Diagnostic testing (DTx) costs: a hidden barrier to accessing histology-independent technologies (HITs)

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INTRODUCTION

- HITs are increasingly studied as novel technologies targeting specific genomic alterations, irrespective of tumour site of origin. These therapies enable the targeting of patient populations with rare and often overlooked cancer types.
- Economic evaluations for HIT therapies can give highly variable results depending on 1) the prevalence of the biomarker mutation in patients; 2) the uncertainty in mutation prevalence estimates; and 3) the cost of diagnostic tests. This could lead to two extreme scenarios: a negative decision regarding the HIT or approval only if DTx with next-generation sequencing (NGS) is universally available.
- These challenges have been documented in published literature but there is lack of consensus on how to resolve these issues when incorporating DTx costs in economic evaluations.

OBJECTIVE

- To investigate how the uncertainty around gene prevalence estimates impact the cost-effectiveness of an HIT product due to the high cost of DTx, and to present possible solutions using different implementation approaches and risk-sharing schemes.

METHODS

- A case study was developed using prevalence and incidence data from NTRK fusions[1] in 28 tumour types* to assess how mutation prevalence and associated uncertainty impacted the cost-effectiveness and budget impact of a hypothetical HIT product.
- The case study only included the cost of NTRK testing with NGS (i.e., £350[2]) and excluded any drug-related costs or disease health-related costs. The incremental quality-adjusted life year (QALY) value was assumed to be equal across all tumour types (i.e., 0.833[1]). The assumptions were applied to focus on the impact of DTx costs and to allow direct assessment of the impact of mutation prevalence on the incremental cost-effectiveness ratios (ICER).
- For each histology, the number needed to screen, incremental costs to identify a single patient, the ICER and the budget impact of NTRK fusion testing vs. no testing provision was calculated. The weighted average of the incremental costs per histology was used to calculate a histology-independent ICER.
- The threshold at which NTRK testing is not cost effective was estimated assuming a United Kingdom perspective and the National Institute for Health and Care Excellence's (NICE) decision threshold of £40,000 (based on the midpoint of NICE's threshold range of £30,000 to £50,000). [3]
- Based on this threshold, scenarios with a phased implementation strategy and risk-sharing for the DTx were explored to alleviate uncertainties around gene prevalence estimates and the cost burden of DTx.

ADDITIONAL SOLID TUMORS

METHODS (cont.): SCENARIO ANALYSES

- Scenario analyses were based on identified strategies undertaken by health systems in England and the Netherlands:
  - England: Due to the absence of testing infrastructure for NTRK fusions, a phased implementation approach for DTx was undertaken by the National Health Service for entrectinib and larotrectinib. This approach initially targets high-prevalent mutations and younger populations.[4]
  - Netherlands: A risk-sharing agreement to manage the uncertainty around the number of patients eligible for treatment with an NTRK inhibitor was implemented in the Netherlands.[5]
- Three scenarios that incorporated these approaches were explored:

Scenario 1

Phased implementation (based on cost-effectiveness criteria): A prevalence-based approach in which a set of histologies is selected to be initially tested for NTRK fusions until DTx is widely available for all other histologies. Histologies for which DTx is cost effective were included while those below the estimated prevalence threshold for cost-effectiveness were excluded from the analysis.

Scenario 2

Risk-sharing: A risk-sharing agreement that incorporates the costs of DTx and includes all histologies in the analysis; it assumes that the manufacturer temporarily funds a portion of the DTx costs for histologies with a mutation prevalence below estimated prevalence threshold for cost-effectiveness. The proportion of funding was set at 73.89% to yield a histology-independent ICER of £40,000.

Scenario 3

Phased implementation (based on budget-impact criteria) + risk-sharing: A phased implementation approach based on budget impact combined with a risk-sharing agreement. Histologies below the budget impact threshold of £1,500,000 were selected for DTx coverage and assumed 100% manufacturer funding for those histologies with a mutation prevalence below the estimated threshold for cost-effectiveness.

All scenarios assume temporary mechanisms for the first year of market entry, as the infrastructure for NGS testing improves until widely available for all histologies. However, this analysis does not aim to be prescriptive on the design of market entry schemes.

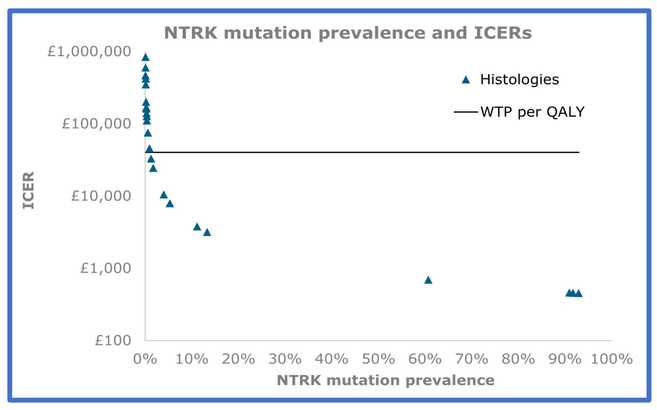
RESULTS

- The histology-independent ICER for NTRK fusion testing resulted in £146,938 (95% confidence interval [CI] £121,918, £180,603), significantly exceeding the cost-effectiveness threshold of £40,000 per additional QALY.
- However, significant variation was observed across histologies:
  - The histology with the highest gene prevalence (mammary analogue secretory carcinoma, NTRK mutation prevalence = 92.90%) had an ICER of just £452; the histology with the lowest prevalence (high-grade glioma, NTRK mutation prevalence = 0.05%) had an ICER of £840,336.
  - This variation was exacerbated when uncertainties around prevalence estimates were considered, particularly for low-prevalence histologies. The ICER for a histology with low NTRK prevalence (e.g., high-grade glioma) ranged from £697,210 to £1,032,816 (based on the 95% CI), making DTx for NTRK fusions in rare tumours unlikely to ever be cost effective.

Threshold for cost-effectiveness

- When NTRK mutation prevalence fell below 1.05%, DTx was not cost effective.
- Eighteen of the 28 included tumour types failed to meet the threshold due to a mutation prevalence below 1.05% (Figure 1).

FIGURE 1: ICER of histologies with NTRK fusion per mutation prevalence



Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay

Scenario analyses

- The scenario analyses resulted in improved cost-effectiveness and budget impact outcomes (Figure 2). However, these scenarios highlighted a set of important trade-offs:
  - While phased implementation approaches improved cost-effectiveness outcomes, these also significantly limited the eligible population for DTx and therapy.
  - While risk-sharing maximised the eligible population (and ensured overall cost-effectiveness), the degree of cost-sharing required by a single company is unlikely to be commercially viable or economically appropriate (i.e., given that NGS may have broader use and benefit beyond NTRK fusion testing).

FIGURE 2: Cost-effectiveness and budget impact results from scenario analyses

	Annual eligible population	ICER (95% CI)	Incremental budget impact per year (95% CI)
Base case	278 in 28 histologies	£146,938 (£122,849, £182,655)	£34,037,087 (£27,533,016, £40,357,189)
Phased implementation of DTx (based on CE)	105 in 10 histologies	£5,868 (£4,975, £7,384)	£513,135 (£416,021, £605,764)
Risk-sharing of DTx	278 in 28 histologies	£40,000 (£33,437, £49,728)	£9,265,837 (£7,495,943, £10,984,384)
Phased implementation (based on BI) + risk-sharing	143 in 21 histologies	£4,311 (£3,625, £5,382)	£513,135 (£416,021, £605,764)

Abbreviations: BI, budget impact; CE, cost-effectiveness; CI, confidence interval; DTx, diagnostic testing; ICER, incremental cost-effectiveness ratio

FOOTNOTE:

* Tumour types included: appendix; breast; cervix; cholangiocarcinoma; colorectal; congenital mesoblastic nephroma; gastro-oesophageal junction; gastrointestinal stromal tumour; head and neck squamous cell carcinoma; high-grade glioma; infantile fibrosarcoma; mammary analogue secretory carcinoma; melanoma; neuroendocrine; non-small cell lung cancer; ovarian; pancreatic; papillary thyroid tumour; paediatric high-grade glioma; paediatric melanoma; prostate; renal cell carcinoma; salivary gland; secretory breast carcinoma; sinonasal adenocarcinoma; soft tissue sarcoma; thyroid; and uterine.

Presented at ISPOR Europe | November 6–9, 2022 | Vienna, Austria

DISCUSSION & CONCLUSION

The cost-effectiveness of HITs highly depends on NGS service provision. Progress in the adoption of multigene DTx would improve access to HITs and limit decisions driven by tumour-specific prevalence estimates and associated DTx costs.

This case study demonstrated that ICER calculations on DTx are heavily influenced by both the prevalence of the cancer gene mutation as well as the uncertainty in these inputs.

Phased implementation strategies for DTx combined with risk-sharing agreements that include the cost of the DTx present an opportunity to relieve the risk and cost burden on both the health system and the manufacturer. However, the broader application of NGS testing and wider economic benefits beyond NTRK testing need to be more formally considered to ensure an appropriate balance of risk-sharing considerations whilst also ensuring that risk-sharing schemes are commercially viable and encourage appropriate investment in innovation.

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