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The Challenges of Evaluating Individualised Therapies in Health Technology Assessment: a Thematic Review

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Background

Individualised therapies such as adeno-associated virus vectors, antisense oligonucleotides, small interfering RNA and gene editing technologies (e.g. CRISPR/Cas-9) are emerging as "platform technologies" with the potential to be adapted across multiple conditions. This offers exciting opportunities, particularly for rare diseases, but also brings complex challenges for health technology assessment (HTA). As more of these therapies approach reimbursement, the need to address methodological and system-wide issues grows. A NICE's HTA Innovation Laboratory (HTA Lab) project[1] has explored these challenges.

Methodology

We aimed to identify and summarise economic modelling approaches in i) published cost-effectiveness analysis of individualised therapies in the literature and ii) by HTA organisations, and iii) committee discussion from HTA reports of individualised therapies.

Following a pre-specified protocol, a systematic search of Medline, Embase, the Cochrane Database of Systematic Reviews and International HTA Database (INAHTA) was conducted on 21 January 2025. A structured review of publicly available HTA reports was conducted across the HTA agencies listed below. A total of 68 HTA reports and 27 economic evaluations were identified.

For articles identified in the literature, key variables extracted included population and setting, indication, intervention, platform type, comparator, outcome, modelling approach, health states and events, use of surrogate relationships, uncertainties, author related challenges and limitations. For HTA reports, committee discussions on cost-effectiveness evidence and limitations were extracted.

Organisation	Country	No. of HTA reports
AIFA	Italy	2
AWMSG	Wales	1
CDA-AMC	Canada	9
HAS	France	4
ICER	USA	8
IQWiG	Germany	9
NCPE	Rep. Ireland	5
NICE	England	13
PBAC	Australia	3
PHARMAC	New Zealand	1
SMC	Scotland	6
TLV	Sweden	3
ZIN	Netherlands	4

Outcomes and themes identified

Six challenging key themes for evaluating individualised therapies were identified:

Comparative evidence

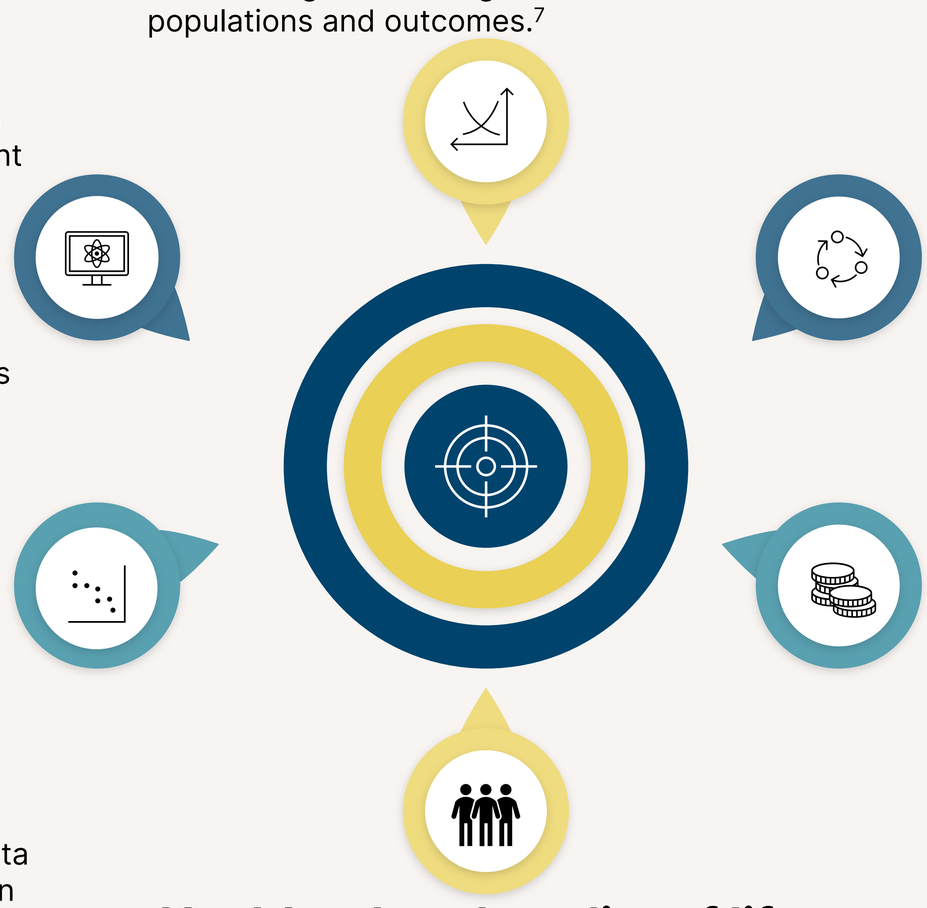
- Indirect treatment comparisons often used to derive treatment effect but involve heterogeneous trial data.[6]
- Methodological challenges include mismatched populations and outcomes.[7]

Surrogate endpoints

- Use of unvalidated biomarkers or surrogate endpoints to estimate treatment effect produces uncertainty in estimates.[4]
- Relevance to long-term benefit and patient experience is unclear.[5]

Modelling approach

- Modelling structures often fail to capture disease progression.[8]
- Uncertainty in modelling inputs was raised including approach to transition matrices and treatment effect waning.[7,8]



Evidence generation

- Short, small, single arm trials create uncertainty in measured clinical outcomes.[2]
- Lack of follow up data creates challenges in long term extrapolation and decision-making.[3]

Cost and resource use

- Service redesign required for specialist delivery and screening unaccounted for.[10]
- Inconsistent or missing costs related to infrastructure, training and treatment eligibility testing.[8]

Health related quality of life

- Health related quality of life data frequently missing and derived from proxies (e.g., clinicians completing vignettes).[9]

Conclusion and future work

The evaluation of individualised therapies presents a complex combination of challenges, many of which are familiar from rare disease and ATMP settings but may now arise more frequently as platform technologies expand. To support timely and consistent access, HTA organisations may need to adapt existing methods or processes where current approaches prove disproportionate. NICE may explore targeted pilot projects through its HTA Lab to test potential solutions and support future evaluations.

Limitations of this review include the exclusion of other types of individualised therapies, such as personalised mRNA treatments and n-of-1 therapies, as these therapies fell out of scope. This means that additional HTA challenges specific to such technologies may not have been identified. There is also potential for selection bias, as the review focused on a restricted set of HTA organisations. Nonetheless, a degree of international perspective was maintained due to the geographical spread of agencies selected.

References

1. NICE HTA Lab, https://www.nice.org.uk/what-nice-does/our-research-work/hta-lab/hta-lab-projects
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6. TLV 2018, Onpattro (patisiran) Basis for decisions in the county councils.
7. NICE 2021, TA733
8. NICE 2019, HST10
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