ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Economic Evaluation

Cost-Effectiveness and Budget Impact of Future Developments With Whole-Genome Sequencing for Patients With Lung Cancer

Martijn J.H.G. Simons, MSc, Carin A. Uyl-de Groot, PhD, Valesca P. Retèl, PhD, Joanne M. Mankor, MSc, Bram L.T. Ramaekers, PhD, Manuela A. Joore, PhD, Wim H. van Harten, PhD

ABSTRACT

Objectives: This study aimed to investigate the cost-effectiveness, budget impact (BI), and impact of uncertainty of future developments concerning whole-genome sequencing (WGS) as a clinical diagnostic test compared with standard of care (SoC) in patients with locally advanced and metastatic non–small cell lung cancer.

Methods: A total of 3 likely scenarios to take place within 5 years (according to experts) were simulated using a previously developed, peer reviewed, and published decision model. The scenarios concerned "WGS results used for treatment selection" (scenario 1), "WGS-based biomarker for immunotherapy" (scenario 2), and "off-label drug approval for WGS results" (scenario 3). Two diagnostic strategies of the original model, "SoC" and "WGS as a diagnostic test" (base model), were used to compare our scenarios with. Outcomes were reported for the base model, all scenarios separately, combined (combined unweighted), and weighted by likelihood (combined weighted). Cost-effectiveness, BI, and value of information analyses were performed for WGS compared with SoC.

Results: Total costs and quality-adjusted life-years for SoC in metastatic non–small cell lung cancer were €149 698 and 1.235. Incremental outcomes of WGS were €1529/0.002(base model), −€222/0.020(scenario 1), −€2576/0.023(scenario 2), €388/0.024(scenario 3), −€5041/0.060(combined unweighted), and −€1715/0.029(combined weighted). The annual BI for adopting WGS for this population in The Netherlands ranged between €682 million (combined unweighted) and €714 million (base model). The consequences of uncertainty amounted to €3.4 million for all scenarios (combined weighted) and to €699 000 for the diagnostic yield of WGS alone (combined weighted).

Conclusions: Our findings suggest that it is likely for WGS to become cost-effective within the near future if it identifies more patients with actionable targets and show the impact of uncertainty regarding its diagnostic yield. Modeling future scenarios can be useful to consider early adoption of WGS while timely anticipating on unforeseen developments before final conclusions are reached.

Keywords: budget impact, cost-effectiveness, decision analytic model, future scenarios, implementation, molecular diagnostics, value of information, whole-genome sequencing.

VALUE HEALTH. 2023; 26(1):71–80

Introduction

Health technology assessment (HTA) is used to evaluate new technologies for implementation to the broader audience. It requires data that are often obtained from many sources, for example, randomized controlled trials (RCTs) or real-world data, which take time to produce or are simply not available.[1,2] In the meantime, potentially effective technologies can remain restricted to the research setting and, hence, withheld from the public.[3]

In early stages of medical technology development, an HTA can be performed to guide optimal implementation, based on current knowledge and informed assumptions.[4] This so-called early HTA can consist of many types of analyses, to determine boundaries for potential cost-effectiveness and the budget consequences for adopting a new technology.[5] It enables us to timely anticipate on developments, which can be important in complex and fast-moving fields where current knowledge can be easily outdated by new evidence. The related uncertainty can be reduced by drafting and analyzing scenarios.[6] Scenario drafting is useful to explore where experts' concerns lie, parameterize unknown variables, and inform model-based analyses.[7,8] Subsequently, modeling scenarios can inform strategic choices of policy makers or research groups, by exploring different future developments regarding a new technology, and quantify the impact on expected costs and health outcomes.[7–9] Although examples of working with scenarios in healthcare exist, only a few were quantified and integrated into cost-effectiveness analysis (CEA).[7,10–12]

When data are not yet available to proof clinical utility and the cost-effectiveness of a health intervention is unclear, value of information (VOI) analysis can be useful to estimate the consequences of uncertainty.[1,13,14] Nevertheless, the extent to which VOI can say something about the consequences of uncertainty is conditional upon the model and the specified parameter uncertainty it is applied on.[13] By integrating scenarios into a decision model and applying VOI analysis, it is possible to calculate the expected consequences of uncertainty that may arise in the near future that otherwise would have been unknown—therefore, in a way, being an extra step ahead of the dynamics of development.

A recent example is that of molecular diagnostics within the field of clinical oncology in The Netherlands. Advanced and metastatic cancers harbor many different genetic aberrations[15] that can be used for treatment selection.[16] These molecular targets are mostly tested sequentially, using several diagnostic tests or test panels. Currently, the use of whole-genome sequencing (WGS) is being investigated for this purpose,[17] because it can detect all known and potentially new molecular targets simultaneously.[18,19] Nevertheless, WGS is not yet widely implemented in clinical practice, given that it is expensive and there is limited evidence of its added clinical value because of its novelty. Uncertainty that is caused by this lack of knowledge was explored by drafting several scenarios about possible futures regarding the implementation of WGS, based on experts' opinion.[9] In addition, an early CEA was performed to estimate threshold values for WGS to become cost-effectiveness in a population of patients with non–small cell lung cancer (NSCLC).[20] The drafted future scenarios can be integrated into the cost-effectiveness model that was used, to estimate the expected costs, effects, and impact of uncertainty of different future developments related to WGS in lung cancer. The results could be used to improve informed policy decisions regarding the implementation of WGS, but, more importantly, it could also substantiate that this type of analytic approach is generalizable to new technologies in other disease areas as well.

Therefore, the objective is to investigate the cost-effectiveness, budget impact (BI), and impact of uncertainty of future developments concerning WGS as a clinical diagnostic test compared with standard of care (SoC) in patients with locally advanced and metastatic NSCLC.

Methods

Overview

Outcomes (costs in 2020 euros, life-years [LYs], and quality-adjusted LYs [QALYs]) of scenarios of possible future

Table 1. Adjustments to the base model for the 3 most likely future scenarios.

Future scenarios	Likelihood			Description of the scenario parameters*	Adjustments to the base model
	Mean	Median	80% HDI		
1. WGS results used for treatment selection[†]	55.3	68.3	15.5-99.0	Additional actionable targets for on-label targeted therapies are identified by WGS.	New biomarker: "on-label targets," added to the decision tree
				Increase of 4.0% additional on-label targets identified	Proportion on-label targets: 4.0%
				Decrease of 33.3% in cost of WGS per patient[‡]	Cost WGS: €1667
2. WGS-based biomarker for immunotherapy	45.3	45.5	0.3-81.3	New biomarker based on WGS becomes available that predicts treatment response to immunotherapy.	PD-L1 replaced with new biomarker for immunotherapy based on WGS
				It is prevalent in 20.0% of patients with advanced lung cancer.	New biomarker predicts treatment response in 20.0% of the patients.
				Increase of 10.0% of physicians that offer WGS to their patients	Uptake WGS: 90.0%
				Increase of 10.0% of patients who prefer WGS over SoC	
3. Off-label drug approval for WGS results	47.3	43.9	25.2-92.3	Off-label drug prescription is allowed outside clinical trials to target actionable targets identified by WGS.	New biomarker: "off-label targets," added to the decision tree
				Off-label targets are identified by WGS in 5.0% of the patients.	Proportion off-label targets: 5.0%
				Increase of 15.0% of physicians that offer WGS to their patients	Uptake WGS: 97.5%[§]
				Increase of 20.0% of patients who prefer WGS over SoC	

Note. The likelihood scores of the scenarios were derived from a previous study.[9] The uptake of WGS in the base model was set at 80.0%. Note that the uptake of WGS was set at 100% for all analysis for comparability reasons, except for the analysis of all scenarios (combined weighted).
HDI indicates high density interval; PD-L1, programmed death-ligand 1; SoC, standard of care; WGS, whole-genome sequencing.
*The parameter values represent the suggested change between the status quo and the scenario parameter values.
[†]Turnaround time was part of the scenario but not included in the model.
[‡]For change in costs, we used the suggested percental change between the status quo and the scenario parameter values.
[§]An average increase for the uptake of WGS was calculated based on the increase in physicians that offer WGS and patients who prefer WGS over SoC.

developments with WGS were estimated using a previous developed cost-effectiveness model.[20] Costs and effects were discounted with a discount rate of 4.0% and 1.5%, respectively, according to the Dutch guidelines.[21] Furthermore, sensitivity, VOI, and BI analyses were performed.

Base Model

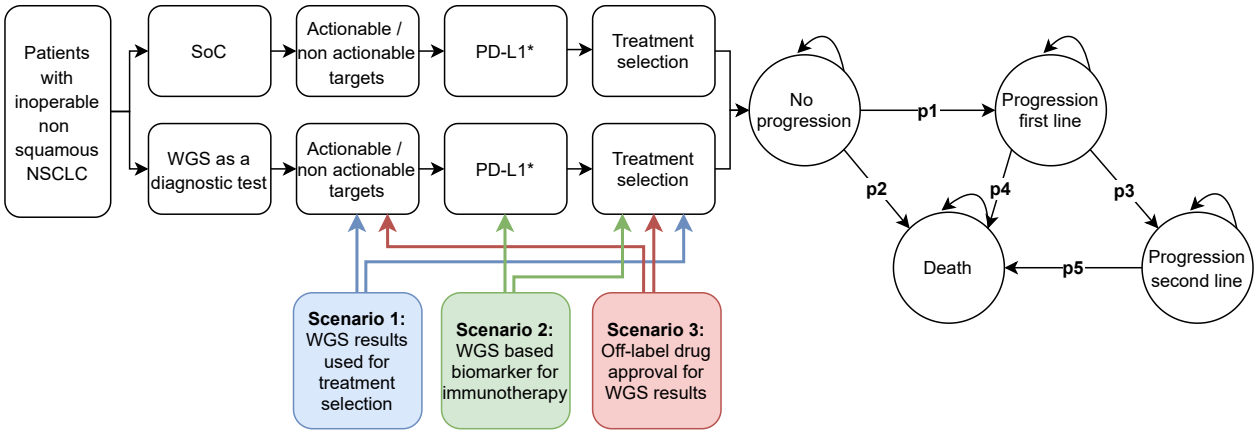
The model simulated the costs and health outcomes of WGS as a diagnostic test compared with molecular diagnostics that are currently used in clinical practice, for patients with inoperable (stage IIIB, C/IV) nonsquamous NSCLC.[20] The model existed of a decision tree representing the diagnostic pathway, including treatment decision, and a state transition model representing the disease progression. This model was chosen for current analysis given that it was recently developed, validated, and included the complete cycle from diagnostic pathway including treatment decisions up to disease progression and death.[20] This made it possible to implement future scenarios on different aspects of the diagnostic pathway and their impact on long-term health outcomes and costs.

Three diagnostic strategies were modeled in the previous study: "SoC," "WGS as a diagnostic test," and "SoC followed by WGS."[20] The first diagnostic strategy consisted of molecular tests that are currently used in the Dutch practice (fluorescence in situ hybridization, immunohistochemistry, a next-generation sequencing multigene panel, and Archer FusionPlex [Invitae Corp]). These tests were used to test for actionable targets that could be treated with targeted therapies. Patients without actionable targets were tested for programmed death-ligand 1 (PD-L1) expression levels for treatment selection of immunotherapy (with or without chemotherapy). This testing strategy was considered as the most effective way of testing for all common actionable targets for the lowest possible costs.[20] In the second diagnostic strategy, WGS was used to detect actionable targets. In this strategy, immunohistochemistry was still used to test for PD-L1 because WGS cannot detect this target. The third diagnostic strategy was similar to the first strategy, but this time WGS was used in case no actionable target was found with the SoC tests. Additionally, each diagnostic strategy included a biopsy success rate, referring to biopsies containing enough tumor cells for the molecular diagnostic test at hand. In addition, a technical success rate was added, referring to the performance of the diagnostic tests. When no test results were available because of failure, patients were assigned to the "target unknown" group in the model.

The actionable targets that were included in the model were epidermal growth factor receptor mutations (exon 19, 21, T790M, nonclassic, and other), anaplastic lymphoma kinase rearrangements, ROS proto-oncogene 1 rearrangements, B-Raf proto-oncogene (V600) mutations, neurotrophic tropomyosin receptor kinase (kinase 1, 2, and 3) gene fusions, and PD-L1 expression level. Nonactionable targets in the model were MET proto-oncogene (amplifications and exon 14 skipping), rearranged during transfection proto-oncogene rearrangement, and Kirsten rat sarcoma virus proto-oncogene. It was assumed that WGS was capable of reliably detecting additional molecular targets in the aforementioned genes with targeted therapies available in routine practice, which are missed in SoC.[20] These additional targets were labeled as "Target X." All molecular targets in the model were mutually exclusive.

The treatment strategies in the model were based on clinical expert consultation[20] and the Dutch clinical guidelines.[22] The actionable targets (including Target X) were treated with first-line targeted therapies. Patients with nonactionable targets were treated with first-line immunotherapy based on their PD-L1 expression levels. Patients in the "target unknown" group were treated with immunotherapy and platinum doublet chemotherapy (PDCT). After disease progression in the first line, patients switched to second-line targeted therapies, immunotherapies, or chemotherapies. Patients received best supportive care after progressing for the second time, which included symptom management.

Figure 1. General structure of the base-model with indications where the scenarios apply. The left part (rounded rectangles) indicates the decision-tree representing the diagnostic pathway. The right part (circles) indicated the state transition model which simulates disease progression. The diagnostic strategies 'SoC' and 'WGS as a molecular diagnostic test' of the initial cost-effectiveness analysis represented the base-model of current research. The scenarios concerned alternative future developments of the strategy 'WGS as a diagnostic test' of the base-model. The scenarios 'WGS results used for treatment selection' (scenario 1) and 'off-label drug approval for WGS results' (scenario 3) had influence on the actionable targets found in the decision-tree of the model and consequently the treatment decision regarding on- and off-label targeted therapy. The scenario 'WGS based biomarker for immunotherapy' (scenario 2) had influence on the biomarker for immunotherapy, PD-L1, in the decision-tree of the model and consequently the treatment decision regarding immunotherapy.



NSCLC indicates non–small cell lung cancer; PD-L1, programmed death-ligand 1; SoC, standard of care; WGS, whole-genome sequencing.
*, in case no actionable target or no target was found, treatment decision was based on the PD-L1 expression levels.

Table 2. Modeled outcomes of the base model and the future scenarios of WGS versus SoC.

Scenarios	Total discounted values, Mean (CrI)		
	Life-year	QALY	Costs
Base model			
SoC	1.879 (1.757-2.011)	1.235 (1.080-1.396)	€149 698 (141 299-158 674)
WGS as a diagnostic test	1.883 (1.761-2.015)	1.238 (1.082-1.398)	€151 227 (142 713-160 241)
Future scenarios of WGS*			
All scenarios (combined unweighted)	1.990 (1.830-2.163)	1.295 (1.114-1.495)	€144 657 (135 870-154 362)
WGS-based biomarker for immunotherapy (scenario 2)	1.925 (1.779-2.083)	1.258 (1.086-1.439)	€147 122 (138 452-156 530)
All scenarios (combined weighted)†	1.933 (1.789-2.100)	1.264 (1.097-1.454)	€147 983 (138 265-157 852)
off-label drug approval for WGS results (scenario 3)	1.922 (1.791-2.059)	1.259 (1.097-1.463)	€150 086 (141 645-159 231)
WGS results used for treatment selection (scenario 1)	1.914 (1.785-2.049)	1.255 (1.095-1.420)	€149 476 (140 977-158 655)

Note. The uptake of WGS was set at 100% for all analyses for comparability reasons, except for the analysis of all scenarios (combined weighted).
CrI indicates credible interval; ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; QALY, quality-adjusted life-year; SoC, standard of care; WGS, whole-genome sequencing.
*All scenarios were compared with SoC of the base model. Note that the future scenarios were sorted by iNMB in descending order.
†Intermediate results on life-years, QALYs, and costs for every combination of active future scenarios during the 3000 can be found in Appendix F in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

After treatment selection, patients entered the state transition model that existed of 4 mutually exclusive health states that reflected no disease progression, progression in the first line (of treatment administration), progression in the second line, and death. Transitions of patients between the health states depended on the selected treatment and were modeled using 1-month cycle lengths. The model had a societal perspective and a lifetime horizon. Extensive details on the model, including the model parameters, can be found in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

Given that "WGS as a diagnostic test" had the highest chance of becoming cost-effective compared with "SoC" in the original study,[20] these 2 diagnostic strategies were used as a starting point of the current research. We will refer to this as the base model. Subsequently, in addition to the base model, 3 future developments regarding WGS were modeled as alternative scenarios of the original diagnostic strategy: "WGS as a diagnostic test."

Scenarios Regarding WGS

In a previous study, a Delphi panel approach was used to create scenarios on several different possible future pathways for the implementation of WGS into clinical practice in patients with metastatic lung cancer.[9] These scenarios were scored on likelihood of taking place within a time horizon of 5 years by international multidisciplinary experts and are listed in Table 1.[9] The 3 future scenarios that were scored as most likely in this study were selected for further exploration in the current analysis. These scenarios concerned alternative future developments of the strategy "WGS as a diagnostic test" of the base model and affect various parts of the structure and inputs, as shown in Figure 1.

The most likely ranked scenario was about WGS being widely available as a clinical molecular diagnostic, further referred to as "WGS results used for treatment selection" (scenario 1). To simulate this scenario, a new actionable biomarker, called "on-label targets," was added to the decision tree. Patients with these targets were treated with on-label targeted therapies.

The second scenario was about the discovery of a new actionable biomarker for immunotherapy that could only be detected with WGS, further referred to as "WGS-based biomarker for immunotherapy" (scenario 2). To simulate this scenario, a new biomarker that predicts treatment response to immunotherapy was implemented in the decision tree of the model. Patients in which no actionable target was found for targeted therapy could receive immunotherapy based on this new biomarker instead of PD-L1 expression levels.

The third scenario was about the approval of off-label drug prescription for additional molecular targets that are not targeted in routine practice, further referred to as "off-label drug approval for WGS results" (scenario 3). To simulate this scenario, a new actionable biomarker, called "off-label targets," was added to the decision tree. Patients with these targets were treated with off-label targeted treatments.

Simulating these scenarios using the previously developed decision model enables us to estimate their impact on the model outcomes. Furthermore, a parameter representing the uptake of WGS was added at the start of the decision tree of the base model. This parameter represented the percentage of patients who would actually receive WGS. The remainder of the patients received currently used diagnostics as in SoC. A full description of the scenarios can be found in Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

Incorporating Scenarios Into the Model

Model adjustments were made to incorporate the scenarios into the base model and are listed in Table 1.[9] In the previous study in which the scenarios were created, a "status quo" was described, based on the literature and experts' opinions, before the scenarios.[9] This status quo included relevant base-case parameter values from which the scenarios deviated. To simulate each scenario in current analysis, the suggested changes between the status quo and scenario parameter values of previous study[9] were applied to the original parameter values of the base model. This was done because WGS concerns a rapidly involving field and some of the suggested parameter values in the scenarios were already caught up by reality by the time of writing. In these particular cases, using the absolute values would have caused the likelihoods of the scenarios to be incorrect, given that they would be higher than the known values of the original model. The

Table 2. Continued

Incremental (vs SoC), Mean (CrI)			Cost-effectiveness	
Life-year	QALY	Costs	ICER	iNMB
—	—	—	—	—
0.004 (−0.034 to 0.044)	0.002 (−0.023 to 0.029)	€1529 (109-3021)	€636 582	−€1336
0.112 (0.024-0.210)	0.060 (−0.001 to 0.132)	−€5041 (−8847 to 1393)	−€84 462	€9815
0.047 (−0.029 to 0.126)	0.023 (−0.026 to 0.078)	−€2576 (−5857 to 516)	−€111 577	€4422
0.054 (−0.014 to 0.158)	0.029 (−0.012 to 0.099)	−€1715 (−6848 to 1838)	−€58 754	€4050
0.043 (0.002-0.092)	0.024 (−0.004 to 0.057)	€388 (−1264 to 2162)	€16 238	€1525
0.035 (−0.006 to 0.081)	0.020 (−0.007 to 0.051)	−€222 (−1840 to 1501)	−€11 263	€1796

adjusted model that was used to simulate the scenarios of current research was made available in the Zenodo repository.[23]

Model Assumptions

Model assumptions were made because several model parameters relevant to the scenarios were unknown. These assumptions were discussed with clinical oncology experts (J.M. and M.P.) who witnessed the complete lifecycle of the scenarios and model creation and are listed in the Appendix C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006. In "WGS results used for treatment selection" (scenario 1), it was assumed that on-label targets were treated with first-line targeted therapies, followed by second-line chemotherapy (in case of disease progression), because most on-label actionable targets are currently treated with this strategy. For the treatment response on overall survival (OS) and progression-free survival (PFS) of these first-line on-label targeted therapies, the same proxy was used as in the base model in case of missing survival data. Furthermore, on-label treatment costs and serious adverse events (SAEs) were assumed to be comparable with those of the latest generation targeted therapies that are currently being used in clinical practice. This was assumed because the on-label targeted therapies would most likely also concern new drugs.

In "WGS-based biomarker for immunotherapy" (scenario 2), it was assumed that patients who had a positive test result for the new biomarker for immunotherapy would receive first-line immunotherapy, followed by second-line PDCT. This is because it is believed that patients who benefit from immunotherapy will not need the addition of chemotherapy in the first line to experience the most health gain. Patients who had a negative test result were treated with first-line immunotherapy combined with PDCT and second-line single agent chemotherapy, because this is still believed to be best possible treatment strategy in case no actionable target is found. Patients who had a positive test result with the new biomarker had the same treatment response, as patients with PD-L1 $\geq$ 50% who are currently treated with immunotherapy in clinical practice. Patients who had a negative test result were assumed to have a treatment response equal to that of patients with any PD-L1 expression level who are currently treated with immunotherapy combined with PDCT. This is because we assumed that responders to the new biomarker would be comparable with patients who currently have PD-L1 $\geq$ 50% and nonresponders with patients with any PD-L1 expression level. Treatment responses to second-line chemotherapy in both subgroups were assumed to be equal to the base model.

For "off-label drug approval for WGS results" (scenario 3), it was assumed that off-label targets and corresponding treatments were similar to the ones in the academic/specialized hospital setting of The Netherlands. Consequently, first-line off-label treatment was a summary of all off-label treatments that were provided followed by second-line chemotherapy. The treatment response on OS and PFS of off-label treatments was unknown, and therefore, the same proxy was used as in the base model in case of missing survival data. Finally, the costs and SAEs of off-label treatments were also unknown. Therefore, we assumed that these were equal to the average of the costs and SAEs of the off-label treatments that were available from the literature.

Base-Case Analyses

For the base-case analyses, the model was analyzed probabilistically using 3000 Monte Carlo iterations. Outcomes were reported for all scenarios separately, combined unweighted (combined unweighted), and combined weighted by likelihood (combined weighted). For comparability reasons, the uptake of WGS was set at 100% for the base case, the individual scenarios, and for all scenarios (combined unweighted). A willingness to pay (WTP) threshold of €80 000 per QALY was used for calculating the incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (iNMB).[24] BI of each scenario was calculated for an incidence of 5000 patients with advanced NSCLC in The Netherlands per year[25] from a payer's perspective for 2021 to 2025, taking the uptake of WGS of each scenario into account. The BI was performed according to the Dutch guidelines,[26] and more details are listed in Appendix D in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

To calculate the outcomes of all scenarios combined (combined weighted), the likelihoods for each scenario taking place from the original published research were parameterized (Table 1).[9] During each model iteration, random samples were drawn from a beta distribution using the mean and 80% high density interval. If the drawn value was higher or equal to a randomly generated number, a scenario was assumed to take place during that particular model iteration. Weighing the scenarios by likelihood resulted in an outcome of the possible future cost-effectiveness of WGS conditional upon the future scenarios. We validated the modeled likelihoods of our approach by comparing it with the original data.[9]

More details on the validation process are listed in Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

Sensitivity Analyses

The influence of different parameters on the outcomes of each scenario was tested with one-way deterministic sensitivity analysis, by varying their values based on the standard error (SE). When not available, 15% of the mean was used for the SE.

Probabilistic sensitivity analysis was performed by drawing random values from prespecified distributions using the Monte Carlo simulations. A cost-effectiveness acceptability curve was created, showing the probability of the base model and each scenario being cost-effective given an increasing WTP threshold for the ICER.

Sensitivity analyses were performed on the model assumptions that were made for each future scenario, by creating alternative versions, further referred to as scenario sensitivity analysis (SSA). The model assumptions were based on what clinical experts would believe to be realistic to represent clinical practice in the near future. With the SSA, we used more extreme parameter values to deviate from this plausible reality and to reflect on what clinical practice could look like further into the future. This was done to investigate the impact of parameters that are currently believed to be important on the model outcomes. Parameter adjustments for the SSA are listed in Appendix D in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

The expected value of perfect information (EVPI) was calculated for the investigated patient population in The Netherlands, to assess the impact of uncertainty.[13] The expected value of partial perfect information (EVPPI) was calculated, by simulating the model with 20 000 iterations and using the Sheffield Accelerated Value of Information framework.[27] This was done to identify which particular parameters contribute most to the impact of uncertainty.[13]

Results

Future Scenario Analysis

The outcomes of the base model and future scenario analysis are listed in Table 2. The scenarios "WGS results used for treatment selection" (scenario 1) and "WGS-based biomarker for immunotherapy" (scenario 2) dominated SoC in terms of cost-effectiveness, and "off-label drug approval for WGS results" (scenario 3) resulted in more QALYs and more costs (iNMB: €1525). When modeling all scenarios combined weighted by likelihood, the scenario "WGS results used for treatment selection" (scenario 1) was active in 55.8%, "WGS-based biomarker for immunotherapy" (scenario 2) in 46.3%, and "off-label drug approval for WGS results" (scenario 3) in 46.9% of the 3000 model iterations. Additional results are listed in Appendix F in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

The annual BI was €708 million for SoC, €714 million for "WGS as a diagnostic test" (base model), €707 million for "WGS results used for treatment selection" (scenario 1), €696 million for "WGS-based biomarker for immunotherapy" (scenario 2), €709 million for "off-label drug approval for WGS results" (scenario 3), €682 million for all scenarios (combined unweighted), and €700 million for all scenarios (combined weighted), over the lifetime of patients who are diagnosed in The Netherlands in 2021. Additional results on BI can be found in Appendix F in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

Sensitivity Analyses

Results of the deterministic sensitivity analysis are displayed in Appendix G in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006. Results of the probabilistic sensitivity analysis are displayed in Figure 2. The 95% credible intervals show that all future scenarios (except for "WGS-based biomarker for immunotherapy" [scenario 2]) result in less costs compared with SoC in most model iterations. It is also shown that all future scenarios result in more QALYs compared with SoC in most model iterations.

Figure 3 shows the probabilities for WGS of the base model and the future scenarios of WGS being cost-effective compared with SoC, given an increasing WTP threshold for the ICER. The probabilities for cost-effectiveness were 2.6% for "WGS as a diagnostic test" (base model), 98.5% for "WGS results used for treatment selection" (scenario 1), 99.8% for "WGS-based biomarker for immunotherapy" (scenario 2), 95.1% for "off-label drugs approval for WGS results" (scenario 3), 100.0% for all scenarios (combined unweighted), and 85.9% for all scenarios (combined weighted) compared with SoC, given a WTP threshold of €80 000 per QALY.

The population EVPI for the base case and the future scenarios of WGS are shown in Figure 4. It showed that the impact of uncertainty is €180 587 for "WGS as a diagnostic test" (base model), €83 285 for "WGS results used for treatment selection" (scenario 1), €11 914 for "WGS-based biomarker for immunotherapy" (scenario 2), €389 318 for "off-label drug approval for WGS results" (scenario 3), €0 for all scenarios (combined unweighted), and €3.4 million for all scenarios (combined weighted), given a WTP threshold of €80 000 per QALY.

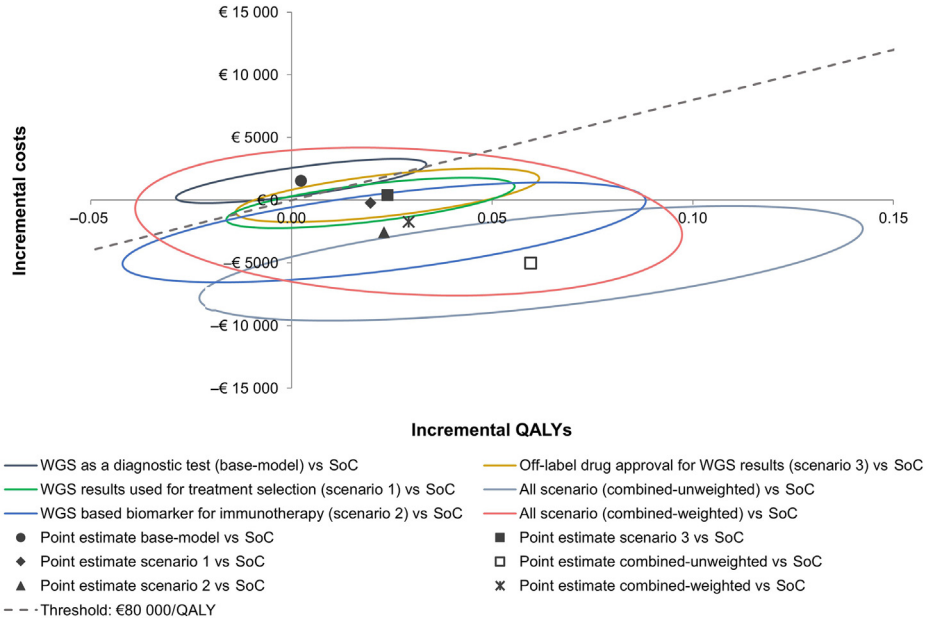
The EVPPI showed that the consequences of uncertainty amounted to €699 000 for the diagnostic yield of WGS, that is, proportion of patients with on-label targets and off-label targets and who had a positive test result for the new biomarker for immunotherapy, alone for all scenarios (combined weighted), given a WTP threshold of €80 000 per QALY. Additional results on EVPPI can be found in Appendix H in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.

Results of the SSA are listed in Appendix I in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006. The scenarios "WGS results used for treatment selection" (scenario 1) and "off-label drug approval for WGS results" (scenario 3) resulted in more LYs, QALYs, and costs, and "WGS-based biomarker for immunotherapy" (scenario 2) in less costs. All scenarios (combined unweighted) and all scenarios (combined weighted) resulted in more LYs, QALYs, and less costs. The probabilities for cost-effectiveness were 77.6% for "WGS results used for treatment selection" (scenario 1), 100.0% for "WGS-based biomarker for immunotherapy" (scenario 2), 48.1% for "off-label drugs approval for WGS results" (scenario 3), 100.0% for all scenarios (combined unweighted), and 76.2% for all scenarios (combined weighted) compared with SoC, given a WTP threshold of €80 000 per QALY. In the SSA, the population EVPI showed the impact of uncertainty is €3 million for "WGS results used for treatment selection" (scenario 1), €0 for "WGS-based biomarker for immunotherapy" (scenario 2), €10.2 million for "off-label drug approval for WGS results" (scenario 3), €0 for all scenarios (combined unweighted), and €5.1 million for all scenarios (combined weighted), given a WTP threshold of €80 000 per QALY.

Discussion

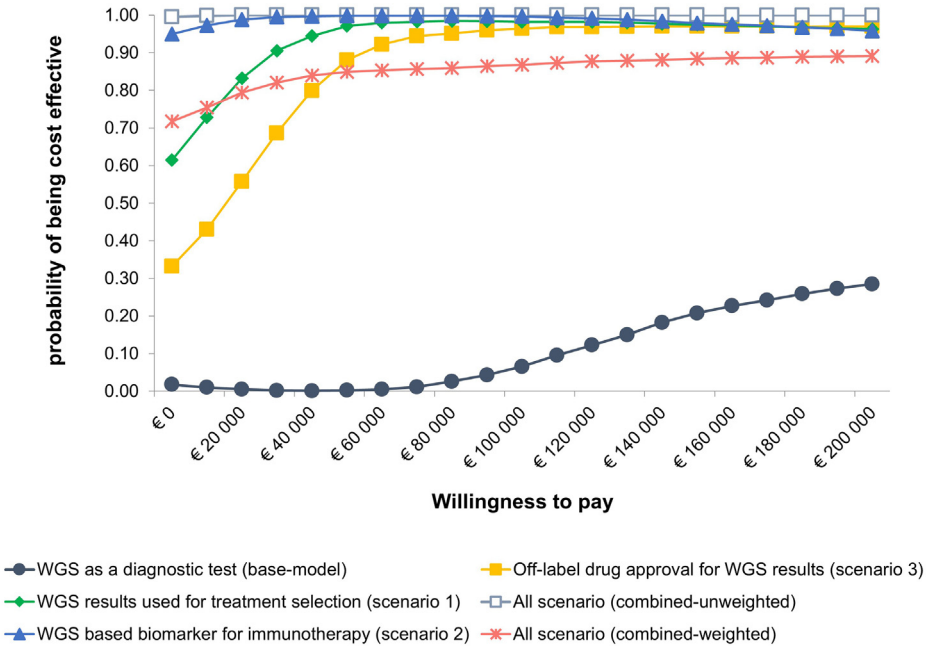
This study investigated the cost-effectiveness, BI, and consequences of uncertainty of future developments concerning WGS as a clinical diagnostic test in patients with locally advanced and metastatic NSCLC. By modeling future scenarios of WGS using a decision analytic model, we showed that, in contrast to "WGS as a diagnostic test" (base model), all future scenarios, including all

Figure 2. Cost-effectiveness plane of WGS of the base model and future scenarios versus SoC. The ellipses represent the 95% CI of 3000 iterations of the comparison of WGS as a diagnostic test (base model), WGS results used for treatment selection (scenario 1), WGS-based biomarker for immunotherapy (scenario 2), off-label drug approval for WGS results (scenario 3), all scenarios (combined unweighted), and all scenarios (combined weighted) versus SoC. The size of the ellipses of WGS-based biomarker for immunotherapy (scenario 2), all scenarios (combined unweighted), and all scenarios (combined weighted) are larger because more patients are affected by them, causing more uncertainty in health gain.



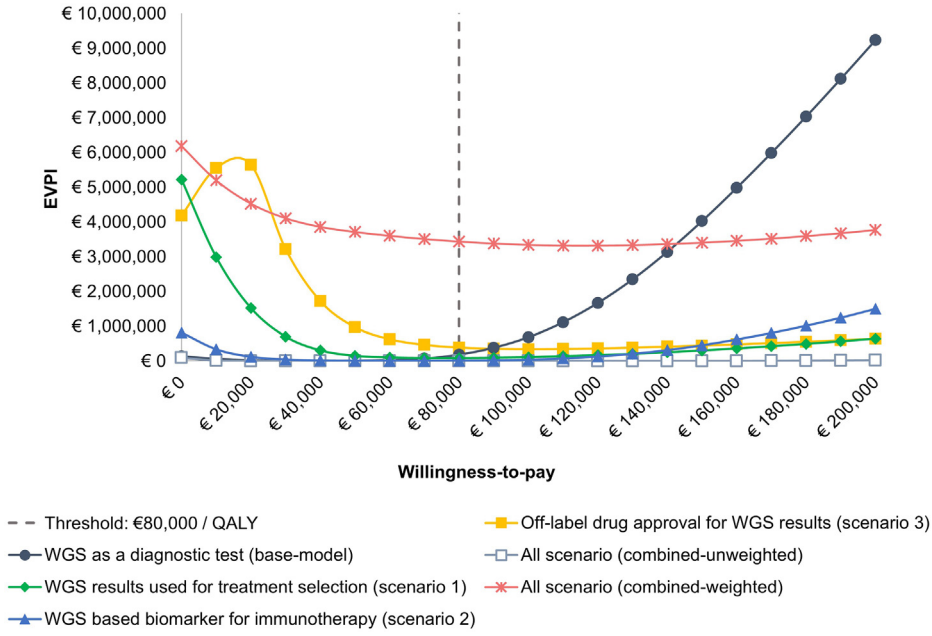
CI indicates confidence interval; QALY, quality-adjusted life-year; SoC, standard of care; WGS, whole-genome sequencing.

Figure 3. CEAC of WGS of the base model and future scenarios versus SoC. The figure shows pairwise comparisons of WGS as a diagnostic test (base model), WGS results used for treatment selection (scenario 1), WGS-based biomarker for immunotherapy (scenario 2), off-label drug approval for WGS results (scenario 3), all scenarios (combined unweighted), and all scenarios (combined weighted) versus SoC.



CEAC indicates cost-effectiveness acceptability curve; SoC, standard of care; WGS, whole-genome sequencing.

Figure 4. EVPI of WGS of the base model and future scenarios versus SoC. The EVPI is calculated for an incidence of 5000 patients with advanced NSCLC per year over a time horizon of 5 years. The effective population was discounted using a discount rate of 4.0%.



EVPI indicates expected value of perfect information; NSCLC, non–small cell lung cancer; QALY, quality-adjusted life-year; SoC, standard of care; WGS, whole-genome sequencing.

possible combinations between the scenarios, were cost-effective compared with SoC, with the iNMB ranging between €1525 for "WGS results used for treatment selection" (scenario 1) and €9815 for all scenarios (combined unweighted).

The annual BI for SoC was €708 million and for adopting WGS ranged between €682 million (combined unweighted) and €714 million (base model), based on the Dutch population. The abovementioned results of scenarios 1 and 3 were driven by the proportion of eligible patients who could be treated with on- and off-label targeted therapy, respectively. These treatments are expensive but more cost-effective than immunotherapy, which is provided for these particular patients in the base model. With SSA, it was assumed for both scenarios that these patients would have a better treatment response, which slightly decreased the probability of cost-effectiveness. This was caused by a longer treatment period with these expensive on- and off-label targeted therapies because of a better PFS. The abovementioned results of the scenario "WGS-based biomarker for immunotherapy" (scenario 2) were driven by the proportion of patients who benefit from immunotherapy and were treated with this costly treatment. Nevertheless, patients who did not benefit were still treated with immunotherapy with PDCT combination, but for a shorter period because of disease progression. Especially in the SSA, these patients were only treated with PDCT, which resulted in scenario 2 becoming more cost-effective than in the base-case analyses. Essentially, all scenarios of WGS were cost-effective compared with the base case because more patients were identified who could be treated with effective treatments, leading to a better stratification. These findings reveal unanticipated results and variations between scenarios and demonstrate a wide range of possible thresholds for cost-effectiveness, which can be informative for decision makers regarding the implementation of WGS.[7,10,11]

Nevertheless, a downside is that the modeled scenarios cover only a part of the possible future of WGS as a clinical diagnostic test and there is always the possibility that alternative noncost-effective scenarios are missed with the current analyses.[7,12] Obviously, there is also the possibility that a scenario will not take place at all. We took this into account, by incorporating the estimates of likelihood of each scenario into the analyses. This also resulted in a cost-effective scenario of WGS, "all scenarios" (combined weighted), that came with some uncertainty. By analyzing this, we found that the consequences of uncertainty amounted to €699 000 for the diagnostic yield of WGS, that is, the proportion of patients who receive an alternative treatment decision because of WGS, alone. Eventually, WGS could become cost-effective compared with SoC, given that more genes will be targeted and more cost-effective treatments become available over time.[28] There is enough evidence that suggests that there are many targets available or under investigation in advanced cancers that can be detected with WGS but not with SoC.[15,19,29-32] As the number of targets keeps increasing, it will become more likely that simultaneously testing will become the most effective approach.[15,28,33]

A strength of this research is that analyzing quantified future scenarios, including their potential uncertainty, provides a comprehensive understanding of what possible future developments hold and what their potential impact on health benefits and costs are concerning a new technology before it is even widely implemented. Furthermore, the performed analyses can be applied in any type of research that includes decision analytic models.

There were some limitations to current research. First, we were not able to explore temporal correlations between scenarios that could influence the outcomes of interest. Nevertheless, we tried to avoid introducing temporal correlations during the scenario

drafting process as much as possible, by creating coherent scenarios that were independent from one another.[9] Second, the likelihoods of the future scenarios had multimodal distributions, making them difficult to use for random sampling during Monte Carlo simulations, although we validated our approach and did not find any mentionable differences between the modeled and original reported likelihoods of the scenarios that we analyzed. Third, we were not able to determine the survival for the responder and nonresponder groups for immunotherapy because of strong correlations between model parameters. Therefore, we assigned unadjusted survival curves of the base model that were likely to represent OS and PFS of both subgroups and only calculated different treatment costs as a consequence of the scenario. Nevertheless, this could still lead to a biased estimation of the treatment costs given that survival affects the duration of treatment administration and moment of subsequent treatment application. We tried to minimize this by performing extensive sensitivity analyses. Fourth, there were some treatments for rare mutational targets in the model, for which no RCT data were available. For these cases, we used the same assumptions as in the original study from which the base model originated, which are listed in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.07.006.[20] This is a common problem in precision medicine, because it is hard to design RCTs for rare diseases because of limited resources and high operational costs. Possible solutions for this problem could be new designs such as umbrella and basket trials, because they enable to study multiple treatments for specific genetic changes in one cancer type and rare mutations in multiple cancer types, respectively,[34] although they come with their own flaws that need to be taken into account.[34] Fifth, we were aware that using a SE rate of 15% for parameters when no real-world data were available seems a bit arbitrary. Nevertheless, we believed that the likelihoods of the scenarios provided by experts would sufficiently capture the uncertainty of the scenarios. We chose to stick to the 15% as was used for the SE rate in the original CEA[20] for consistency and comparability reasons.

Current findings can be informative for policy makers to guide early adoption of WGS, given that they provide extensive information on expected costs, effects, and even cost-effectiveness of possible futures that are deemed most likely by experts to take place within the near future. According to our findings, the field of clinical oncology could move into a direction where WGS will become cost-effective as a molecular diagnostic test in patients with NSCLC. This finding supports policy makers to timely anticipate on the adoption of WGS. In light of the uncertainties, it seems advisable to accompany adoption with further research.

Future research should be focused on the use of WGS data for biomarker development, treatment decision support for targeted therapies (on- and off-label) and immunotherapies, and other factors that are related to diagnostic yield of WGS, given that these factors showed the greatest potential in all future scenario. Although currently only a specific subgroup of patients with NSCLC benefits from precision medicine, the obtained data could then potentially be used for a better stratification leading to more patients receiving better treatment. By the time real-world data relevant to the modeled scenarios become available, a full CEA should be performed for validation purposes. This enables us to further support, reject, or adjust decisions that might be made in the near future regarding WGS as a clinical diagnostic test in oncology. Furthermore, current analysis could be repeated using different scenarios that are based on new knowledge about WGS that will be obtained in the future.

Conclusions

Our findings suggest that WGS as a diagnostic test in NSCLC could become cost-effective within the near future if it detects more patients with actionable targets and shows the impact of uncertainty regarding its diagnostic yield. Modeling future scenarios can be useful to consider early adoption of WGS, while timely anticipating on unforeseen developments relevant to its implementation before final conclusions are reached.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.07.006.

Article and Author Information

Accepted for Publication: July 8, 2022

Published Online: August 13, 2022

doi: https://doi.org/10.1016/j.jval.2022.07.006

Author Affiliations: Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, The Netherlands (Simons, Ramaekers, Joore); Care And Public Health Research Institute, Maastricht University, Maastricht, The Netherlands (Simons, Ramaekers, Joore); Erasmus School of Health Policy and Management/Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands (Uyl-de Groot); Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute-Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands (Retèl, van Harten); Department of Health Technology and Services Research, University of Twente, Enschede, The Netherlands (Retèl, van Harten); Department of Pulmonary Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands (Mankor).

Correspondence: Manuela A. Joore, PhD, Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, P. Debyelaan 25, P.O. Box 5800, Maastricht 6202 AZ, The Netherlands. Email: m.joore@mumc.nl

Author Contributions: *Concept and design:* Simons, Uyl-de Groot, Retèl, Joore, van Harten
Acquisition of data: Simons, Mankor
Analysis and interpretation of data: Simons, Uyl-de Groot, Retèl, Mankor, Ramaekers, Joore, van Harten
Drafting of the manuscript: Simons, Uyl-de Groot, Retèl, Ramaekers, Joore, van Harten
Critical revision of paper for important intellectual content: Simons, Uyl-de Groot, Retèl, Mankor, Ramaekers, Joore, van Harten
Statistical analysis: Simons, Uyl-de Groot, Retèl, Joore, van Harten
Obtaining funding: Uyl-de Groot, Retèl, Joore, van Harten
Administrative, technical, or logistical support: Simons, Uyl-de Groot, Retèl, Mankor, Joore, van Harten
Supervision: Uyl-de Groot, Retèl, Ramaekers, Joore, van Harten

Conflict of Interest Disclosures: Drs Simons and Retèl have received grants from governmental funding of medical research by The Netherlands Organisation for Health Research and Development (ZonMw). Dr Retèl has received grants from Agendia BV and Intuitive BV outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by ZonMw, Netherlands (grant number 846001002), the Dutch Cancer Society, Netherlands, and the Dutch healthcare insurance company Zilveren Kruis-Achmea, Netherlands.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Acknowledgment: The authors thank Dr Marthe Paats from the Erasmus Medical Centre for providing expert opinion within the field of clinical oncology. The authors also thank Dr Sabine Grimm from the Maastricht University Medical Centre for providing support on the value of information analyses. Furthermore, the authors thank all members of the Technology Assessment of Next-Generation Sequencing in Personalized Oncology consortium (https://zenodo.org/communities/tango-wgs/?page=1&size=20) and the funding organizations: ZonMw (grant numbers 846001002), the Dutch Cancer Society, and the Dutch healthcare insurance company Zilveren Kruis Achmea for making this research possible.

REFERENCES

1. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation*. Oxford, United Kingdom: Oxford university press; 2006.
2. Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute for Clinical Excellence (NICE). *Lancet*. 2002;360(9334):711–715.
3. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the Economic Evaluation of Health Care Programme*. 3rd ed. Oxford, United Kingdom: Oxford University Press; 2005.
4. Retèl VP, Hummel MJ, van Harten WH. Review on early technology assessments of nanotechnologies in oncology. *Mol Oncol*. 2009;3(5-6):394–401.
5. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making*. 2012;32(5):722–732.
6. Peterson GD, Cumming GS, Carpenter SR. Scenario planning: a tool for conservation in an uncertain world. *Conserv Biol*. 2003;17(2):358–366.
7. Retèl VP, Joore MA, Linn SC, Rutgers EJ, van Harten WH. Scenario drafting to anticipate future developments in technology assessment. *BMC Res Notes*. 2012;5:442.
8. Doble B, John T, Thomas D, Fellowes A, Fox S, Lorgelly P. Cost-effectiveness of precision medicine in the fourth-line treatment of metastatic lung adenocarcinoma: an early decision analytic model of multiplex targeted sequencing. *Lung Cancer*. 2017;107:22–35.
9. van de Ven M, Simons M, Koffijberg H, et al. Whole genome sequencing in oncology: using scenario drafting to explore future developments. *BMC Cancer*. 2021;21(1):488.
10. Garrison Jr LP, Veenstra DL. The economic value of innovative treatments over the product life cycle: the case of targeted trastuzumab therapy for breast cancer. *Value Health*. 2009;12(8):1118–1123.
11. Ramwadhdoebe S, Van Merode GG, Boere-Boonekamp MM, Sakkers RJ, Buskens E. Implementation by simulation; strategies for ultrasound screening for hip dysplasia in the Netherlands. *BMC Health Serv Res*. 2010;10:75.
12. Lindenberg M, Retèl V, Rohaan M, van den Berg J, Haanen J, van Harten W. Evaluating different adoption scenarios for TIL-therapy and the influence on its (early) cost-effectiveness. *BMC Cancer*. 2020;20(1):712.
13. Fenwick E, Steuten L, Knies S, et al. Value of information analysis for research decisions-an introduction: report 1 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. *Value Health*. 2020;23(2):139–150.
14. Rothery C, Strong M, Koffijberg HE, et al. Value of information analytical methods: Report 2 of the ISPOR Value of Information Analysis Emerging Good Practices Task Force. *Value Health*. 2020;23(3):277–286.
15. Mosele F, Remon J, Mateo J, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol*. 2020;31(11):1491–1505.
16. Marquart J, Chen EY, Prasad V. Estimation of the percentage of US patients with cancer who benefit from genome-driven oncology. *JAMA Oncol*. 2018;4(8):1093–1098.
17. Samsom KG, Bosch LJW, Schipper LJ, et al. Study protocol: whole genome sequencing Implementation in standard Diagnostics for Every cancer patient (WIDE). *BMC Med Genomics*. 2020;13(1):169.
18. Priestley P, Baber J, Lolkema MP, et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature*. 2019;575(7781):210–216.
19. van der Velden DL, Hoes LR, van der Wijngaart H, et al. The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. *Nature*. 2019;574(7776):127–131.
20. Simons M, Retèl VP, Ramaekers BLT, et al. Early cost effectiveness of whole-genome sequencing as a clinical diagnostic test for patients with inoperable stage IIIB,C/IV non-squamous non-small-cell lung cancer. *Pharmacoeconomics*. 2021;39(12):1429–1442.
21. Hakkaart-van Roijen L, van der Linden N, Boumans C, Kanters T, Tan SS. Costing manual [Kostenhandleiding]. Institute for Medical Technology Assessment Erasmus Universiteit Rotterdam. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjL_rKMwIz5AhVOSGwGHfs1AAQQFnoECAMQAQ&url=https%3A%2F%2Fwww.zorginstituutnederland.nl%2Fbinaries%2Fzinl%2Fdocumenten%2Fpublicatie%2F2016%2F02%2F29%2Frichtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg%2FRichtlijn%252Bvoor%252Bhet%252Buitvoeren%252Bvan%252Beconomische%252Bevaluaties%252Bin%252Bde%252Bgezondheidszorg%252B%2528verdiepingsmodules%2529.pdf&usg=AOvVaw1hBjBlc-hALKF10rLEXxa_. Accessed June 18, 2022.
22. Richtlijnendatabase. Federatie Medisch Specialisten. https://richtlijnendatabase.nl/richtlijn/niet_kleincellig_longcarcinoom/startpagina_-_niet-kleincelling_longcarcinoom.html. Accessed February 21, 2022.
23. Simons M, Retèl V, Ramaekers B, Joore M. Cost-effectiveness and budget impact model of future developments with whole-genome sequencing for lung cancer patients. *Zenodo*. 2022. https://doi.org/10.5281/zenodo.5942159.
24. Ziektelast in de praktijk. Zorginstituut Nederland. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwiA5Oq6wYz5AhUgwzgGHXCED68QFnoECA4QAQ&url=https%3A%2F%2Fwww.zorginstituutnederland.nl%2Fbinaries%2Fzinl%2Fdocumenten%2Frapport%2F2018%2F05%2F07%2Fziektelast-in-de-praktijk%2FZiektelast%2Bin%2Bde%2Bpraktijk_definitief.pdf&usg=AOvVaw2ffwm5YRklSuFzLqZ0RoQ8. Accessed November 1, 2021.
25. NKR-cijfers. IKNL. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwiv9pbSwYz5AhXHxzgGHR8DBDEQFnoECAcQAQ&url=https%3A%2F%2Fiknl.nl%2Fnkr-cijfers&usg=AOvVaw1mPoHY7utOLFtzwz1uRBqn. Accessed October 21, 2021.
26. Budget Impact Analyses: Leidraad rekentool. ZonMw. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwjqnr3Nwoz5AhX08DgGHUo5DlMQFnoECAcQAQ&url=https%3A%2F%2Fwww.zonmw.nl%2Fnl%2Fonderzoek-resultaten%2Fdoelmatigheidsonderzoek%2Fbudget-impact-analyse-bia%2F&usg=AOvVaw2q_pA_W_NNbWdVSKUkDEk7. Accessed June 18, 2022.
27. Strong M, Oakley JE, Brennan A. Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. *Med Decis Mak*. 2014;34(3):311–326.
28. Steuten L, Goulart B, Meropol NJ, Pritchard D, Ramsey SD. Cost effectiveness of multigene panel sequencing for patients with advanced non-small-cell lung cancer. *JCO Clin Cancer Inform*. 2019;3(3):1–10.
29. Hagemann IS, Devarakonda S, Lockwood CM, et al. Clinical next-generation sequencing in patients with non-small cell lung cancer. *Cancer*. 2015;121(4):631–639.
30. Monkhorst K, Samsom K, Schipper L, et al. Validation of whole genome sequencing in routine clinical practice. *Ann Oncol*. 2020;31:11890.
31. Roepman P, Bosch L, Samsom K, et al. WGS implementation in standard cancer diagnostics for every cancer patient (WIDE). *Ann Oncol*. 2019;30(suppl 5):v575.
32. Trédan O, Wang Q, Pissaloux D, et al. Molecular screening program to select molecular-based recommended therapies for metastatic cancer patients: analysis from the ProfiLER trial. *Ann Oncol*. 2019;30(5):757–765.
33. Tan AC, Lai GGY, Tan GS, et al. Utility of incorporating next-generation sequencing (NGS) in an Asian non-small cell lung cancer (NSCLC) population: incremental yield of actionable alterations and cost-effectiveness analysis. *Lung Cancer*. 2020;139:207–215.
34. Strzebonska K, Waligora M. Umbrella and basket trials in oncology: ethical challenges. *BMC Med Ethics*. 2019;20(1):58.