and economic model of the first CRISPR-based therapy for sickle-cell disease

Method
- Critically review The NICE HTA submission of exa-cel for SCD, identifying methods and commentary around trial design, economic model, indirect treatment comparison (ITC) methodology, incorporation of real-world evidence (RWE), modeling of cure, extrapolation of trial outcomes, and the latest HTA outcome

Review of previous NICE appraisals of cell and gene therapies

Aim
- Identify main challenges in HTA submissions (including economic models) for cell and gene therapies

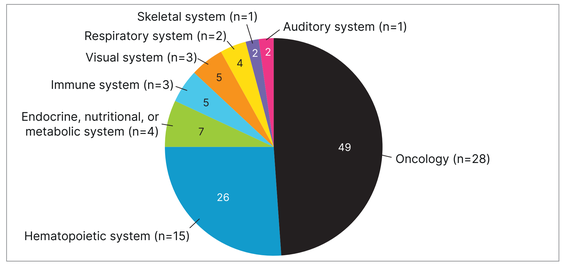
Method
- Identify the NICE appraisals of all approved cell and gene therapies
- Critically review commentary on trial design, ITC methodology, incorporation of RWE, modeling of cure, and the latest HTA outcome
- Assess implications for CRISPR-based interventions

Results

A total of 58 ongoing clinical trials of CRISPR therapies were identified across a range of indications (Figure 2).

- Most were Phase 1/2 trials, addressing advanced and debilitating diseases for highly specific patient populations, with small sample sizes.
- Most of the trials were in oncology indications (49%), followed by hematopoietic indications (26%) and other disease areas (25%), such as those affecting the immune system and visual system.
- None of the trials were designed to generate comparative data against the standard of care; all trials were either single-arm trials, or trials with sequential/dose escalation arms, which is likely to lead to challenges for HTA agencies that require a comparison of efficacy against the standard of care.

Figure 2: Breakdown of disease areas of CRISPR therapies in current clinical trials (n=58)



The NICE appraisal of exa-cel for SCD identified challenges regarding the single-arm design of the pivotal trial submitted as primary evidence, as well as the generalizability of the trial patient population and certainty of long-term efficacy (Table 1).

Table 1: NICE appraisal of exa-cel for SCD

	Company approach	HTA feedback
Clinical trial	HTA feedback	Highly specific patient population that might not be generalizable to the intended UK patient population.
Mechanism of action	Editing of autologous CD34+ hematopoietic stem cells.	None.
Model type	Markov model with 4 states: (1) vaso-occlusive crisis (VOC), the number of VOCs informs the risk of (2) acute complications, (3) chronic complications, and (4) death.	Uncertainty was noted around the relationship between VOC events and the risk of developing complications, which was informed by external data as trial follow-up was too short to capture long-term complications.
ITC use in the economic model	No ITC used. The baseline frequency of VOCs of patients included in the trial was used to inform the standard-of-care arm, assuming that patients maintain the same frequency of VOC for the modeled time horizon.	Clinical experts noted that limited data are available to validate model inputs because evidence is often incomplete and outdated.
External data/ RWE for comparison	External data from a UK study was used to inform mortality for standard of care.	Patient characteristics of the populations in the external data and trial data were not generalizable (mainly due to differences in age and severity of disease).
Modeling of (long-term) efficacy	Based on trial outcomes, a functional cure was assumed for 96.6% of people, and a standardized mortality ratio of 1.25 was applied to patients with a functional cure. The observed effect size (96.6%) was assumed to remain over a lifetime horizon.	Uncertainty around the durability of the treatment effect. In response the company noted that there is "no known biological mechanism that could reverse the genetic edit, which supports the durability of the exa-cel treatment effect." Clinical experts stated they would be assured after 2-5 years of follow-up.

Specific to CRISPR is its ability to permanently edit DNA, allowing for the permanent modification of harmful mutations that cause disease. Therefore, depending on its application, CRISPR can arguably be considered a disease modifier, rather than a therapy that induces a treatment effect. This distinction became apparent in the NICE appraisal—although exa-cel does not directly edit the underlying mutation causing SCD, it does permanently alter the genetic landscape by activating a gene responsible for producing fetal hemoglobin, which prevents the harmful sickling of red blood cells.

The permanence of exa-cel's mechanism of action in irreversibly modifying a patient's DNA raises questions about whether the uncertainties around long-term efficacy are justified. Notably, in the discussion of the durability of response and the assumed curative effect of exa-cel, the company noted that there was "no known biological mechanism that could reverse the genetic edit, which supports the durability of the exa-cel treatment effect."

To further anticipate challenges for CRISPR therapies, previous NICE appraisals of gene therapies were reviewed (Table 2).

Table 2: Overview of HTA challenges in previous NICE appraisals of cell and gene therapies

	NICE submission	Mechanism of action	Key criticism	NICE HTA outcome
Monogenic diseases	Etranacogene dezaparvovec (Hemophilia B)[3]	Deliver functional copy of faulty gene	Uncertainty around the ITC and the long-term effect	Initial draft not recommended, final in progress
	Atidarsagene autotemcel (Metachromatic leukodystrophy)[4]		Uncertainty around the size and sustainability of the treatment effect	Recommended within its marketing authorization
	Voretigene neparvovec (Inherited retinal dystrophies)[5]		Uncertainty regarding the sustainability of the treatment effect	Recommended within its marketing authorization
	Onasemnogene abeparvovec (Spinal muscular atrophy)[6]		Uncertainty regarding the long-term effect	Recommended with restrictions
	Nusinersen (Spinal muscular atrophy)[8]	Act on mRNA to enhance the production of functional SMN protein	Complicated model structure, uncertainty regarding the duration of treatment effect	Recommended with restrictions
	Betibeglogene autotemcel (Beta-thalassemia)[7] (Spinal muscular atrophy)[6]	Deliver genetically modified autologous hematopoietic stem cells	Uncertainty around external data and the long-term effect	Discontinued
Oncology indications	Brexucabtagene autoleucel (B-cell leukemia)[9]	Chimeric antigen receptor T-cell therapy	Long-term durability of treatment effect, ITC	Recommended within the Cancer Drugs Fund
	Axicabtagene ciloleucel (Large B-cell lymphoma)[10]		Uncertainty regarding durability, which was resolved with additional 60-month follow-up data	Recommended within its marketing authorization
	Tisagenlecleucel (B-cell leukemia)[11]		ITC, extrapolated survival and cure fractions	Recommended within the Cancer Drugs Fund

Of the identified nine additional NICE appraisals, six were for monogenic diseases and three were for oncology indications. The majority of the appraisals (7/9) relied on single-arm trials.

Key criticisms from NICE concerned the indirect treatment comparisons that were used to inform comparative efficacy and the real-world evidence used for external validation. Concerns were frequently raised regarding the alignment of the patient populations between the trials and the real-world studies, as well as with the trials used in the indirect treatment comparisons. In addition, the highly specific patient populations of the submitted trials were frequently criticized, as they limit the generalizability of the trial findings to a broader patient population.

Common concerns identified across all gene therapy appraisals, including the assessment of exa-cel, included reliance on single-arm trials, highly specific patient populations, and uncertainty regarding long-term efficacy. However, none of the gene therapies had a similar mechanism of action to the CRISPR therapy exa-cel, which involves permanent editing of DNA.

Conclusions

While CRISPR therapies are transforming the clinical landscape, payers still need to be convinced of their comparative clinical and cost-effectiveness. The review of gene therapy submissions suggests that current evidence generation approaches for innovative therapies are often scrutinized by payers.

Given that the ongoing trials of CRISPR therapies are not designed to generate comparative evidence around efficacy, nor are they designed with large sample sizes, challenges around establishing comparative efficacy and the generalizability of the trial results are to be anticipated. Manufacturers of CRISPR-based interventions will need to evolve their evidence generation strategies to avoid bottlenecks in patient access to innovative and potentially curative treatments.

Currently, HTA agencies mostly assess interventions that primarily induce a treatment effect, rather than interventions that permanently modify a disease process itself, as CRISPR therapies potentially do. Given the uniqueness of this approach, and the likely emergence of more CRISPR therapies similar to exa-cel that entail permanent DNA editing, the stringent evaluation criteria by HTA agencies around long-term efficacy may need to be re-evaluated.

References

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