Research Article

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Personalized Medicine

Cost–effectiveness of alternative *NTRK* testing strategies in cancer patients followed by histology-independent therapy with entrectinib: an analysis of three European countries

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Aim: To explore variations in the cost–effectiveness of entrectinib across different testing strategies and settings. **Methods:** Four testing strategies where adult cancer patients received entrectinib if they tested positive for *NTRK* gene fusions compared with 'no testing' and standard of care (SoC) for all patients were evaluated. **Results:** Immunohistochemistry for all patients followed by RNA-based next-generation sequencing after a positive result was the optimal strategy in all included countries. However, the incremental net monetary benefit compared with SoC was negative in all countries, ranging between international euros (int€) -206 and -404. In a subgroup analysis with only *NTRK*-positive patients, the incremental net monetary benefit was int€ 8405 in England, int€ -53,088 in Hungary and int€ 54,372 in The Netherlands. **Conclusion:** Using the cost–effectiveness thresholds recommended by national guidelines, none of the testing strategies were cost-effective compared with no testing. The implementation of entrectinib is unlikely to become cost-effective in Hungary, due to the large cost difference between the entrectinib and SoC arms, while there might be more potential in England and The Netherlands.

Plain language summary: Histology-independent pharmaceuticals are a new phenomenon in cancer care. Most chemotherapies are prescribed based on the tumor's (primary) location, while histology-independent therapies are prescribed based on genetic markers in the tumor DNA. In this study, the added value of the histology-independent treatment entrectinib, which is aimed at cancer patients with so-called *NTRK* gene fusions, was investigated. Because these patients must be identified before they can be given entrectinib, various strategies for diagnostic testing were considered. An economic model was programmed to gain insight into the costs and health outcomes associated with the different testing strategies. The same analysis was done for three different countries (England, Hungary and The Netherlands) using local data. In all three countries, the health gains from receiving entrectinib may be large for patients with *NTRK* gene fusions. However, treatment with entrectinib was also much more expensive than standard-care treatment, especially in Hungary. In each of the three countries, all evaluated testing strategies were found to offer a negative net benefit to society (i.e., a net loss). This may be partially explained by the fact that *NTRK* gene fusions are rare, meaning that a large group of cancer patients has to receive (costly) testing while, subsequently, only a few patients enjoy the benefit of switching to a treatment that is more effective for them (i.e., entrectinib). Nonetheless, in England and Hungary, even if the most accurate test was provided for free, the net benefit to society of implementing entrectinib remained negative. Further changes, such as a reduction in the price of entrectinib, may therefore be needed.

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In a move toward more precise cancer care, several therapies targeting specific genetic tumor markers have emerged on the market. Among these are histology-independent (also called tumor-agnostic) therapies, which are prescribed solely based on genetic markers of the tumor, without regard for its tissue of origin. The first histology-independent treatments to receive approval from the EMA and US FDA were larotrectinib and entrectinib [1,2]. Both are prescribed for tumors with *NTRK* gene fusions (which cause overexpression of TRK proteins) and both are inhibitors of TRK proteins [3–6].

The advent of larotrectinib and entrectinib has challenged reimbursement authorities and health economists tasked with evaluating their cost–effectiveness. The main challenges include uncertainty about the pharmaceuticals' efficacy due to the use of single-arm (as opposed to randomized controlled) trials. Because of the lack of control arms in TRK inhibitor trials, there is insufficient knowledge about the health outcomes under the standard of care (SoC) among patients with *NTRK* fusions. While historical data could be used to construct a synthetic control arm [7,8], historical data likely pool *NTRK*-positive (*NTRK*+) and *NTRK*-negative (*NTRK*-) patients, given that oncology patients were not tested for *NTRK* fusions in the past. To assess whether using such pooled historical data is appropriate and to be able to adjust historical data where necessary, knowledge of the prognostic value of carrying an *NTRK* gene fusion is imperative. Yet, limited data on the prognostic value of *NTRK* fusions are available. In a previous study, where the current authors performed an economic evaluation of entrectinib in The Netherlands, possible approaches to address these (and other) challenges were proposed [9]. The study was also designed to accurately model the health and cost consequences of testing eligible cancer patients to identify those with oncogenic *NTRK* fusions. Because the previous study concentrated on The Netherlands, the testing strategy that was suggested by a group of Dutch experts was modeled [10]. However, other testing strategies are possible for the identification of *NTRK*+ patients.

In this study, to investigate the potential impact of alternative *NTRK* testing strategies on the cost–effectiveness and budget impact of entrectinib, four different *NTRK* testing strategies were compared. Additionally, the optimal *NTRK* testing strategy may differ between countries due to differences in healthcare systems. The original model reflecting the Dutch setting was therefore also adapted for the English and Hungarian healthcare systems. England and Hungary both have highly centralized single-payer healthcare systems, while healthcare is more decentralized in The Netherlands, with curative care being covered by competing private health insurers [11]. All three countries provide universal healthcare to their residents but, while England and The Netherlands achieve broad coverage, Hungary offers a more limited benefits package [11–13]. Other key differences between the three countries given the context of this study are the available healthcare resources, medical practice patterns and the infrastructure and price-setting for genomic testing (and subsequent treatment).

Methods

Target population

The target population comprised adult patients with locally advanced or metastatic solid tumors who had received one or more lines of treatment and were willing to undergo further (testing and) treatment [9]. While entrectinib is indicated for all *NTRK*+ tumors, only the tumor types for which data were available from the entrectinib registration trials [14] were incorporated into the current model. The included cancers were breast, bile duct (i.e., cholangiocarcinoma), colorectal, endometrial, ovarian, pancreatic and thyroid cancer, as well as neuroendocrine tumors, non-small-cell lung cancer (NSCLC), sarcoma, secretory carcinoma of the breast and secretory carcinoma of the salivary gland.

Model structure

The model consists of a decision tree followed by a microsimulation model (see Supplementary Figure 1). The decision tree reflects the testing phase and covers the period from the decision to test for potential eligibility for entrectinib until the start of treatment. The microsimulation model reflects the time from the start of treatment until death and has a cycle length of one month. A comprehensive description of the original model is published elsewhere [9]. To align with national health technology assessment (HTA) guidelines, analyses were performed from

a healthcare payer perspective for England, a healthcare perspective for Hungary and a societal perspective for The Netherlands [15–17]. Costs and effects were discounted with the prescribed discount rates in each country: 3.5% for costs and effects in England, 3.7% for costs and effects in Hungary and 4% for costs and 1.5% for effects in The Netherlands. The nationally recommended cost–effectiveness thresholds (after severity weighting) were €36,000 (int€ 35,576) for England, 4,921,820 forint (int€ 21,294) for Hungary and €80,000 (int€ 69,666) for The Netherlands.

Decision tree to model testing phase

Four *NTRK* testing strategies were explored in the decision tree. All strategies included next-generation sequencing panels used to screen tumor RNA (RNA-NGS) for *NTRK* fusions and/or immunohistochemistry (IHC) tests to assess TRK protein expression [4,18–20]. RNA-NGS tests can detect oncogenic *NTRK* fusions with high sensitivity and specificity. However, RNA-NGS tends to be expensive. IHC tests are generally more affordable than RNA-NGS tests, but also less accurate. The following testing strategies were included: IHC test for all tumor types (Strategy 1), RNA-NGS test for all tumor types (Strategy 2), IHC test followed by RNA-NGS in patients with a positive IHC test result for all tumor types (Strategy 3) and stratified test strategies depending on the *NTRK* fusion prevalence and TRK wild-type protein expression of the tumor types (Strategy 4) [10].

In the first two strategies, all patients receive the same test: IHC in Strategy 1 and RNA-NGS in Strategy 2. Strategy 3 is a sequential strategy, in which patients first undergo an IHC test, followed by RNA-NGS for those with a positive IHC test result. In this strategy, the false positives of the IHC test are identified with the RNA-NGS test (though false-negative results are missed), while costs are saved by not having to perform the more expensive RNA-NGS test for all patients. However, in tumor types with high *NTRK* fusion prevalence (>90%) or wild-type TRK protein expression, adding an IHC test has little value. In the former, the reason is that most patients will test positive (because of the high *NTRK* prevalence) and still need an additional, confirmatory RNA-NGS test, leading to increased costs. In the latter, there will be many false-positive test results after the IHC test, because IHC testing does not distinguish between wild-type and fusion protein expression. Therefore, Strategy 4 uses RNA-NGS tests (without preceding IHC tests) for patients with tumor types with high *NTRK* fusion prevalence (>90%) or wild-type TRK protein expression (Supplementary Table 1 shows which tumor types fall into these categories). All other patients in Strategy 4 are subject to the sequential testing protocol used in Strategy 3.

Microsimulation to model treatment

In the intervention group, patients first enter the decision tree and subsequently (those who survive beyond the duration of the testing phase) enter the microsimulation model [9]. The individual-level state transition model included the health states "alive and on treatment", "alive and off treatment" and "dead". Patients received entrectinib if they had tested *NTRK*+ in the decision tree and were treated with SoC if they had tested *NTRK*-. In the comparator group, patients did not receive testing (i.e., they skipped the decision tree and went straight into the microsimulation model) and were all given SoC.

Model parameters

Table 1 presents the country-specific values for the input parameters. More detail on the data sources and assumptions for the input parameters is given next as well as in the Supplementary Materials.

Transition probabilities

Decision tree

The probabilities of patients needing biopsies and rebiopsies to enable testing, as well as the test properties of IHC and RNA-NGS tests (see Supplementary Table 2), were based on estimates from the literature and assumed to be similar across countries [9,22,27]. The wait times for various stages of the testing phase were based on publicly available sources in England and based on expert judgment in Hungary and The Netherlands. Patient mortality during the testing phase was based on tumor-specific estimates of weekly mortality [9]. Although weekly mortality was assumed to be similar across countries, the probability of dying during the testing phase differed between the three countries because of differences in wait times.

Table 1. Input parameters.

Input parameter	England	Hungary	Netherlands	Source	Ref.
Purchasing power parity (local currency in $)	0.667865	152.550219	0.757906	OECD.Stat	[21]
Purchasing power parity (EU average in $)	0.66			OECD.Stat	[21]
Testing phase					
Cost biopsy	£727 (int€ 694)	Ft 5919 (int€ 27)	€166 (int€ 138)	Supplementary Table 4	
Cost RNA-NGS	£350 (int€ 334)	Ft 300,000 (int€ 1347)	€1857† (int€ 1552)	Supplementary Table 4	
Costs IHC	£150 (int€ 143)	Ft 45,000 (int€ 202)	€426 (int€ 356)	Supplementary Table 4	
NTRK prevalence (by tumor type)	Similar across countries			Supplementary Table 1	
IHC sensitivity and specificity (by tumor type)	Similar across countries			Supplementary Table 2	
RNA-NGS sensitivity and specificity	100%	100%	100%	Assumption	
Probability biopsy RNA-NGS	0.098	0.098	0.098	Bins *et al.* assumption: similar across countries	[22]
Probability rebiopsy RNA-NGS	0.159	0.159	0.159	Bins *et al.* assumption: similar across countries	[22]
Probability biopsy IHC	Equal to RNA-NGS			Assumption	
Duration waiting time Biopsy requested until biopsy done Rebiopsy requested until rebiopsy done (Re-) biopsy done until IHC test results (Re-) biopsy done until RNA-NGS results Final test results available until start of treatment	 5 days 5 days 5.5 days 21 days 7 days	 14 days 9 days 5 days 14 days 17.5 days	 10.5 days 14 days 3.5 days 10 days 5.5 days	EN: NHS England HU: Expert judgement by oncologist NL: Expert judgement by 3 clinical geneticists and 1 oncologist (mean estimate was used)	
Treatment phase					
Treatment costs SoC (per month, weighted average)	£3105 (int€ 2964)	Ft 393,688 (int€ 1768)	€2084 (int€ 1741)	Supplementary Table 6	
Treatment costs, entrectinib (per month)	£5232 (int€ 4994)	Ft 2,199,642 (int€ 9851)	€5912 (int€ 4938)	Roche	
Adverse event costs (per event, weighted average)	£912 (int€ 870)	Ft 193,732 (int€ 870)	€1042 (int€ 870)	Supplementary Table 6	
Informal care costs (per h)	NA	NA	€14.77 (int€ 12.34)	Zorginstituut Nederland	[17]
Related nonhospital and unrelated (hospital + nonhospital) healthcare costs per year (except year before death)	NA	NA	€4453 (at age 58, increases with age; int€ 3719)	PAID	[23]
Healthcare costs in last year-of-life	€8994 (int€ 8586)	Ft 1,140,365 (int€ 5121)	€58,064 (at age 58, increases with age; int€ 48,499)	EN: Luta *et al.* HU: Assumption that ratio between last-year-of-life cost and cost in other years is same as in EN NL: PAID	[24]
Starting age in years	58			Doebele *et al.*	[14]
Proportion females	0.59			Doebele *et al.*	[14]
OS *NTRK*- (by tumor type)	Similar across countries			Supplementary Table 3	
TTD *NTRK*- (by tumor type)	Similar across countries			Supplementary Table 3	
OS entrectinib	Exponential, similar across countries			Roche	
TTD entrectinib	Exponential, similar across countries			Roche	
HR *NTRK*+ OS adjusted	1.44			HMF	
HR *NTRK*+ TTD adjusted	1.37			HMF	
Tumor distribution	Similar across countries			Supplementary Table 1	
Utilities: time to death	Similar across countries			Versteegh *et al.*	[25]
Informal care use	NA	NA	Dependent on time to death	de Groot *et al.*	[26]

†Weighted mean because price of RNA-NGS tests varies across included tumor types.
EN: England; Ft: Forint; HMF: Hartwig Medical Foundation; HR: Hazard ratio; HU: Hungary; IHC: Immunohistochemistry; int€: International euros; NA: Not applicable; NHS: National Health Service; NL: The Netherlands; *NTRK*+: *NTRK* fusion-positive; OS: Overall survival; PAID: Practical Application to Include Disease Costs; RNA-NGS: Next-generation sequencing panel of tumor RNA; SoC: Standard of care; TTD: Time to treatment discontinuation.

Microsimulation model

Time to treatment discontinuation (TTD) and overall survival (OS) in *NTRK*+ patients receiving entrectinib were based on the entrectinib trials [9,14]. For *NTRK*- patients receiving SoC, TTD and OS were estimated using registry data from 1596 Dutch *NTRK*- cancer patients (Supplementary Table 3). Patients from the registry data were included in the TTD and OS estimations only if they had one of the tumor types that were included in the entrectinib trials [9,14]. Previous studies suggest that patients with *NTRK* fusions face a worse disease prognosis than patients without *NTRK* fusions [9,28]. To account for this, a hazard ratio (HR) was applied for TTD and OS in *NTRK*+ patients. That is, TTD and OS in *NTRK*+ patients receiving SoC were calculated by applying the HRs for *NTRK*+ patients to the TTD and OS that were estimated for *NTRK*- patients receiving SoC. See Huygens *et al.* [9] for more detail. The HRs were assumed to be equal across the three countries.

Costs

Costs are reported in the national currency and in international euros (int€), calculated using purchasing power parities (PPP) from OECD.Stat [21,29]. PPPs were used to account for price level differences between countries. The cost year was 2021. Country-specific costs for biopsies, tests, entrectinib and SoC pharmaceuticals (Supplementary Tables 4–6) were included. It was assumed that the treatments provided in England were similar to the treatments described in Dutch guidelines. In Hungary, several treatments provided in England and The Netherlands were not available, hence, only the treatments that were available in Hungary were included in the SoC cost calculations. Costs for adverse events in England and Hungary were based on the Dutch estimates reported by Huygens *et al.* [9] and converted to 2021 Hungarian forints and British pounds using PPPs [30].

Based on research where healthcare costs were found to increase steeply in people's last year of life [24], separate cost figures for the last year of life were used in this model. The estimated costs in the last year of life were specific to cancer patients and came from Luta *et al.* for England and the Practical Application to Include Disease Costs (PAID) for The Netherlands [23,24]. Because no country-specific data were available for Hungary, the last-year-of-life costs were calculated based on the assumption that the ratio between the last-year-of-life costs and costs in other years was the same in Hungary as in England (because both countries use a healthcare perspective, while a societal perspective is used in The Netherlands).

Unlike in England and Hungary, the health economic guidelines in The Netherlands prescribe the inclusion of healthcare costs unrelated to the disease of interest [17]. The Dutch healthcare costs unrelated to cancer were estimated using PAID [23]. Additionally, informal care costs were included for The Netherlands. Productivity costs were excluded, as patients in this model have an advanced stage of cancer and were assumed to have already been out of the workforce so that no additional productivity losses are faced during the period that the model covers [31].

Utilities

As previous research has found that quality of life decreases as patients approach death, patient utility was incorporated into the model as a function of proximity to death [25]. Age- and gender-specific utility at different proximities to death were obtained from a study that estimated the relationship between proximity to death and SF-6D utility using a linear regression model [25]. The study used quality of life and survival data from a Dutch cancer registry [25]. The estimated OS distributions from the microsimulation were used to estimate proximity to death for the patients in the current model, after which the corresponding utility values were applied. Because of a lack of appropriate data for England and Hungary, the utilities were assumed to be similar in all three countries.

Analyses

Cost–effectiveness analysis

For all three countries, cost–effectiveness analyses were performed for the different testing strategies. An additional analysis was conducted in which only the subgroup of *NTRK*+ patients were considered and the health and cost consequences of *NTRK* testing were excluded. The latter analysis reflects a scenario in which *NTRK* testing is already part of the SoC (e.g., as part of broader gene fusion panel testing), so the introduction of *NTRK* testing does not need to be considered when evaluating the implementation of entrectinib. To investigate the possible benefits of future price drops for RNA-NGS (which might be expected as further technological improvements are made and the use of gene sequencing becomes more widespread), an analysis to identify the cost of RNA-NGS at which it becomes cost-effective (i.e., INMB is zero) to provide RNA-NGS to all patients eligible for *NTRK* testing was also performed. Cost–effectiveness is presented as incremental cost–effectiveness ratios (ICER) as well as incremental

Table 2. Intermediate outcomes per strategy.

Strategy	Average wait time (days)			Number of false positives (per 100,000 patients tested)	Number of false negatives (per 100,000 patients tested)	Number of patients treated with entrectinib (per 100,000 patients tested)		
	EN	HU	NL	all	all	EN	HU	NL
IHC for all	14.7	22.4	8.4	4938	50	5123	5064	5170
RNA-NGS for all	28.7	36.5	15.6	0	0	323	317	332
IHC then RNA-NGS	15.8	23.2	9.1	0	50	270	269	279
Stratified†	16.7	24.1	9.5	0	46	276	274	285

†In the Stratified strategy, direct RNA-NGS testing is used for tumor types with high *NTRK* prevalence or wild-type TRK protein expression, while IHC followed by RNA-NGS after a positive result is used for other tumor types.
EN: England; HU: Hungary; IHC: Immunohistochemistry; NL: The Netherlands; RNA-NGS: Next-generation sequencing panel of tumor RNA.

net monetary benefit (INMB). Fully incremental analysis was used for ICERs, meaning the strategies were ranked by ascending cost and ICERs for each strategy were calculated by comparing it to the next best alternative [32]. The INMB for each of the testing strategies was calculated by comparing it to the "no testing" strategy.

Sensitivity analysis

The effect of uncertainty around the model parameters on the results was assessed using univariate sensitivity analysis and probabilistic sensitivity analysis (PSA). In the univariate analysis, parameter values were varied by a maximum of 20% deviation from the original input value (except for HRs, for which the values from the estimated 95% CIs were used). In the PSA, parameter values were varied simultaneously according to predefined distributions for all three countries (see Supplementary Table 7). After investigating the stability of the results for varying sample sizes/number of iterations, the univariate analysis was performed with 5000 patient samples, and the PSA was performed with 1000 iterations of 1000-patient samples.

Budget impact analysis

For all three countries, the budget impacts of the four *NTRK* testing strategies were estimated by multiplying the estimated annual incremental healthcare costs by the expected annual number of patients tested. The number of patients tested each year per country was determined by multiplying the number of expected *NTRK*+ patients by the number of patients to be tested to identify one *NTRK*+ patient [33]. In line with national HTA guidelines, a healthcare payer perspective was taken for England and a healthcare perspective was taken for Hungary and The Netherlands. The time horizon of the budget impact analyses was 5 years, though additional analyses were performed to align with national HTA guidelines, assuming a 3- and 4-year time horizon for England and Hungary, respectively [16,17,34]. The incremental budget impact of each of the *NTRK* testing strategies compared with SoC is presented in absolute values and expressed as percentages of cancer care expenditure and cancer care expenditure [35,36].

Results

Cost–effectiveness analysis

The outcomes for the four *NTRK* testing strategies and for the comparator (no *NTRK* testing, SoC provided to all patients) are provided next for England, Hungary and The Netherlands.

Intermediate outcomes

Table 2 presents, for each testing strategy, the average wait time between the decision to receive *NTRK* testing and the start of entrectinib treatment for those who test positive. Also presented are the number of patients receiving entrectinib treatment and the number of false-positive and false-negative test results (per 100,000 patients tested).

In all three countries, average wait times are lowest in the IHC-for-all strategy (14.7, 22.4 and 8.4 days for England, Hungary and The Netherlands, respectively) and highest for the RNA-NGS-for-all strategy (28.7, 36.5 and 15.6 days, respectively). For all strategies, Hungary had the highest average wait time, while The Netherlands had the shortest wait time. The metastatic cancer patients in the current model tend to have a short life expectancy, and some patients are expected to die during the testing phase before receiving treatment. Because of this, longer average wait times result in a smaller number of patients treated with entrectinib, as shown in Table 2.

Because test sensitivity and specificity were assumed to be equal across the three countries, the proportions of false-positive and false-negative results were also equal across the countries, as reflected in the single columns for these measures in Table 2. Table 2 shows that the IHC-for-all strategy renders a high number of false positives (4938 per 100,000 patients tested compared with 0 for the other strategies). For all three countries, the number of patients treated with entrectinib was also much higher for the IHC-for-all strategy than for the other strategies. Given the high number of false positives in the IHC-for-all strategy, many of the patients identified as *NTRK*+ and receiving entrectinib do not actually carry oncogenic *NTRK* fusions and likely do not receive any benefit from entrectinib treatment. Although there were no false-positive results in the IHC-then-RNA-NGS and stratified scenarios, there were some false-negative results (50 and 46 per 100,000 patients tested, respectively). False-negative results mean that some *NTRK*+ patients are incorrectly identified as *NTRK*- and wrongfully receive SoC instead of entrectinib.

Cost–effectiveness results

Cost–effectiveness outcomes for the testing strategies are presented in Table 3. Costs and effects are shown, and incremental costs and effects and cost–effectiveness ratios are compared with the next best alternative. For dominated strategies (strategies with a higher cost yet equal or fewer quality-adjusted life years [QALY] than another strategy), no incremental costs, effects and cost–effectiveness ratio are presented. Nonetheless, INMB is calculated for each testing strategy, comparing the strategy to the no-testing base case.

The ranking of the strategies is the same for all countries, both in terms of ICERs and INMB. The no-testing strategy rendered the lowest costs and lowest number of QALYs, while RNA-NGS for all had the highest costs and QALYs. For all countries, the IHC-then-RNA-NGS option had the highest INMB. The strategy results in fewer QALYs than the stratified and RNA-NGS-for-all strategies, caused by a higher number of unidentified *NTRK*+ patients (false negatives) not receiving entrectinib treatment (see Table 2). Nonetheless, the issue of false negatives appeared to be offset by the cost-savings from performing RNA-NGS for a smaller group of patients (i.e., only those who receive a positive IHC result first). However, all estimated ICERs (int€ 89,196 for England, int€ 138,135 for Hungary and int€ 142,663 for The Netherlands) were above national cost–effectiveness thresholds and all estimated INMB values were negative. This implies that the implementation of *NTRK* fusion testing and subsequent treatment would cause a net loss to the healthcare system and is not cost-effective (Tables 4 & 5).

When considering only the subgroup of *NTRK*+ patients and focusing only on treatment (i.e., excluding the cost and health effects associated with testing for *NTRK* fusions), the implementation of entrectinib was estimated to be cost-effective in England and in The Netherlands. The INMB was int€ 8405 in England, int€ -53,088 in Hungary and int€ 54,372 in The Netherlands. The incremental cost of treating *NTRK*+ cancer patients with entrectinib instead of SoC was much higher in Hungary than in England and The Netherlands (int€ 97,525 in Hungary compared with int€ 41,439 in England and int€ 50,603 in The Netherlands). Finally, in England and Hungary, the provision of RNA-NGS to all patients eligible for *NTRK* testing (and subsequently providing entrectinib to *NTRK*+ patients) would not be cost-effective even at zero cost for RNA-NGS. In The Netherlands, RNA-NGS would have to reduce by 90%, to int€ 162, before testing all patients with RNA-NGS would be cost-effective.

Sensitivity analysis

The outcomes of the univariate sensitivity analysis are shown in Supplementary Figure 2. Outcomes were similar across the three countries. In all countries, the parameters that most impacted cost–effectiveness outcomes included the cost of entrectinib treatment, the HR for OS in *NTRK*+ patients and utility values. IHC test specificity is a key parameter in the IHC-for-all, IHC-then-RNA-NGS and stratified strategies, while the cost of RNA-NGS was highly influential in the RNA-NGS-for-all strategy. In England, *NTRK* prevalence was less influential than in Hungary and The Netherlands, while the cost of taking a biopsy was more influential.

The outcomes of the PSA are shown in cost–effectiveness planes in Figure 1, and cost–effectiveness acceptability curves (CEAC) are presented in Figure 2. For the latter, the limits on the x-axes were set at roughly fivefold the nationally recommended cost–effectiveness thresholds. The cost–effectiveness planes looked similar across the three countries. For the RNA-NGS, IHC-then-RNA-NGS and stratified strategies, uncertainty in the model parameters mostly affected estimated QALY outcomes. For the IHC strategy, parameter uncertainty also affected estimated cost outcomes. As shown in the univariate analysis, IHC test specificity is an important parameter, as higher (lower) specificity causes fewer (more) false-positive test results, hence, fewer (more) patients unnecessarily treated with entrectinib and lower (higher) cost outcomes. The CEACs also appeared similar across the countries. The

Table 3. Cost–effectiveness outcomes for all strategies.

Strategy	Cost (int€)			Effect (QALY)			Incremental cost (int€)			Incremental effect (QALY)			ICER (int€)			INMB (vs SoC)		
	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL
No testing	26,695	17,505	64,503	0.95927	0.95685	0.98459												
IHC then RNA-NGS	27,038	18,031	65,108	0.96311	0.96065	0.98883	343	526	606	0.00385	0.00381	0.00425	89,196	138,135	142,663	-206	-404	-310
Stratified[†]	27,052	18,108	65,140	0.96317	0.96070	0.98890	14	–	32	0.00006	–	0.00006	242,668	Extendedly dominated	502,431	-218	-480	-338
RNA-NGS for all	27,248	19,113	66,298	0.96384	0.96132	0.98962	196	1082	1158	0.00067	0.00066	0.00072	293,640	1,629,295	1,834,617	-391	-1465	-1445
IHC for all	29,077	22,329	67,472	0.96353	0.96114	0.98907	–	–	–	–	–	–	Dominated	Dominated	Dominated	-2231	-4687	-2657

[†]In stratified strategy, direct RNA-NGS testing is used for tumor types with high *NTRK* prevalence or wild-type TRK protein expression, while IHC followed by RNA-NGS after a positive result is used for other tumor types.
EN: England; HU: Hungary; ICER: Incremental cost–effectiveness ratio; IHC: Immunohistochemistry; INMB: Incremental net monetary benefit; int€: International euros; NL: The Netherlands; QALY: Quality-adjusted life year; RNA-NGS: Next-generation sequencing panel of tumor RNA; SoC: Standard of care.

Table 4. Cost–effectiveness outcomes for *NTRK*-positive patient subgroup, testing excluded.

Strategy	Cost (int€)			Effect (QALY)			Incremental cost (int€)			Incremental effect (QALY)			ICER (int€)			INMB (vs SoC)		
	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL
SoC	23,621	8661	60,978	0.7159	0.7146	0.7296												
Entrectinib	67,729	111,480	112,545	2.0685	2.0576	2.1862	41,439	97,525	50,603	1.4010	1.3912	1.5068	29,577	70,100	33,582	8405	-53,088	54,372

EN: England; HU: Hungary; ICER: Incremental cost–effectiveness ratio; INMB: Incremental net monetary benefit; int€: International euros; NL: The Netherlands; QALY: Quality-adjusted life year; SoC: Standard of care.

Table 5. Budget impact analysis.

	5-year incremental budget impact (int€)			Percentage of incremental budget impact due to test costs			Budget impact as percentage of total health expenditure			Budget impact as percentage of total cancer care expenditures		
	EN	HU	NL	EN	HU	NL	EN	HU	NL	EN	HU	NL
IHC then RNA-NGS	156,347,606	37,874,049	76,879,546	65.85	52.19	81.39	0.02	0.11	0.03	0.27	1.23	0.29
Stratified	162,707,341	43,612,999	81,027,374	66.50	57.76	81.95	0.02	0.12	0.03	0.28	1.41	0.31
RNA-NGS for all	247,205,447	117,721,977	233,475,628	74.22	81.90	92.65	0.03	0.34	0.08	0.42	3.81	0.88
IHC for all	1,066,761,912	340,863,660	326,279,464	8.80	4.32	15.62	0.11	0.97	0.11	1.82	11.03	1.23

EN: England; HU: Hungary; IHC: Immunohistochemistry; int€: International euros; NL: The Netherlands; RNA-NGS: Next-generation sequencing of tumor RNA.

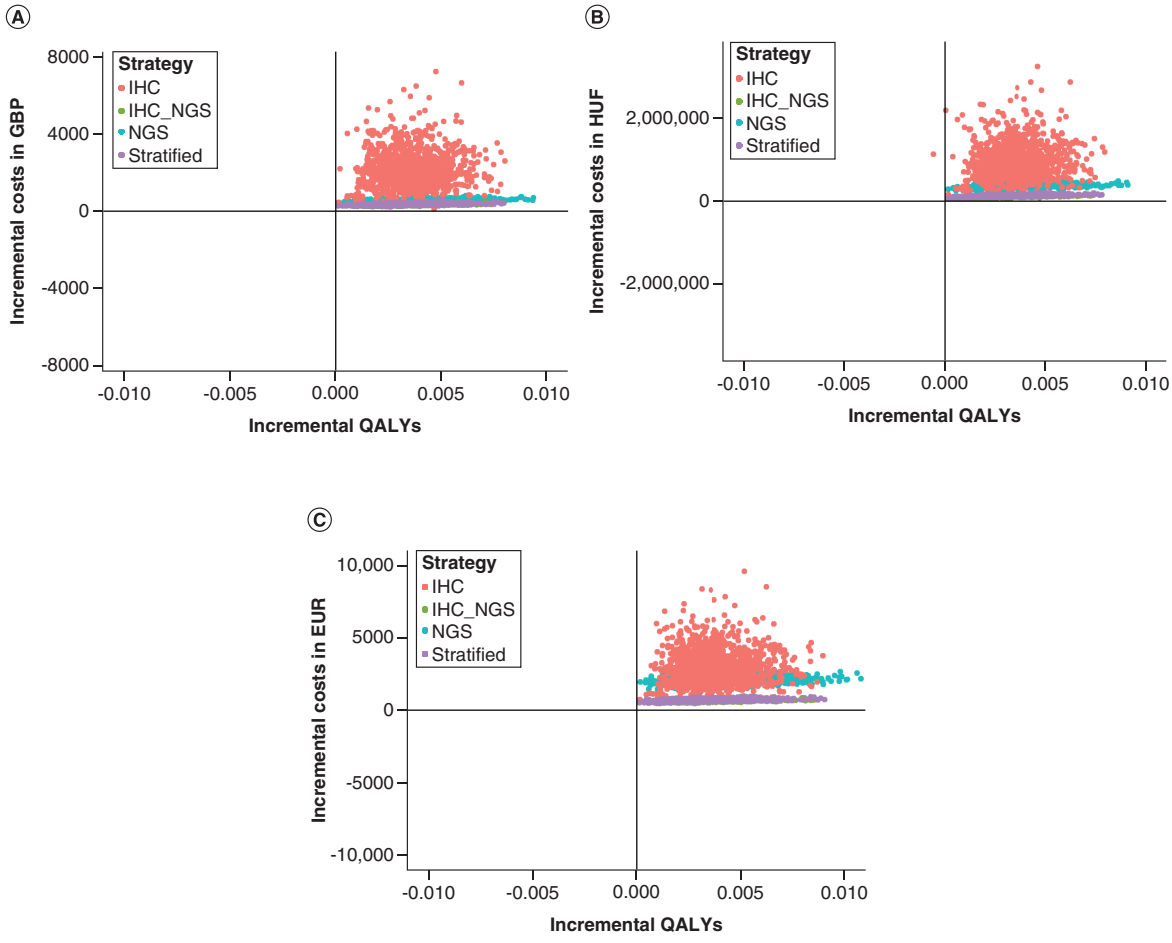

Figure 1. Cost–effectiveness planes. (A) England, **(B)** Hungary, **(C)** The Netherlands.
IHC: Immunohistochemistry; NGS: Next-generation sequencing; QALY: Quality-adjusted life year.

IHC-then-RNA-NGS and stratified strategies had similar curves, but IHC-then-RNA-NGS had a slightly higher probability of being cost-effective at all threshold values. For all countries, the IHC strategy had a low probability of being cost-effective even at very high threshold values.

Budget impact analysis

The total 5-year budget impact of the no-testing scenario, in which the entire target population (i.e., adult patients with locally advanced or metastatic solid tumors who had received one or more lines of treatment) is treated with SoC, was estimated to be int€ 6,472,649,274 in England, int€ 1,136,924,382 in Hungary and int€ 6,444,222,855 in The Netherlands. For the testing scenarios, the annual number of patients receiving *NTRK* testing was estimated to be 102,040 in England, 14,801 in Hungary and 26,476 in The Netherlands.

The incremental budget impact figures for the four testing strategies compared with no testing are reported in Table 6. See Supplementary Table 8 for the budget impact results with country-specific time horizons. In England, the incremental five-year budget impact of implementing the IHC-then-NGS strategy, which was identified as the most optimal out of the four testing strategies, would be int€ 156,347,606, which is 0.02% of current healthcare expenditure and 0.27% of current cancer care expenditure [35,36]. Testing costs made up 65.85% of the incremental budget impact of the IHC-then-RNA-NGS strategy.

Although the 5-year incremental budget impact of IHC then RNA-NGS was lowest in absolute figures in Hungary (int€ 37,874,049), the relative impact was higher than in the other two countries, with the budget impact taking up 0.11% of total healthcare expenditure and 1.23% of cancer care expenditure [35,36]. Just over half (52.19%) of the incremental budget consists of testing costs. In The Netherlands, testing costs made up a larger portion of the 5-year incremental budget impact (int€ 76,879,546), as 81.39% comprised testing costs. The

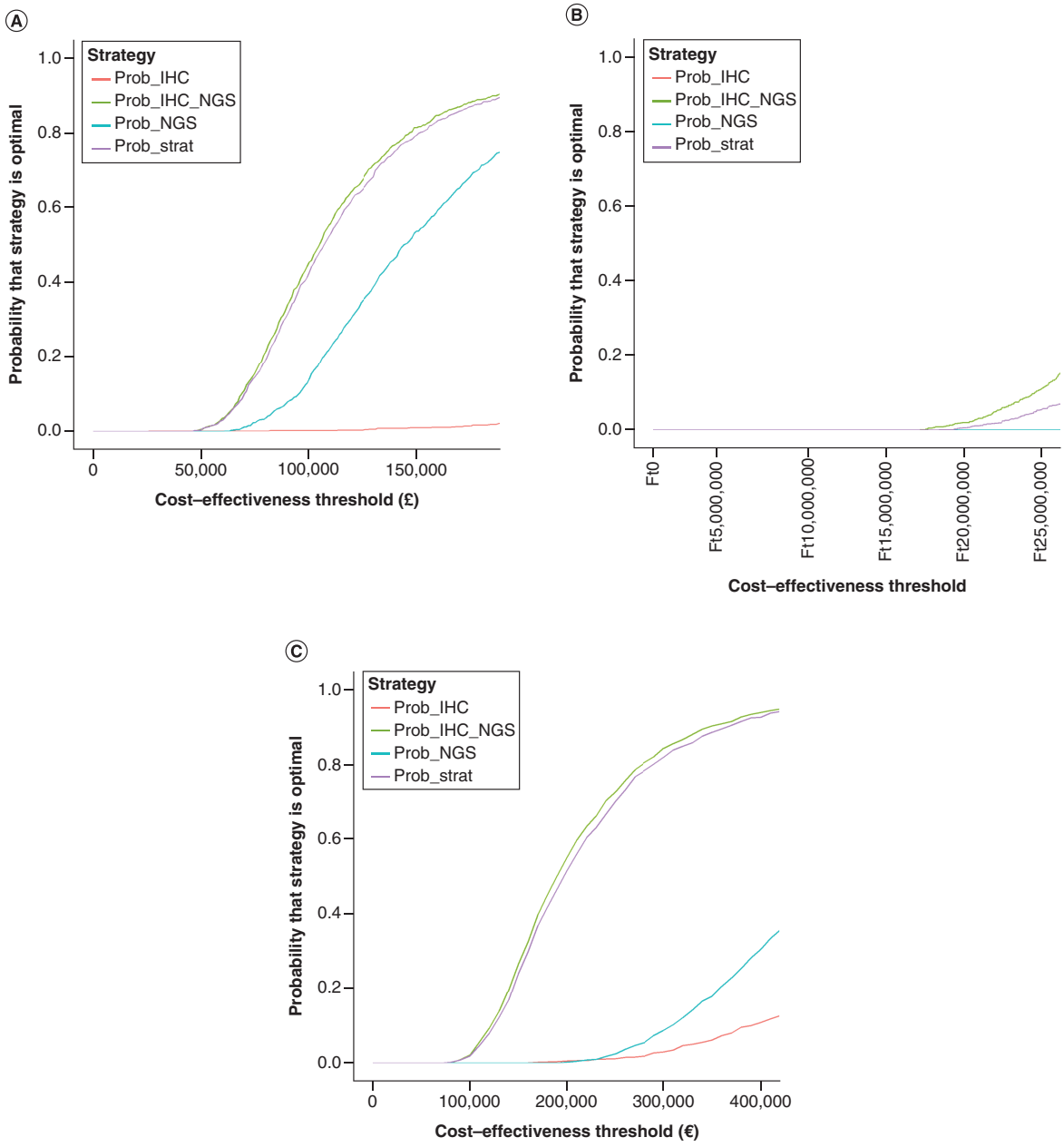

Figure 2. Cost–effectiveness acceptability curves. (A) England, **(B)** Hungary, **(C)** The Netherlands.
IHC: Immunohistochemistry; NGS: Next-generation sequencing.

relative impact on care expenditure in The Netherlands is similar to that in England, with the incremental budget being 0.03% of healthcare expenditure and 0.29% of cancer care expenditure [35,36].

In all three countries, the budget impact of IHC then RNA-NGS was lowest and the budget impact of IHC for all was highest. The percentage of the total budget going to testing was lowest in the IHC-for-all strategy (8.80, 4.32 and 15.62% for England, Hungary and The Netherlands, respectively) because many more (false-positive) patients are treated with entrectinib (see Table 2) in this strategy than in the other testing strategies.

Discussion

While the TRK inhibitors entrectinib and larotrectinib were the first histology-independent therapies on the market, several other pharmaceuticals targeting specific genetic markers are already in use and many more are expected to become available, allowing for more personalized (cancer) care [37]. As we have argued previously when evaluating

the cost–effectiveness of targeted (or personalized) treatments, it is important to include an accurate representation of the testing pathway that is needed to identify eligible patients [38]. In this study, we incorporated the period in which *NTRK* testing is performed in a cost–effectiveness analysis of entrectinib treatment and assessed several different testing strategies. Herewith, we provided an example of how the modeling of testing pathways can be approached and how HTA methods can be used to aid decision-making on which testing strategy to implement. We performed analyses for three countries to investigate whether there might be differences in the cost–effectiveness of *NTRK* testing and entrectinib treatment across different settings, and we found differences, indeed.

The results showed that the implementation of entrectinib is unlikely to be cost-effective in Hungary. Even in the subgroup analysis of *NTRK*+ patients, where the costs and effects of introducing *NTRK* testing were excluded, the INMB of entrectinib was far below zero, at int€ -53,088. Indeed, the incremental costs of entrectinib compared with SoC were large in Hungary, at int€ 97,525, compared with int€ 41,439 in England and int€ 50,603 in The Netherlands. Hungary has a lower income per capita and lower healthcare expenditure than England and The Netherlands. These results could imply that expensive targeted treatments like entrectinib may bring limited value in lower-income countries, and more cost-effective healthcare may have to be prioritized first. Nonetheless, (large) discounts on the price of entrectinib in Hungary could improve its cost–effectiveness results.

The results look more promising for England and The Netherlands, where the *NTRK*+ subgroup analysis showed a positive INMB for entrectinib compared with SoC. This suggests that entrectinib has the potential to be cost-effective. Nonetheless, all the evaluated testing strategies rendered a negative INMB compared with the base case scenario, in which *NTRK* testing was not performed and entrectinib was not provided. In line with these results, the National Institute for Health and Care Excellence (NICE) has not recommended entrectinib for routine use in the English NHS because of its unconvincing cost–effectiveness results but, due to its potential to be cost-effective, NICE did recommend entrectinib to be included in the Cancer Drugs Fund [39]. In The Netherlands, too, entrectinib was recommended for temporary conditional reimbursement. In both England and The Netherlands, the national HTA agencies have entered into an agreement with the manufacturer of entrectinib regarding further data collection, both through additional clinical trials (STARTRK-2 and STARTRK-NG) and through real-world evidence collection among patients receiving entrectinib [40,41]. After a period of data collection, a final health economic analysis and reimbursement decision will follow. While such conditional reimbursement schemes can ensure timely market access for patients who might benefit from treatment, withdrawing pharmaceuticals from the market once additional evidence negates their cost–effectiveness can be difficult in practice [42,43]. In an attempt to counter any such issues, the agreement between the Dutch HTA organization and the manufacturer explicitly states that all parties involved during the conditional reimbursement period will cooperate in case the reimbursement of entrectinib is discontinued [41]. The agreement also includes a communication plan to ensure patients understand the temporary nature of the current reimbursement decision in place.

Note that the incremental costs, effects and ICERs for the *NTRK*+ subgroup analysis were similar between England and The Netherlands. Yet, because the cost–effectiveness threshold recommended by Dutch HTA guidelines is much higher than the NICE threshold (€80,000 vs €36,000 in this case), INMB outcomes are different for the countries (int€ 8,405 in England vs int€ 54,372 in The Netherlands), resulting in different conclusions regarding the interventions' cost–effectiveness. These differences could be justifiable if the values of national thresholds were set based on assessments of opportunity cost and/or societal preferences and so reflected real differences between national settings. However, cost–effectiveness thresholds have historically been based on little to no evidence [44,45]. The current results illustrate that differences in the thresholds are not inconsequential and might cause (poorly justified) differences in reimbursement decisions across countries.

Clear differences can be seen between the cost–effectiveness outcomes for the main analysis, in which the full *NTRK* test-treatment pathway was assessed, and the outcomes for the subgroup analysis, in which the testing phase was left out of consideration. This illustrates that including required tests in the economic evaluation of a new treatment may alter reimbursement decisions, supporting the argument we have previously made that testing should be incorporated in the economic model if it is part of the decision problem (e.g., if the testing is to be newly introduced in clinical practice, or to be introduced for additional patient groups) [38]. Given that national cost–effectiveness analyses are often based on global models from manufacturers that are adapted to the local setting, and given that testing pathways may vary across countries, we encourage modelers working on country adaptations to ensure that national testing strategies are accurately reflected in (country adaptations of) cost–effectiveness models.

Many have argued in favor of the expansion of genetic testing in healthcare [46]. This could mean that, in the future, all cancer patients find out whether they carry *NTRK* gene fusions (or other genetic alterations) as part of

standard care, thereby changing the cost–effectiveness outcomes for entrectinib. However, more widespread use of genetic testing does not automatically mean *NTRK* gene fusions are identified. First, note that whole-genome sequencing (WGS) is DNA-based and, in contrast to RNA-NGS, is not able to determine if a detected *NTRK* fusion is functional and indeed causes overexpression of TRK proteins [4]. That is, if WGS were to be implemented for all cancer patients, an additional RNA-NGS panel would be needed to identify *NTRK*+ patients. Also, if broad genetic testing to establish a genetic profile or 'passport' for all citizens were implemented, as has been suggested by some, separate genetic tests (including RNA-NGS panels) would be necessary to enable targeted cancer care. This is because many cancer drugs target genetic markers in the tumor DNA, which is different from the patients' germline DNA that would be sequenced when creating a genetic profile.

Finally, the finding that the provision of RNA-NGS to all patients is not cost-effective in England and Hungary even at zero cost for the RNA-NGS test suggests that the expected price drops in NGS technology alone are insufficient to make the implementation of *NTRK* testing and subsequent treatment cost-effective. Further changes may be needed in the test-treatment pathway, such as a price reduction for entrectinib.

Limitations

For The Netherlands, we previously illustrated how registry data containing genomic and clinical parameters can be used to construct a control arm for single-arm trial data. As explained in the Methods section, we used the Dutch registry data to estimate survival and TTD among *NTRK*- patients and to estimate a HR for *NTRK*+ patients [9]. In this study, where we also assess cost–effectiveness for England and Hungary, we were unable to perform a similar analysis for England and Hungary, due to data and resource limitations. This shows one of the limitations of single-arm trial data; local data and resources may be insufficient to estimate a control arm for the national setting, causing uncertainty about the treatment's effectiveness. Moreover, the publicly available data on the patient populations in clinical trials tends to be limited and insufficient to determine the extent to which patients in the trial population and the control population are comparable so issues of confounding and selection bias cannot be sufficiently addressed [47,48]. Indeed, even after estimating a control arm using a Dutch population of cancer patients, large uncertainty remains about entrectinib's effectiveness in The Netherlands as we cannot establish to what extent the patients and the healthcare practices in the US-based entrectinib trials can be compared with the patients and healthcare practices in the Dutch database. Other approaches for estimating a control arm to single-arm trial data have been suggested, including the use of trial patients who did not respond to the treatment as a proxy for control arm patients [49] and basing control arm estimations on trial patients' progression-free survival during the most recent prior therapy [49,50]. However, these methods require patient-level trial data, which may not always be available to modelers. As argued by many others, randomized controlled trials have many advantages over their alternatives and are generally preferred [51].

Furthermore, because of the small sample size of the entrectinib trials, no tumor type-specific estimates of treatment effectiveness were available. We, therefore, had to assume that the effectiveness of entrectinib is homogeneous across tumor types, despite prior research suggesting this may be inaccurate [52]. Although we did estimate tumor type-specific effectiveness for the SoC arm, we deemed it inappropriate to present tumor type-specific ICER and INMB estimates, given the possibility that entrectinib effectiveness is heterogeneous. If indeed there is such heterogeneity, the single ICER values we estimated might be biased, as the proportional distribution of tumor types in the entrectinib trials may differ from the proportional distribution in clinical practice.

Another data limitation in this study was that we assumed the Dutch costs for adverse events (adjusted using PPP conversion factors) and Dutch estimates of the relationship between SF-6D utility and proximity to death to apply to England and Hungary as well. We also used list prices to obtain the costs of entrectinib, while actual costs may be lower due to discounts, potentially improving the cost–effectiveness of the implementation of entrectinib.

Conclusion

HTAs of histology-independent cancer treatments have proven challenging, for various reasons. This study has helped to provide possible approaches to address some of the challenges. Furthermore, we provided cost–effectiveness estimates for the implementation of the histology-independent therapy entrectinib in three different countries. Out of four *NTRK* testing strategies assessed, the optimal strategy was the same in England, Hungary and The Netherlands. The strategy starts with an IHC test (which assesses TRK protein expression) for all patients, followed by an RNA-NGS test (which looks at the tumor RNA to identify *NTRK* gene fusions) for patients who receive a positive result on the IHC test. Nonetheless, the implementation of *NTRK* testing followed by treatment with

entrectinib is likely not cost-effective in Hungary. In England and The Netherlands, the implementation of entrectinib was also not found to be cost effective, though the results from a subgroup analysis of *NTRK*+ patients suggested that entrectinib has the potential to be cost-effective.

Future perspective

In high-income countries, many of the low-hanging fruits in terms of blockbuster medications have already been plucked. We expect the move toward pharmaceuticals that are targeted at smaller (sub)groups of patients to continue. Due to the resulting small sample sizes, randomized controlled trials become more difficult to conduct, which in turn complicates the evaluation of the cost–effectiveness of new healthcare interventions. Over the next years, we expect to see methodological advancements to deal with this challenge, both in terms of trial design and the statistical methods used to interpret trial data.

A focus on stratifying patients into smaller, more specific groups also requires the increased use of (genetic) testing. To date, most economic evaluations of test-treatment combinations have assumed the test to only be used to stratify toward the one (new) treatment under consideration. However, we expect increased use of broad gene panels in clinical practice, particularly in cancer care, meaning that a single test may be able to identify a range of genetic markers and can result in various treatment choices. We may see larger, more complex models over the coming years to enable the assessment of the health and cost outcomes of broad gene panels, as well as possible new methodological approaches to prevent such models from becoming too unwieldy.

Finally, the proliferation of small patient groups may lead to limited availability of alternative pharmaceuticals within each patient group and, consequently, reduced negotiation power for purchasers of pharmaceuticals. We may therefore see alternative negotiation strategies become more commonplace, such as 'portfolio agreements' whereby purchasers and manufacturers negotiate prices for a basket of products as opposed to for single pharmaceuticals. We also expect the explicit use of cost–effectiveness research and value-based pricing to increase negotiations between buyers and sellers of pharmaceuticals.

Executive summary

- Histology-independent (or tumor-agnostic) therapies are prescribed based on genetic markers of tumors, without regard for the tumors' tissue of origin.
- Entrectinib is one of the first histology-independent treatments to receive market approval. It is prescribed for tumors with *NTRK* gene fusions.
- To investigate the impact of alternative *NTRK* testing strategies on the cost–effectiveness of entrectinib, four different strategies were compared.
- Analysis was performed for three countries: England, Hungary and The Netherlands.

Methods

- The target population comprised adult patients with locally advanced or metastatic solid tumors who had received one or more lines of treatment and were willing to undergo further (testing and) treatment.
- Local health technology assessment guidelines were followed for the three countries and local data were used if available.
- The model consists of a decision tree (reflecting the testing phase) followed by a microsimulation model (reflecting the time from the start of treatment until death).
- Patients in the intervention arm first enter the decision tree and subsequently enter the microsimulation model, where patients who tested *NTRK*-positive are treated with entrectinib and those who tested negative with standard of care (SoC). Patients in the comparator arm receive no testing and go straight into the microsimulation model, where they receive SoC.
- Four testing strategies were evaluated: Immunohistochemistry (IHC) test for all tumor types (IHC for all), RNA-based next-generation sequencing (RNA-NGS) for all tumor types (RNA-NGS for all), IHC test followed by RNA-NGS in patients with a positive IHC test result for all tumor types (IHC then RNA-NGS) and stratified test strategies depending on the *NTRK* fusion prevalence and TRK wild-type protein expression of the tumor types (stratified).
- RNA-NGS tests have high sensitivity and specificity but tend to be expensive, while IHC tests are cheaper and less accurate.

Results

- The comparator, no testing (and SoC for all patients), rendered the lowest amount of quality-adjusted life-years. The RNA-NGS-for-all strategy provided the highest number of quality-adjusted life years.
- The no-testing strategy was the cheapest option, while IHC for all was the most expensive. The latter is explained by the fact that many more patients incur the costs of entrectinib in this strategy than in others due to a high false-positive rate.

- Using nationally recommended cost–effectiveness thresholds, the optimal strategy was found to be IHC then RNA-NGS. However, all testing strategies had a negative incremental net monetary benefit (INMB) compared with no testing (ranging from int€ -206 to -4687), implying they are not cost-effective.
- A subgroup analysis focusing only on *NTRK*+ patients and excluding the cost and health outcomes associated with *NTRK* testing found negative INMB for Hungary (int€ -53,088), but positive INMB for England and The Netherlands (int€ 8405 and int€ 54,372, respectively).

Conclusion

- The implementation of *NTRK* testing followed by treatment with entrectinib is likely not cost-effective in Hungary. In England and The Netherlands, the implementation of entrectinib was also not found to be cost-effective, though the results from a subgroup analysis of *NTRK*+ patients suggested that entrectinib has the potential to be cost-effective.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pme-2022-0070

Author contributions

H Vellekoop, S Huygens, M Versteegh and MR Mölken outlined the concept and broad methods for this study. H Vellekoop, S Huygens and M Versteegh programmed the health economic model. H Vellekoop, L Szilberhorn and R Koleva-Kolarova collected country-specific data for the input parameters. H Vellekoop wrote the manuscript. All authors provided multiple rounds of critical feedback on both the study methods and the manuscript.

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