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Manuscript Title **Appraising the costs of genomic testing for histology independent technologies: An illustrative example for *NTRK* fusions.**

Running Title Economic impact of testing for HI-technologies

Authors

Lucy Beresford, MSc (0000-0001-6803-5566)
Centre for Reviews and Dissemination, University of York, United Kingdom

Peter Murphy, MSc (0000-0001-8864-1416)
Centre for Reviews and Dissemination and Centre for Health Economics, University of York, United Kingdom

Professor Sofia Dias, PhD (0000-0002-2172-0221)
Centre for Reviews and Dissemination, University of York, United Kingdom

Lindsay Claxton, MSc* (0000-0002-1795-7568)
Centre for Reviews and Dissemination, University of York, United Kingdom

Matthew Walton, MSc* (0000-0003-1932-3689)
Centre for Reviews and Dissemination, University of York, United Kingdom

Robert Metcalf, MBChB, PhD
The Christie Hospital, Manchester, United Kingdom

Helene Schlecht, PhD
Genomic Diagnostic Laboratory Manchester, Centre for Genomic Medicine, Manchester, United Kingdom

Christian Ottensmeier, MD, PhD, FRCP
Cancer Sciences Division, University of Southampton, United Kingdom

Marta Pereiram, MSc
Genomic Diagnostic Laboratory Manchester, Centre for Genomic Medicine, Manchester, United Kingdom

Dr Robert Hodgson, PhD (0000-0001-6962-2893)
Centre for Reviews and Dissemination, University of York, United Kingdom
** These authors contributed equally to this work.*

Contact information for corresponding author

Lucy Beresford, MSc
Centre for Reviews and Dissemination,
University of York, UK

Email: lucy.beresford@york.ac.uk
Phone: 01904 321044

Précis

The cost of testing to identify individuals eligible for histology-independent technologies will have a substantial impact on the overall cost-effectiveness of these novel drugs.

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Objective: Histology-independent (HI) technologies are authorised for advanced/metastatic cancer patients if they express a particular biomarker regardless of its position in the body. Although this represents an important advancement in cancer treatment, genomic testing to identify eligible individuals for HI technologies will require substantial investment and impact their cost-effectiveness. Estimating these costs is complicated by several issues which not only impact the overall cost of testing, but also on the distribution of testing costs across tumour types.

Methods: Key issues that should be considered when evaluating the cost of genomic testing to identify those eligible for HI technology are discussed. These issues are explored in illustrative analyses where costs of genomic testing for *NTRK* fusions in England for recently approved HI technologies are estimated.

Results: The prevalence of mutation, testing strategy adopted and current testing provision impact the cost of identifying eligible patients. The illustrative analysis estimated the cost of RNA-based NGS to identify one individual with an NTRK fusion ranged between £377 and £282,258. To improve cost-effectiveness, testing costs could be shared across multiple technologies. An estimated, additional ~4,000 patients would need to be treated with other HI therapies for testing in advanced/metastatic cancer patients to be cost-effective.

Conclusions: The cost of testing to identify individuals eligible for HI technologies impact the drug's cost-effectiveness. The cost of testing across tumour types varies owing to heterogeneity in the mutation's prevalence and current testing provision. The cost-effectiveness of HI technologies may be improved if testing costs could be shared across multiple agents.

Highlights

What is already known about the topic?

Histology-independent (HI) technologies are authorised for advanced/metastatic cancer patients if they express a particular biomarker regardless of its position in the body. Identifying patients eligible for HI technologies will require substantial investment in genomic testing which will have repercussions for the cost-effectiveness of the technology.

What does the paper add to existing knowledge?

This study highlights the key issues that need to be considered when evaluating the cost of genomic testing to identify those eligible for histology independent technologies. The illustrative example of NTRK fusion shows that costs of testing may vary between tumour types, owing to differences in the prevalence of the biomarker and current testing provision. Testing costs could be reduced if costs are shared across multiple HI technologies.

What insights does the paper provide for informing healthcare related decision making?

An accurate estimation of testing costs is important when considering the cost-effectiveness of histology-independent technologies in a health technology assessment setting. Given the heterogeneity in testing costs across tumour types, limiting authorization for HI technologies in tumour types where testing is value for money may be appropriate. With the advancement of testing services and future HI technologies becoming available, the cost of testing is likely to improve.

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Introduction

The development of targeted therapies for the treatment of multiple tumours represents an important advancement in oncological treatment.[1] Regulatory approvals typically cover a single or small number of tumour types for currently available targeted therapies, though there are exceptions.[2,3]

Unlike other targeted therapies, drugs with a histology-independent (HI) marketing authorisation are not restricted for use in a particular tumour type or anatomical site but are offered to all patients based on the presence of a particular mutation. The nature of these approvals potentially represents an important advancement in the approach to the treatment of cancer but also create novel challenges with regards to the implementation of these drugs, and how estimates of the clinical and cost-effectiveness, necessary for reimbursement agencies such as the National Institute of Health and Care Excellence (NICE) in England, can be generated.[4]

One such challenge is the identification of those eligible for treatment, as all advanced and metastatic patients with solid tumours may be tested for target mutations[5]. Such a testing programme will require substantial expansion of, and continued investment in, existing testing services that will impact the cost of implementing HI technologies. Accurate estimations of testing costs is therefore important when estimating the value of HI technologies from a health technology assessment (HTA) perspective. The estimation of testing costs is also complicated by several significant issues which not only impact the absolute magnitude of these costs but also their distribution across tumour types.

To address some of these factors the paper first presents a narrative overview of the key issues that should be considered when evaluating a HI technology in a HTA setting. Following recent NICE approval of two HI drugs targeting neurotrophic tyrosine receptor

kinase (*NTRK*) fusions- entrectinib and larotrectinib[5,6] - we develop an illustrative example evaluating these issues in the context of implementing testing for *NTRK* fusions. In a concluding section, we explore the potential role of cost-sharing and the challenges of implementing such an approach in a HTA setting.

Key Considerations

The costs associated with identifying patients eligible for a HI technology is driven by several factors including the prevalence of the target mutation, testing strategy adopted, current testing provision and positioning of testing in the treatment pathway.

The prevalence of the mutation targeted by HI technologies is an important factor that influences the overall cost of testing. As the prevalence of a mutation reduces, the number of patients who need testing to identify one individual eligible for a HI technology increases. Furthermore, the prevalence of a mutation can vary significantly between different tumour types: for example, *NTRK* fusions were detected in 92.87% of patients with secretory breast carcinoma but only 0.05% of patients with hepatocellular carcinoma.[7] This variability contributes significantly to heterogeneity in the costs of testing.

Evidence on the target mutation's prevalence in each tumour type can be sparse or completely absent. Limited knowledge of which tumour types harbour specific mutations will likely mean there will be some tumour types where it is unknown whether prevalence of the mutation is greater than zero. For example, a recent systematic review[7] demonstrated that estimates of *NTRK* fusion prevalence are currently available for many tumour types, but not all. For tumour types where there is no or limited evidence of specific mutations occurring, consideration should be given to whether testing is appropriate. Where testing is planned, analysts and decision makers may need to make assumptions regarding the prevalence of mutations attributed to 'unrepresented' tumour types. For example, it may be deemed

reasonable to use the average *NTRK*-fusion frequency across the tumour types with known frequencies to represent the tumour types with unknown frequencies. Alternatively, the prevalence of a fusion may be related to that of a specific tumour type based on similar tumorigenesis.

A variety of tests are available to identify the presence of a target mutation in patients with cancer. These include DNA- and RNA-based panel tests, whole genome sequencing (WGS), immunohistochemistry (IHC), fluorescent in-situ hybridisation (FISH) and reverse transcription polymerase chain reaction (RT-PCR), each of which are associated with advantages and limitations.[8] Each test determines the presence or absence of mutations in different ways, from identifying a known driver mutation using targeted tests in DNA and RNA, to sequencing the entire genome, or determining the level of expression of a particular protein. The suitability of a test will likely depend on the target mutation and the test's diagnostic accuracy, the prevalence of the mutation within each tumour type and current testing provision. Tests may be combined as part of a testing strategy. This approach uses a cheaper test with a lower sensitivity as a first-line test, followed by a more diagnostically accurate and expensive test to confirm the presence of mutation. This allows for diagnostic accuracy to be maintained, while reducing the use of more resource intensive tests. This latter issue may be of relevance as the use of next generation sequencing (NGS) becomes more widespread, rendering the use of strategies built around IHC less relevant.

Testing costs may also be influenced by current testing provision in a particular health service, which may already allow for the identification of target mutations in some tumour types. When the implementation of additional testing displaces current testing for some tumour types, these costs should be considered such that testing costs truly reflect only the *incremental* costs of providing testing to identify the mutation of interest. This would mean

that the testing costs for some tumour types may reduce substantially, and in some cases, render them value for money.

The stage of treatment where testing is offered may influence the cost of testing. It has been suggested that pan-genomic testing in England will be made available to all advanced or metastatic cancer patients.[5] This has consequences for the costs of identifying patients eligible for a HI technology positioned at a second or later line of therapy. Marketing authorisation for entrectinib and larotrectinib state that the therapies should be used when 'no satisfactory treatment options' are available.[5,6] Therefore, the point at which a patient is eligible for entrectinib and larotrectinib is likely to vary between tumour types, depending on current treatment options. For example, in rarer tumours, patients are more likely to receive entrectinib or larotrectinib earlier in the treatment pathway, given the limited treatment options available.[5] There is often significant attrition of patients across lines of therapy due to the combined impact of disease-related mortality and fitness for further treatment. Therefore, if testing occurs at diagnosis of advanced and metastatic disease, only a proportion of people who were tested would benefit from the HI technology. While the absolute costs of testing will remain the same, the costs of testing, relative to the patients who will go on to receive the HI technology, will increase. Further heterogeneity in the testing costs across tumour types as differences in the availability of treatments will mean that a HI technology is available at different lines of therapy for each tumour type.

The key issues that should be explored when considering the costs of testing for HI technologies, and the impact that they have on decision making are summarised in Table 1.

Illustrative Example

The potential impact of each of these key issues outlined above is explored in an illustrative example, considering testing for *NTRK* fusions.

In England, NICE recently approved the use of entrectinib and larotrectinib, targeting *NTRK* gene fusions for patients with advanced/metastatic cancer.[5,6] On average, *NTRK* fusions are rare, occurring in approximately 0.52% of individuals with solid tumours.[7] In some rare tumour types, including infantile fibrosarcoma and secretory carcinoma of the breast and salivary gland, *NTRK* fusions are detected in most patients. However, in common tumours, such as breast and non-small-cell lung cancer (NSCLC), *NTRK* fusions are detected in less than 0.15% of patients.[7]

Prevalence:

The Number Needed to Screen (NNS) is defined as the number of individuals who require testing to identify one individual with mutation and is a function of prevalence and diagnostic accuracy. The NNS is calculated using the following equation:

$$NNS = \frac{1}{Sensitivity \times NTRK\ Prevalence}$$

The cost to identify one patient with an *NTRK* fusion is calculated by multiplying the NNS by the price of the test, which in the case of RNA-based NGS is assumed to be £350 (obtained from a UK Genomics centre).

Table 2 presents the NNS and costs using RNA-based NGS to identify individuals with an *NTRK* fusion in a subgroup of tumour types (the NNS and cost for all tumours with a known *NTRK* fusion are provided in the Supplementary Material). These tumour types were chosen to show a range of *NTRK* fusion prevalences and the resulting impact on testing costs. As RNA-based NGS is the gold-standard of testing for gene fusions, owing to its 100% sensitivity[10], NNS becomes solely a function of prevalence in this example.

The number of patients requiring testing to identify one patient with an *NTRK* fusion varies considerably depending on the mutation's prevalence. Only 1.1 individuals with secretory

breast carcinoma, need to be tested to detect an individual with an *NTRK* fusion. Resulting costs per identified patient are therefore £377. This contrasts with NSCLC, where the prevalence of an *NTRK* fusion is low, and over 800 individuals require screening to identify one patient with an *NTRK* fusion, hence the estimated cost of testing for NSCLC is around £282,258.

The type of test employed to detect individuals with an *NTRK* fusion influences the NNS due to different levels of diagnostic accuracy. IHC can be used to detect *NTRK* fusions; however, as the sensitivity (Sn) of this test is poorer (Sn = 87.9.%)[11], the NNS is higher, as shown in Table 2. Compared to RNA-based NGS, more individuals require testing to identify one patient with an NTRK fusion when using IHC. In NSCLC, an additional 111 individuals would need to be screened using IHC to identify one patient with an *NTRK* fusion. The impact of sensitivity on the NNS is less in tumour types where *NTRK* fusion frequency is higher.

Although the diagnostic accuracy of IHC is poorer, the lower cost of these tests (£150) means that they could still be considered in an approach to identify patients with *NTRK* fusions. Table 2 shows that the cost of *NTRK* fusion testing is less when IHC is utilised, with costs reduced to £184 to identify one *NTRK* fusion-positive patient with secretory breast carcinoma, to £137,620 to identify one *NTRK* fusion-positive patient with NSCLC- less than half of the cost compared to using RNA-based NGS.

Testing Strategy

Tests may be combined as part of a testing strategy, where confirmatory tests verify that the identified mutation is expressed. The European Society of Medical Oncology (ESMO) proposed using IHC followed by confirmatory RNA-based NGS when the prevalence of *NTRK* fusion is rare.[12]

The following equation was used to calculate the cost of ESMO-recommended testing strategy to identify one individual with an *NTRK* fusion.

$$Cost\ to\ identify\ patient\ with\ NTRK\ fusion = \left((NNS_{IHC} \times Cost_{IHC}) + \left(NNS_{C\_RNA\ NGS} \times Cost_{RNA\ NGS}\right)\right)$$

Confirmatory RNA-based NGS is required for patients who have a positive IHC test. The NNS with confirmatory RNA-based NGS (described in the equation as $NNS_{C\_RNA\ NGS}$) was estimated using the sensitivity and specificity (Sp) of IHC (Sn = 87.9% and Sp = 81.10%)[11] and the tumour-specific *NTRK* fusion prevalence using the equation below.

$$NNS_{C\_RNA\ NGS} = \frac{(Sn\ \times NTRK\ prevalence) + ((1 - Sp)\ \times (1 - NTRK\ prevalence))}{(Sn\ \times NTRK\ prevalence)}$$

Table 3 summarises the cost and NNS for the ESMO-recommended testing strategy. As IHC, is used for first-line screening for large numbers of patients, the cost of testing to identify one eligible individual is cheaper than using RNA-based NGS alone, ranging from £540 in patients with secretory breast carcinoma to £198,585 in patients with NSCLC.

Average and tumour specific testing costs

Figure 1 presents the additional cost of testing to identify patients eligible for Trk-inhibitors for the tumour types where the prevalence of *NTRK* fusions is known (see Supplementary Material for further details). Across all tumour types with a known *NTRK* fusion, the weighted average cost using ESMO-recommended testing strategy is £75,182, or £106,617 using RNA-based NGS. The cost of testing using RNA-based NGS varies substantially across tumour types, ranging from £377 to £700,000 to identify one individual with an *NTRK* fusion, driven by differences in the prevalence of *NTRK* fusions.

Unrepresented Tumour Types

The testing costs in tumour types where the prevalence of the target mutation is unknown should be considered, as these will be covered by a HI approval of the technology. The

prevalence of *NTRK* fusions has been identified in over 30 tumours, meaning that around 82,420 advanced and metastatic patients will require testing in England. Given that the annual incidence of patients diagnosed with advanced and metastatic cancer in England is approximately 115,717 [13], the *NTRK* fusion prevalence in the remaining 33,297 patients is unknown (see Supplementary Material for details).

To estimate the cost of testing in unrepresented tumour types, the prevalence of *NTRK* fusions could be assumed to be the average (0.52%). Alternatively, as *NTRK* fusions have not yet been identified in these unrepresented tumours, it could be assumed that the prevalence of *NTRK* fusions is much less - such as the lowest known *NTRK* fusion prevalence (0.05%). The additional costs associated with testing in these tumour types based on these assumptions is presented in Table 4.

If the estimated testing cost was based on the average *NTRK* fusion prevalence, the average cost to identify eligible individuals is estimated to be between £47,564 and £67,308. If the *NTRK* fusion prevalence of the unrepresented tumour types were assumed to be 0.05%, the additional, average cost to identify one individual with an *NTRK* fusion is between £492,084 and £700,000.

Apportioning Testing Costs

As the previous analysis shows, the provision of histology-independent technologies targeting *NTRK* fusions will require significant investment in genomic services, owing to the current absence of wide-scale testing for *NTRK* fusions in the NHS. This high cost is a direct consequence of the rarity of *NTRK* fusions, which means that large numbers of individuals must be screened to identify a single patient eligible for treatment. The extent of these costs will have significant bearings on reimbursement decisions for entrectinib and larotrectinib and more generally, may be indicative of a barrier to implementing HI technologies.

The provision of wide scale genomic testing which may allow for the identification of other relevant mutations is likely to represent a public good: it would be non-rivalrous as there is only a marginal cost of adding another target, and is non-excludable as any manufacturer can request a target genetic sequence to be added to a panel. This may be important where there are multiple targeted therapies available or likely to become available in the near future. Accounting for such positive externalities may be essential, as testing costs may not justify the implementation of a single technology but may be justifiable when shared across multiple technologies. Estimating the magnitude of any positive externalities resulting from testing is non-trivial and an appropriate system for the identification of relevant targeted treatments and an equitable system of how costs are attributed across technologies will need to be established. Costs could, for example, be split equally between technologies or by the size of the eligible population. This may necessitate a coordinating role for health service agencies to potentially set a tariff or oversee the principals upon which cost sharing is applied.

Cost sharing is likely to have some limitations even if methodological and practical challenges of implementation are overcome, as it will require the creation of a common diagnostic strategy that is flexible enough to capture a range of target mutations. This could be difficult as a test's diagnostic accuracy may vary depending on the type of mutation. Notwithstanding, there may be some tumour types where there are few or no targeted treatments available, limiting opportunities for cost sharing. Barriers to reimbursement created by testing costs may therefore remain for some tumour types.

To explore the potential gains from future target therapies, an illustrative analysis was implemented which attempts to estimate the numbers of patients that would need to benefit from pan-cancer testing for it to be cost-effective. The exploratory analysis used an estimate of the net monetary benefit (NMB) per patient treated with entrectinib[14], which is calculated by multiplying the incremental benefit and willingness to pay threshold and then subtracting

the incremental costs. In this analysis, a willingness to pay threshold of £50,000 per quality adjusted life year was assumed[15]. This can then be used to estimate the population NMB by multiplying this by the size of the total population eligible to receive entrectinib, giving an estimate of the total benefits to the NHS of implementing the drug. This can be considered an estimate of entrectinib's contribution to covering the cost of molecular testing.

Table 5 shows that the population NMB generated by entrectinib is much smaller than the total costs to the NHS of implementing molecular testing across all alternative testing strategies. The exploratory analysis shows that the introduction of entrectinib alone is insufficient for testing to be considered cost-effective. If we make the simplifying assumption that the NMB per patient treated with other targeted therapies is the same as that generated by entrectinib, we can consider how many patients would need to be treated with targeted therapies for testing to be cost-effective. This illustrative analysis shows that there would need to be 4,073 additional patients treated with the target therapies, representing ~3% of the current incident advanced cancer population.

Discussion

The development of HI therapies such as larotrectinib and entrectinib potentially represents a significant change in the treatment of cancer. Integral to the provision of HI therapies will be the provision of complementary wide-scale testing to identify patients eligible for treatment. Any such programme is likely to entail significant costs which should be properly evaluated when considering the clinical and cost-effectiveness of HI drugs in a HTA setting.

Our illustrative analyses shows that the provision of testing to determine eligibility for HI technologies will require significant investment in genomic diagnostics services. Based on the tumour specific testing cost and the annual eligible population in each tumour group (see Supplementary Material, Table 4 for further details), we estimated the incremental annual

costs of testing in England to identify all individuals where the frequency of *NTRK* fusions is known to be between £20,341,893 and £28,847,161 depending on the testing strategy adopted. The costs associated with genomic testing are driven by the prevalence of mutations across specific tumour types, with increased rarity increasing the costs of identifying eligible patients. As is shown in the illustrative example of *NTRK* fusions, variability in the prevalence of mutations across tumour types can be significant, ranging from <0.1% to >90%[7]. This has a significant impact on the number of patients that need to be tested and consequently, the costs of identifying patients across specific tumour types varies significantly. Variability in the testing strategy adopted and current testing provision across tumour types further contributes to this heterogeneity.

When considering the most appropriate approach to identifying patients eligible for HI technologies, the sensitivity of a test should be considered. In the case of *NTRK* fusions, the poor sensitivity of IHC (87.9%)[11] means that over 10% of patients will be incorrectly identified as being *NTRK*-fusion negative when they actually harbour the *NTRK* fusion. Even if a testing strategy was to be considered, patients with false-negative results will not be eligible for confirmatory testing. Consequently, patients who harbour the *NTRK* fusion but test negative would not benefit from the promising outcomes of the HI technology.

The cost of testing is likely to be an important contributor to the total costs of implementing HI treatments, and, if all testing costs are attributable to a single HI drug, is likely to render a technology cost-ineffective for some tumour types. Given the variability in testing costs, it may be important for reimbursement agencies to consider an optimised approach, where testing is prioritised in tumour types where prevalence is higher, or where the relative benefits of treatment (which are likely to be variable) are greatest.

Existing HTA guidelines for NICE in England[16] suggesting that the full economic costs of testing should be included may, however, be out of date. Expansion of genomic testing services based on panel tests- where multiple mutations can be screened for in a single test- may mean that a single diagnostic strategy can be used to identify those eligible for a number of targeted therapies. Under such a scenario, testing represents a public good and may plausibly allow testing costs to be shared across multiple technologies. The implementation of cost sharing arrangements is complex and it is currently unclear how costs should be apportioned or who should make such judgments. Importantly, it also requires the availability of other targeted therapies which may prove a limiting factor in some tumour types.

The recent NICE appraisal of larotrectinib and entrectinib (where approval assumed cost sharing) [5,6] represents an important example of the influence of testing costs and the potential for reimbursement agencies to accept the principle of cost sharing. It illustrates the importance of reimbursement and other relevant national agencies to take a coordinated role to set the tariff upon which attributable testing costs for HI technologies can be based. Reimbursement agencies should be transparent in providing information about how decision makers derived the figures used to estimate the proportion of costs that should be attributed to authorised HI technologies, which is likely to be highly informative for other reimbursement agencies facing similar decisions.

The number of HI technologies available is set to increase over the coming years, with the output of 11 HI technologies being sent to NICE for appraisal.[17] This is likely to place additional pressure on reimbursement agencies to approve their use and consider opportunities to address any issues relating to the cost of testing. In this regard, it is notable that NHS England are providing significant investments to UK genomic testing services, with diagnostic and molecular tests set to be available for over 100,000 individuals by 2023.[18] The increased availability of testing and targeted treatments including HI technologies is likely to

increase the possibilities for cost sharing and may improve the cost-effectiveness of genomic testing and HI technologies. A coordinating role for relevant stakeholders and clear methodology will be necessary to ensure that approved HI technologies represent value for money.

Limitations of presented analysis

Owing to the limited literature surrounding *NTRK* fusions, the calculations to estimate the testing costs are built upon several assumptions. First, the *NTRK* fusion frequency for each tumour type was obtained from a systematic review. While this brings benefits in pooling the prevalence across multiple studies, there was significant heterogeneity in the reported frequency of *NTRK* fusions in some tumour types. Many studies have small sample sizes which means the *NTRK* fusion frequency could be over- or underestimated. Second, our analysis neglected some aspects of the testing cost calculation, such as the line of treatment and current testing provision which may impact on testing costs. Third, our study does not consider additional costs associated with providing genomic testing, such as the clinical consultations before/after the test, which may impact the overall cost of testing. We also consider only a limited number of possible testing strategies.

Conclusions

Using a worked example examining the costs of testing for *NTRK* mutations from an English perspective, we explore the key drivers of testing costs for HI treatments. Our analysis highlights that the cost of testing for eligibility for a single HI technology could result in significant ongoing investment in genomic diagnostics services, and that the costs of testing are likely to vary significantly across tumour types. If testing costs are attributable to a single HI drug, it is likely that testing costs will render HI treatments cost-ineffective, at least for some tumour types. Testing costs may impede reimbursement decisions and more generally act as a barrier to implementation. The cost-effectiveness of testing may be improved by

either focusing upon tumour types where prevalence is highest or through the implementation of cost sharing that allows testing costs to be shared across multiple targeted treatments.

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Table 1. Key issues to consider when evaluating the cost of genomic testing for histology-independent (HI) technologies.

	Key Considerations	Impact on Decision-Making
Prevalence of mutation	The prevalence of a mutation can varies significantly between different tumour types and it directly influences the number of individuals that need to be screened to identify one individual eligible for the HI technology.	An optimised approach to drug authorization, where the HI technology is only available to patients with tumour types where the costs of testing are low enough to render the HI technology value for money. Some clinicians may be reluctant to offer *NTRK* fusion testing, or a HI technology in the tumour types where the mutation is very rare or unknown, which may make it difficult for clinicians to manage patient expectations if they know a drug has histology-independent approval.[9]
Type of test	Several tests are available to identify individuals with a mutation. The suitability of the test will likely depend on the target mutation and the test's diagnostic accuracy to correctly detect the respective genetic mutation.	Given that some national reimbursement agencies may define a HI technology's price based on the expected demand of the drug, and the prevalence of the relevant mutation, the accuracy of the test is a crucial aspect that decision-makers need to acknowledge when considering the authorisation of the drug. Decision-makers should consider potential pipeline HI technologies, as choosing a testing approach where multiple target mutations can be tested for simultaneously may mean testing costs can be shared across multiple technologies.
Testing Strategy	Tests may be combined as a part of a testing strategy, where a cheaper test is used at a wider scale, with a more accurate test being used to confirm the presence of a genetic mutation.	
Current provision of testing	The implementation of additional testing may also displace current testing for some tumour types. When that is the case, these costs should be considered such that testing costs truly reflect only the *incremental* costs of testing.	
Line of therapy where testing will occur	Testing may occur at the diagnosis of advanced or metastatic disease, rather at the line of therapy where the HI technology will be given. This will have an influence on the costs of tests, as fewer people originally tested for a mutation will not be eligible for treatment due to disease-related mortality of fitness for further treatment.	Given that the line of therapy where a patient is eligible to receive a HI technology is likely to vary between tumour types, offering testing at diagnosis of metastatic disease is likely to be the most appropriate option. This is likely to be strategically desirable as genomic testing becomes more integrated into the management of cancer patients.

Table 2. Number needed to screen and cost of RNA-based NGS and immunohistochemistry testing in order to identify one patient with an *NTRK* fusion for a subgroup of tumour types.

Tumour Type	Prevalence of *NTRK* fusion	NNS	Cost to identify one eligible individual
RNA-based NGS			
Secretory breast carcinoma	92.87%	1.1	£377
Paediatric differentiated thyroid cancer	24.08%	4.2	£1,454
Paediatric diffuse intrinsic pontine glioma	4.76%	21.0	£7,353
Appendiceal adenocarcinoma	0.56%	178.6	£62,500
Non-small cell lung cancer	0.12%	806.5	£282,258
Immunohistochemistry			
Secretory breast carcinoma	92.87%	1.2	£184
Paediatric differentiated thyroid cancer	24.08%	4.7	£709
Paediatric diffuse intrinsic pontine glioma	4.76%	23.9	£3,585
Appendiceal adenocarcinoma	0.56%	203.2	£30,473
Non-small cell lung cancer	0.12%	917.5	£137,620

NNS, Number Needed to Treat; IHC, Immunohistochemistry; NGS, Next Generation Sequencing

Table 3. Number needed to test and cost of the ESMO-recommended testing strategy in order to identify one patient with an *NTRK* fusion for a subgroup of tumour types.

Tumour Type	Prevalence of *NTRK* fusion	NNS		Cost to identify one eligible individual
		IHC	Confirmatory RNA-NGS	
Secretory breast carcinoma	92.87%	1.2	1.0	£540
Paed. differentiated thyroid cancer	24.08%	4.7	1.7	£1,296
Salivary gland carcinoma	5.08%	22.4	5.3	£5,441
Appendiceal adenocarcinoma	0.56%	203.2	39.2	£44,186
Non-small cell lung cancer	0.12%	917.5	174.2	£198,585

NNS, Number Needed to Treat; IHC, Immunohistochemistry; NGS, Next Generation Sequencing

Table 4. A scenario analysis of the cost of testing for unrepresented tumour types best on two assumed *NTRK* fusion frequencies.

Prevalence *NTRK* Fusion	**ESMO-recommended testing strategy**			**RNA-based NGS**	
	NNS		Cost	NNS	Cost
	First-line	Confirmatory			
0.52%	219	42	£47,564	192	£67,308
0.05%	2275	431	£492,084	2000	£700,000

NNS, Number Needed to Treat; NGS, Next Generation Sequencing

Table 5. An estimate of entrectinib contribution to covering the cost of molecular testing.

Net monetary benefit per patient treated with entrectinib[a]	£6,641
Annual population eligible for treatment with entrectinib[b]	271
Population net monetary benefit generated by entrectinib[c]	£1,799,711
Total cost of testing (RNA-based NGS)[d]	£28,847,161

[a]The net monetary benefit was obtained from Entrectinib for treating NTRK fusion-positive advanced solid tumours [ID1512]. Committee Papers[14] (Page 581 of 644) [b]The calculation of the annual eligible population is detailed in Table 3 of the supplementary material. [c]Calculated by multiplying net monetary benefit per patient and the annual eligible population. [d]Sum of the total testing costs, which is calculated by multiplying the cost to identify one patient with an NTRK fusion and the annual eligible population in each tumour type before adding all of them together

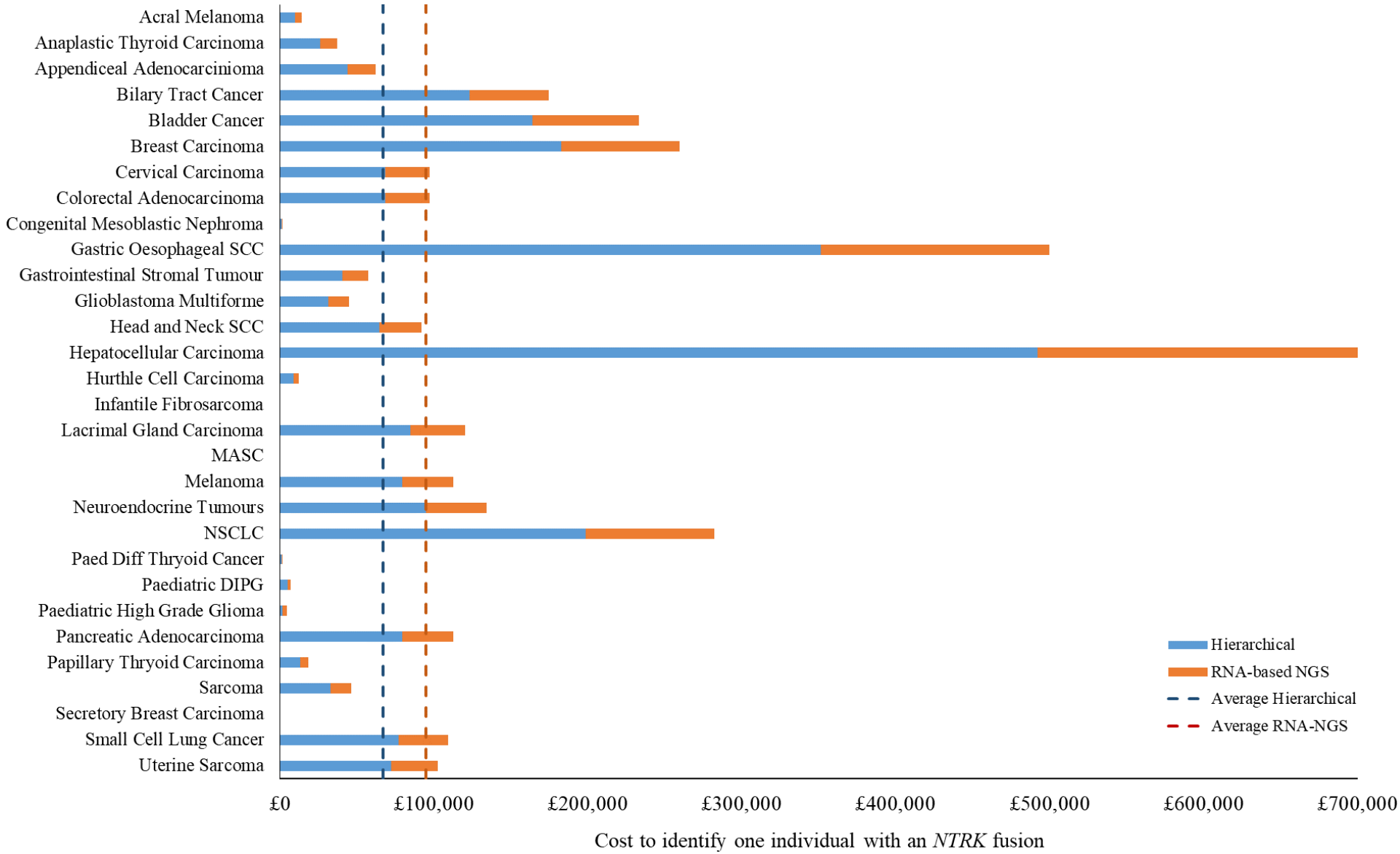

Figure 1. The cost of testing to identify one individual with an NTRK fusion. DIPG, Diffuse Intrinsic Pontine Glioma; NGS, Next Generation Sequencing; MASC, Mammary Analogue Secretory Carcinoma; NSCLC, Non-Small Cell Carcinoma; SCC, Squamous Cell Carcinoma