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Are the hurdles too high for access to gene therapies in the UK?

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BACKGROUND

- Gene therapies have the potential to deliver significant benefit to patients as well as to the National Health Service (NHS) in the UK.
- However, access and reimbursement for gene therapies is inherently challenging.
- Given their one-off nature and high research & development and manufacturing costs, gene therapies are associated with:
  - a complex evidence base;
  - low patient numbers;
  - uncertainty around long-term outcomes (in some cases multiple decades);
  - variability in patient outcomes;
  - issues around affordability and budget impact.

OBJECTIVE

- To explore whether access to gene therapies in a cost-effectiveness market like the UK is feasible via the standard Health Technology Assessment (HTA) routes or whether additional flexibility in decision making is deemed necessary.

METHODS

- We undertook a review of the UK reimbursement decisions for gene therapies over the last 5 years (2018–September 2023) from both the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC).
- In addition, we utilised a published review of NHS England (NHSE) 'smart deals' from the period 2018–2022[1] to identify examples of potentially more complex solutions that have been implemented in terms of pricing and reimbursement.

RESULTS

- Up to September 2023, five gene therapies have been reimbursed in the UK, all of which have benefited from the flexibilities of the NICE Highly Specialised Technology (HST) process and the SMC ultra-orphan process (Table 1).
- Importantly, a sixth gene therapy (betibeglogene autotemcel [Zynteglo] for the treatment of patients with transfusion-dependent beta-thalassaemia) was assessed by NICE through the Single Technology Appraisal (STA) route.
  - This was rejected on the grounds of the clinical trial data being small and insufficient to justify reimbursement, which also led to major uncertainties about the cost effectiveness of the gene therapy.
- A published review of NHSE 'smart deals' (2018-2022)[1] revealed most of these were based on interim funding arrangements, population health arrangements and portfolio deals - and not innovative payment mechanisms linked to outcomes (Table 2).
- Many of the details on what constitutes each of these a "smart deal" are not available in the public domain, especially with regards to pricing where limited to no information were available.
- Some insights are available however from these "smart deals" as summarised in Box 1.

Box 1: 2018–2022 smart deal summary and insights

- Eight were linked to interim funding via managed access agreements, including the Cancer Drugs Fund. In the majority of cases, no clarity was provided on whether the commercial arrangement included anything beyond a simple discount.
- Five were via direct negotiations with NHSE: specialised clinical commissioning guidance, price negotiated directly with NHSE commercial medicines unit, national procurement process (tender).
- Three were NICE HST appraisals with simple discounts being provided.
- Other "smart deals" included:
  - A portfolio deal with Vertex for its cystic fibrosis portfolio;
  - A population health management agreement between NHSE and Novartis for cholesterol / cardiovascular disease;
  - A population health partnership between NHSE and EQRx for cancer drugs.

CONCLUSIONS

- Despite the broad recognition of the innovative and life-changing benefit gene therapies can potentially bring, HTA methods primarily from NICE – which have often been criticized for being behind the times when it comes to evaluating non-traditional drugs such as cell and gene therapies – mean that these therapies cannot become available for patients in the UK through the standard assessment routes of NICE and SMC.
- Indeed, our analysis demonstrated that all gene therapies which have been recommended within the UK via NICE and SMC required specialised ultra-orphan routes for HTA in combination with confidential commercial agreements.
- In the absence of a gene therapy specific HTA route, the assessment via NICE HST and SMC ultra-orphan processes are paramount and currently the only viable way to bring these innovations to UK patients.

Table 1. Gene therapies UK reimbursement status

Gene Therapy	Disease Area	NICE	SMC
Eladocagene exuparvovec (Upstaza) PTC Therapeutics	Aromatic L-amino acid decarboxylase deficiency	HST 26 19 April 2023 Commercial arrangement: Simple discount PAS, list price £3,010,451	Ultra orphan 11 September 2023 Commercial arrangement: Confidential discount
Libmeldy (Atidarsagene autotemcel) Orchard Therapeutics	Metachromatic leukodystrophy	HST 18 28 March 2022 Commercial arrangement: Simple discount PAS, list price £2,875,000	Ultra orphan 11 April 2022 Commercial arrangement: Confidential discount
Zolgensma (Onasemnogene abeparvovec) Novartis Gene Therapies	Neuromuscular SMA Type I	HST 15 07 July 2021 Commercial arrangement: Simple discount PAS & MAA (for part of the population), list price £1,795,000	Orphan 08 March 2021 Commercial arrangement: Confidential discount
Luxturna (Voretigene neparvovec) Novartis	Ophtha Inherited retinal dystrophy caused by confirmed biallelic RPE65 mutation	HST 11 09 October 2019 Commercial arrangement: Simple discount PAS, list price £613,410	Ultra orphan 10 February 2020 Commercial arrangement: Confidential discount
Strimvelis GSK	Adenosine deaminase deficiency–severe combined Immunodeficiency	HST 7 07 Feb 2018 Commercial arrangement: No detail available, price £505,000	Not assessed in Scotland

Table 2. Summary of negotiated smart deals between pharmaceutical industry and NHS England, 2018-2022

Date	Technology	Therapeutic class	Indication	Manufacturer
September 2018	Kymriah	CAR-T cell therapy	B cell precursor acute lymphoblastic leukaemia	Novartis
October 2018	Yescarta	CAR-T cell therapy	Diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma	Gilead Sciences
November 2018	Biosimilar adalimumab	Monoclonal antibody	Multiple	Abbvie, Amgen, Biogen, Mylan / Fujifilm Kyowa Kirin, Sandoz
April 2019	Hepatitis C technologies	Direct acting antivirals	Hepatitis C	Gilead Sciences, Merck Sharp and Dohme, Abbvie
May 2019	Spinraza	Antisense oligonucleotide	Spinal muscular atrophy	Biogen
May 2019	Ocrevus	Monoclonal antibody	Multiple sclerosis	Roche
September 2019	Luxturna	Gene therapy	Retinal dystrophy	Novartis
October 2019	Orkambi, Symkevi, Kalydeco	CTFR modulators	Cystic fibrosis	Vertex Pharmaceuticals
February 2020	Ilaris	Monoclonal antibody	Periodic fever syndromes	Novartis
August 2020	Kaftrio	CTFR modulator	Cystic fibrosis	Vertex Pharmaceuticals
December 2020	Fetcroja, Zavicefta	Antibiotics	Drug-resistant infections	Shionogi, Pfizer
January 2021	Tecartus	CAR-T cell therapy	Relapsed/refractory mantle cell lymphoma	Kite Pharmaceuticals
March 2021	Zolgensma	Gene therapy	Spinal muscular atrophy	Novartis
April 2021	PHESGO (pertuzumab + trastuzumab)	Monoclonal antibodies	HER2-positive breast cancer	Roche
September 2021	Leqvio	Small interfering RNA	Familial hypercholesterolaemia	Novartis
October 2021	Adakveo	Monoclonal antibody	Sickle cell disease	Novartis
October 2021	Oncology pipeline drugs	Miscellaneous	Multiple	EQRx
November 2021	Eliquis, Pradaxa, Xarelto, Lixiana	Direct oral anticoagulants	Atrial fibrillation and stroke prevention	Pfizer, Boehringer Ingelheim, Bayer, Daiichi Sankyo
November 2021	Evrysdi	mRNA splicing modifier	Spinal muscular atrophy	Roche
February 2022	Libmeldy	Gene therapy	Metachromatic leukodystrophy	Orchard therapeutics
March 2022	Darzalex	Monoclonal antibody	Multiple myeloma	Janssen

DISCLOSURES

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REFERENCES

1. PF Media. The UK access environment has been transformed – what are the lessons for pharma and other countries? 2021.