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Value of next generation sequencing (NGS) testing in advanced cancer patients

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ABSTRACT

Objective: The availability of targeted therapies for oncology patients is increasing. Available genomic tests to identify treatment-eligible patients include single gene tests and gene panel tests, including the whole-exome, whole-transcriptome OncoExTra test. We assessed the costs and clinical benefits of test choice.

Methods: A Microsoft Excel-based model was developed to evaluate test choice in patients with advanced/metastatic non-small cell lung cancer (NSCLC), breast, prostate, and colorectal cancer. Treatment pathways were based on NCCN guidelines and medical expert opinion. Inputs were derived from published literature. Annual economic results and lifetime clinical results with OncoExTra testing were projected per-tested-patient and compared with single gene testing and no testing. Separately, results were estimated for a US health plan without the OncoExTra test and with its use in 5% of patients.

Results: Compared with no genomic testing, OncoExTra test use increased costs by $4,915 per patient; however, 82%–92% of individuals across tumour types were identified as eligible for targeted therapy or a clinical trial. Compared with single gene testing, OncoExTra test use decreased costs by $9,966 per-patient-tested while increasing use of approved or investigational targeted therapies by 20%. When considering a hypothetical health plan with 1 million members, 858 patients were eligible for genomic testing. Using the OncoExTra test in 5% of those eligible, per-member per-month costs decreased by $0.003, ranging from cost-savings of $0.026 in NSCLC patients to a $0.009 increase in prostate cancer patients. Cost-savings were driven by reduced treatment costs with increased clinical trial enrolment and reduced direct and indirect medical costs associated with targeted treatments.

Limitations: Limitations include the required simplifications in modelling complex conditions that may not fully reflect evolving real-world testing and treatment patterns.

Conclusions: Compared to single-gene testing, results indicate that using next generation sequencing test such as OncoExTra identified more actionable alterations, leading to improved outcomes and reduced costs.

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Introduction

With an increased emphasis on precision medicine approaches within oncology, FDA approvals of drugs targeting genomic variations within specific patients has been increasing[1]. While these treatments have the potential to improve and extend the lives of patients who receive them, identifying eligible individuals and appropriately utilizing approved targeted therapies or informing clinical trial enrolment in clinical practice remains challenging, especially in the setting of a rapidly evolving treatment landscape. For a given tumour type there may be dozens of potentially actionable genomic alterations and multiple targeted treatment options. In addition, tumour agnostic recommendations have become more common[2].

With the rapid increase in the number of alterations that are actionable, there has been the development of more comprehensive approaches to identify patients who may respond. Despite existing evidence showing the benefits of genomic testing, there remain patients who are not tested[3,4]. Amongst those tested, initial approaches identified alterations in single-genes, but such testing can increase patient burden through the need for repeated biopsies and delay in the initiation of therapy, which has been shown to impact survival[5–7]. The use of next generation sequencing (NGS) techniques with high-throughput analysis allowed for the development of genomic panels that concurrently profile many or all genes of interest, potentially decreasing the time from initial diagnosis to treatment initiation[8]. Genomic profiling panels vary in size, from small, often referring to up to

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50 genes, to comprehensive genomic profiling (CGP) or large panels, for >50 genes or more. CGP assays can include whole-genome, whole-exome, and/or whole-transcriptome sequencing (WGS, WES and WTS respectively). However, the costs and clinical outcomes associated with test choice are not fully understood. Here we consider no testing or single-gene testing in comparison to a comprehensive genomic panel that utilizes WES and WTS.

The OncoExTra test is a commercially available assay that uses WES and WTS to capture alterations in both the DNA and RNA, with paired tumour-normal subtraction to specifically identify somatic alterations. The assay detects single nucleotide variants (SNV), indels, focal copy number alterations, fusions, and alternative transcripts, and TERT promoter region alterations. Tumour mutation burden and microsatellite instability status are also determined. The OncoExTra test has been validated and shown to have a high analytic sensitivity and specificity across alteration types[9]. Key advantages to this type of test include the sequencing of RNA, which allows for detection of rare RNA variants and improves detection of expressed fusions, as recommended by American Society of Clinical Oncology (ASCO)[10], and the ability to identify alterations that are somatic (cancer-specific) and therefore may specifically respond to a targeted therapy. For the majority of solid tumours, both ASCO and NCCN guidelines recommend conducting tumour profiling to inform treatment decisions[10,11], though there is a lack of clarity on the optimal method.

Prior analyses, focused primarily on non-small cell lung cancer (NSCLC), have estimated the economic outcomes associated with various panel tests when compared with single gene or no testing[12–17], but there is a gap in the literature for the impact of profiling tests for other tumour types related to the trade-offs between different types of tests. This is further complicated by the fact that decision making can vary across settings, with some considering standardized testing practices across tumour types while others advocating for consideration of each tumour site separately. In this study, we estimate the difference in budget impact and outcomes between a strategy of testing patients within four common tumour types using the OncoExTra test versus no testing or testing using single-gene tests.

Methods

Overview

A cost-consequence model was developed in Microsoft Excel to estimate the costs and clinical outcomes associated with each genomic testing approach. The model assessed patients diagnosed with advanced/metastatic NSCLC, breast cancer, prostate cancer, and colorectal cancer (CRC), chosen for inclusion as four tumour types with the highest incidence in the US. The underlying prevalence of known alterations and test-specific characteristics were used to determine the NGS-directed approved targeted therapy, investigational treatment, or standard of care treatment they would have received following each test. Costs and clinical outcomes were applied based on the treatment received. Pairwise comparisons between the OncoExTra test and alternative testing approaches (i.e. no testing or single-gene testing) were conducted by comparing total costs and outcomes, and outcomes for a hypothetical health plan with and without the use of the OncoExTra test were also estimated, in line with best practices in economic modelling[18].

Model structure

The model developed for this analysis was multi-purposed, designed to: (1) compare outcomes for the average patient receiving a given testing approach (i.e. no test, single gene testing, OncoExTra testing), and (2) assess the budget impact of introducing the OncoExTra test in a hypothetical one-million member health plan with a proportion of participants using the OncoExTra test. In the latter, the model first estimates the proportion of patients with each cancer type who would be eligible for genomic testing. The model included the four most common cancer types: NSCLC, breast, prostate, and CRC. We limited eligibility to those with advanced or metastatic disease, who are receiving their first line of therapy for which NGS testing would be considered for that tumour type. Therefore, we limited the analysis of prostate cancer patients to those with castration-resistant prostate cancer patients (CRPC), as this is the subgroup for whom genomic testing is often considered relevant for informing the first line of therapy within a clinical practice setting. Within breast cancer, only triple-negative breast cancer (TNBC) patients were considered, as NGS testing is often used earlier in these patients than in those with other subtypes. The estimated number of eligible patients were stratified by insurer; Medicaid, Medicare, or commercial insurance. For both the pairwise comparisons between testing approaches and the population-based analysis, a set of molecular genomic alterations of interest were generated based on those with an associated NCCN-recommended treatment at the time of model development[19], and a proportion of patients with each underlying alteration was assigned based on estimates from the literature (Supplementary Table 1). Treatments for patients identified within each alteration type for which there is an NGS-directed approved therapy were defined based on NCCN guidelines and expert opinion from an oncologist. The underlying genomic alteration prevalence and test choice determined the likelihood that patients would initiate an NGS-directed approved targeted therapy, investigational therapy, or standard of care, each of which differed by tumour type. As a simplification for modelling purposes, we selected a single regimen for each alteration based on expert input. Where the targeted therapy was indicated for wild-type tumours (e.g. cetuximab for *KRAS* wild-type CRC tumours), or where a treatment was indicated regardless of whether the alteration was somatic or germline, the model structure was developed to capture these situations. In the case of an alteration with no approved therapy that is currently being investigated in clinical trials, we assumed that the patient could enrol in a clinical trial, with a proportion enrolling and the remainder receiving standard of care. The model focused on the first line of therapy at which NGS would be used to inform therapy selection with costs

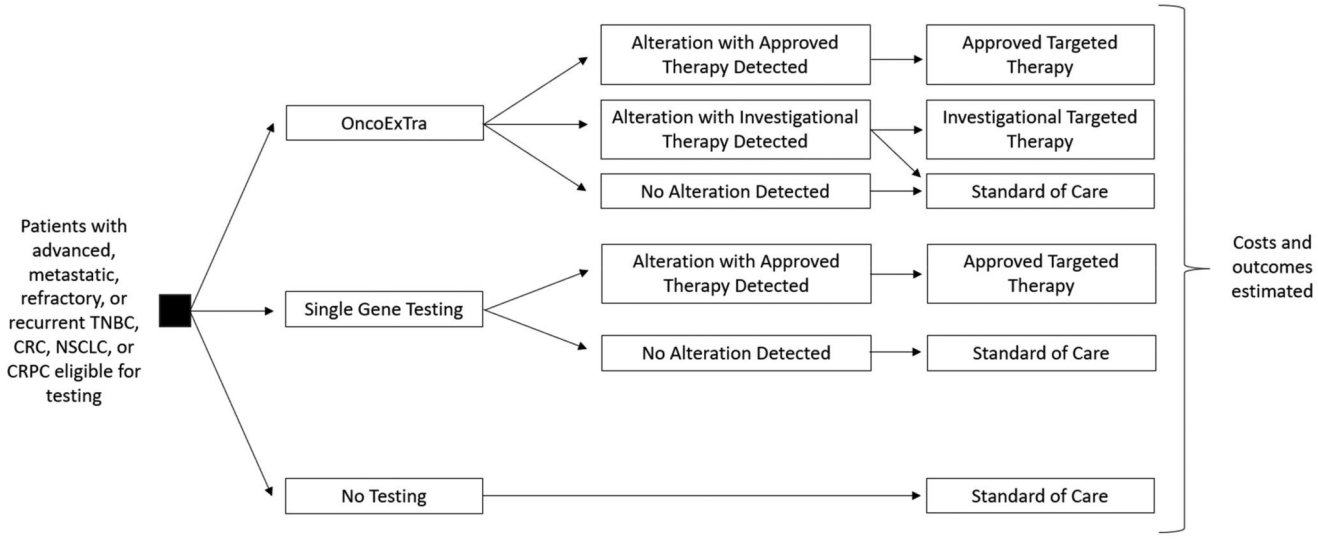

Figure 1. Model schematic. Abbreviations. TNBC, Triple-negative breast cancer; CRC, Colorectal cancer; NSCLC, Non-small cell lung cancer; CRPC, Castration-resistant prostate cancer. Patients entered the model on the left and were assigned a testing approach. Based on test assigned, results could include: (1) detection of an alteration with an approved NGS-directed targeted therapy, (2) detection of an alteration without an approved targeted therapy but with a potential treatment being studied in a clinical trial, or (3) no alteration detected. Treatment choice was based on test result, which determined costs and outcomes.

considered for the one-year period following the test. We limited the economic outcomes to first-year costs given that payers are often more concerned with the near-term impact of decisions on budgets, while reporting lifetime clinical outcomes as they better reflect the impact to patients of treatment choice. All economic results are presented in 2022 USD. Clinical outcomes including actionable genomic alterations detected and overall survival, with the latter calculated based on results from pivotal trials for the relevant targeted therapy[20–43]. A simple model schematic is shown in Figure 1.

Model inputs

Inputs required by the model included those related to demographic and epidemiologic data to identify patients eligible for testing, alteration prevalence estimates among those with each cancer, test characteristics such as cost, analytic sensitivity, market share, and capabilities, as well as treatment-related costs and clinical outcomes. Key parameters are shown in Table 1. Model inputs and corresponding values are shown in Supplementary Tables 1–10.

To estimate the patients eligible for testing, we considered the incidence of each cancer[44], the proportion with metastatic disease, which included both those diagnosed at the time of metastases[44] and those diagnosed at earlier stages before developing metastases[45]. We considered the proportion of breast cancer patients with triple negative disease[44] and the proportion of prostate cancer patients with castration-resistant cancer[46]. The proportion of the population with each insurance type was based on US Census data[47].

Within each cancer, the prevalence of each genomic alteration included in the model was estimated, as well as the proportion of patients with an alteration for which there was no approved therapy but for which we could expect there to be ongoing clinical trials. Such inputs were based on published literature[48–54]. To capture that some patients may have multiple actionable alterations, we relied on expert opinion to determine a hierarchy to identify alterations most likely to be targeted, such that a single treatment regimen could be applied.

For each type of test, we estimated the costs of obtaining a sample and conducting the test, as well as the test sensitivity. Test costs were based on Medicare reimbursement rates, with costs for RNA tests and small panel tests based on generic CPT codes due to lack of test-specific codes[55]. Biopsy costs were based on publicly available Medicare reimbursement rates[56]. In cases where Medicare costs were collected, these values were adjusted to reflect Medicaid and Commercial prices using publicly available inflation factors[57,58]. Analytic sensitivity for each test (i.e. probability that a test could detect an alteration in a patient harbouring one) was based on publicly available data reported by the manufacturers[59–62], with sensitivity for a given test assumed equivalent across alterations. Specificity was assumed to be 100% for all tests, based on expert opinion that false-positives are extremely rare. Some alterations are impossible or challenging to detect without RNA sequencing. As such, tests that did not include RNA sequencing had their sensitivity reduced by 2.5%, based on a published estimate of the proportion of alterations detected only with RNA sequencing[9]. Market share was based on internal estimates, and we assumed that the OncoExTra test would initially be used in 5% of the population, taking share equally from those who would otherwise have received single gene testing or not be tested.

Patients were assigned a treatment regimen based on test results, and accrued costs and experienced clinical outcomes associated with that treatment. As a simplification, we assumed that all patients with a genomic alteration identified received the corresponding targeted therapy but acknowledge that real-world treatment patterns may differ. Product acquisition costs included the treatment of interest as well as supportive care medications that are commonly

Table 1. Model parameters.

Model input	Value				Reference
	TNBC	CRC	NSCLC	CRPC	
Cancer incidence per 100k individuals[a]					
Ages 18–64	280	40	40	130	44
Ages 65+	400	140	260	650	44
Prevalence of alterations with approved therapies[b]	75.0%	72.0%	70.1%	40.5%	44,48–54,75,76
Prevalence of alterations with ongoing clinical trials	16.9%	9.6%	25.6%	43.5%	
OncoExTra test sensitivity	0.99				9
OncoExTra test costs[c]	$2,919				55
Biopsy costs	$304				56
Reflex RNA cost[d]	$3,675				55
Clinical trial eligibility[e]	46%				67
Average annual pharmacy costs[e]					
Targeted therapy	$108,999	$122,702	$146,336	$105,215	63,77
Standard of care[f]	$15,799	$82,306	$108,696	$7,947	
Average annual other direct medical costs[g]					
Targeted therapy	$108,398	$176,737	$126,896	$189,399	64,77
Standard of care[f]	$104,254	$187,891	$126,127	$197,964	
Average annual productivity losses					
Targeted therapy	$769	$3,232	$645	$98	65,66
Standard of care[f]	$2,139	$5,640	$2,139	$674	

Abbreviations. TNBC, Triple-negative breast cancer; CRC, Colorectal cancer; NSCLC, Non-small cell lung cancer; CRPC, Castration-resistant prostate cancer.
[a]Incidence rates reflect the rate of all advanced/metastatic breast and prostate cancers, not strictly TNBC or CRPC.
[b]Sources referenced were used for both the prevalence of alterations leading to targeted therapy and those leading to clinical trials.
[c]Based on Medicare reimbursement rate.
[d]Based on CPT Code 0O19U.
[e]Eligibility amongst those with an alteration detected but without an alteration for which there is an NGS-directed approved targeted therapy.
[f]Standard of care does not include NGS-directed targeted therapies.
[g]Values reflect Medicare costs.

administered in combination with active treatments and were based on publicly available wholesale acquisition costs (WAC) as of July 2022[63], without rebates or discounts applied. Other direct medical costs such as office visits, hospitalizations, and resolving treatment-related adverse events (i.e. non-pharmacy costs) were based on a published claims analysis and adjusted by length of progression-free survival[64]. Specifically, this claims analysis lists all healthcare costs by cost component, allowing us to subtract the pharmacy costs out of the total before incorporating into the model. Productivity costs were based on published estimates, differed by cancer, and were differentially estimated for those who did or did not receive a chemotherapy-based regimen[65,66]. Among those patients with an actionable alteration detected that did not have an approved therapy, we assumed 46% would enrol in a clinical trial, based on observations from practice[67]. Clinical outcomes associated with treatments administered in clinical trials were assumed to be equivalent to the standard of care. Clinical outcomes associated with each NGS-directed approved treatment were based on the pivotal clinical trials used in the approval process (Supplementary Table 9). In cases where the clinical trial was ongoing at the time of approval, we relied upon updated, final estimates from the trial[20–40,68]. For some treatments, the population within the clinical trials may have differed from the population being assessed in the model, with the specific trials shown in Supplementary Table 9. For patients directed to treatment with a test that did not have tumour-normal pairing and therefore did not differentiate between somatic and germline alterations, we assumed that treatment effectiveness was reduced based on a published estimate of the frequency of somatic alterations[69]. However, in cases where a treatment was indicated for both somatic and germline alterations, this adjustment was not applied.

Analyses

To understand the impact of the OncoExTra test, we conducted two primary analyses: pairwise comparisons and a population-based analysis. We first examined the cost and clinical consequences to the average patient tested with the OncoExTra test in a pairwise manner, and estimated the same outcome metrics for those who did not receive genomic testing and those undergoing single-gene testing. As a separate population-based analysis, we estimated the impact to a health plan of using the OncoExTra test in 5% of those eligible for genomic testing based on internal uptake forecasts. A cohort of oncology patients were considered based on the number of eligible patients estimated and the mix of payers, with annual costs and lifetime clinical outcomes assessed for each. To explore the impact of parameter uncertainty on model outcomes, one-way sensitivity analyses were conducted in which each parameter was varied individually ±20% while holding constant the assumption that 5% of patients would be tested with the OncoExTra test. Probabilistic sensitivity analyses were conducted by performing 1,000 model iterations in which all parameters were varied simultaneously, assuming a normal distribution centred on the base case value and with the standard deviation equal to 10% of the base value, and with any additional natural limits imposed (e.g. proportions cannot exceed 100%). To understand the implications of different uptake rates of the OncoExTra test in the population-based analysis, we varied the base case market share of 5% from 2% to 10%. As an

Table 2. Total costs per average patient when comparing the OncoExTra test with no testing or single gene testing.

	TNBC	CRC	NSCLC	CRPC[a]
Testing costs[b]				
No test	$0	$0	$0	$0
Single gene test	$3,155	$2,726	$3,521	n/a
OncoExTra test	$3,380	$3,248	$3,367	$3,235
Δ (OncoExTra test vs. no test)	$3,380	$3,248	$3,367	$3,235
Δ (OncoExTra test vs. single gene test)	$224	$522	−$154	n/a
Pharmacy costs				
No test	$17,340	$88,966	$114,603	$8,257
Single gene test	$82,490	$111,227	$117,441	n/a
OncoExTra test	$84,684	$111,253	$103,212	$37,989
Δ (OncoExTra test vs. no test)	$67,344	$22,287	−$11,390	$29,732
Δ (OncoExTra test vs. single gene test)	$2,194	$26	−$14,229	n/a
Other direct medical costs				
No test	$114,421	$202,998	$132,981	$205,692
Single gene test	$118,550	$196,565	$133,223	n/a
OncoExTra test	$118,774	$195,380	$133,208	$203,427
Δ (OncoExTra test vs. no test)	$4,352	−$7,618	$227	−$2,265
Δ (OncoExTra test vs. single gene test)	$224	−$1,185	−$15	n/a
Productivity losses				
No test	$2,139	$5,640	$2,139	$674
Single gene test	$1,197	$4,962	$1,331	n/a
OncoExTra test	$1,146	$4,714	$1,127	$336
Δ (OncoExTra test vs. no test)	−$993	−$926	−$1,012	−$338
Δ (OncoExTra test vs. single gene test)	−$51	−$248	−$205	n/a
Total costs				
No test	$133,900	$297,604	$249,722	$214,623
Single gene test	$205,392	$315,480	$255,516	n/a
OncoExTra test	$207,982	$314,595	$240,914	$244,987
Δ (OncoExTra test vs. no test)	$74,082	$16,991	−$8,809	$30,364
Δ (OncoExTra test vs. single gene test)	$2,590	−$885	−$14,602	n/a

Abbreviations. TNBC, Triple-negative breast cancer; CRC, Colorectal cancer; NSCLC, Non-small cell lung cancer; CRPC, Castration-resistant prostate cancer.
[a]Single gene testing not performed within CRPC.
[b]Testing costs include all costs associated with performing a test, including the cost of the test itself, a biopsy to obtain the sample, and IHC stains.

exploratory scenario analysis to understand the potential cost implications of treatment discounts and rebates, the population-based analysis was repeated with all pharmacy costs set to 30% below list price.

Results

When conducting pairwise comparisons between the average patient undergoing OncoExTra testing and those not getting tested, we found that use of the OncoExTra test increased costs by $4,915, ranging from a savings of $8,809 per patient with the OncoExTra test in NSCLC to an increase of $74,082 per TNBC patient. Within NSCLC, the cost savings was attributable to a savings of $11,390 per patient in pharmacy costs and a savings of $1,012 in productivity costs, which more than offset the increase of $3,367 and $227 in testing and other direct medical costs, respectively. The cost increase within TNBC was driven by an increase in testing costs of $3,380, an increase in pharmacy costs of $67,344, and an increase in other direct medical costs of $4,352, with a decrease of $993 in productivity losses (Table 2). Savings associated with clinical trial enrolment ranged from $1,340 per TNBC patients to $13,391 per NSCLC patient. The differences in total costs between these cancers were primarily due to the defined standard of care regimens, with NSCLC patients receiving pembrolizumab while TNBC received chemotherapy. When combining tumour types, the use of the OncoExTra test resulted in 91% of patients being identified as eligible to either receive a targeted therapy or enrol in a clinical trial, whereas without testing no patients were eligible. Patients identified as eligible for targeted therapies, inclusive of both NGS-directed approved targeted therapies and investigational treatments, was highest in NSCLC and CRC at 91.8% and 91.4%, respectively. Overall survival was estimated to increase by 0.6 months in prostate cancer, 0.9 months in breast cancer, 3.9 months in NSCLC patients, and 14.2 months in CRC (Table 3).

When comparing the average patient undergoing OncoExTra testing with those undergoing single-gene testing, the OncoExTra test reduced costs by $9,966, ranging from a savings of $14,602 per patient with the OncoExTra test in NSCLC to an increase of $2,590 per TNBC patient. These results included a reduction in pharmacy costs associated with clinical trial enrolment, ranging from $1,340 per TNBC patients to $13,391 per NSCLC patient. The cost savings were also due to a reduction in testing costs of $9,492, as patients undergoing single-gene testing often require multiple tests before an actionable alteration was identified. Additionally, there were further savings attributable to reduced medical costs and a decrease in productivity losses (Table 2). The use of the OncoExTra test resulted in an additional 20.5% of patients being identified as eligible to either receive a targeted therapy or enrol in a clinical trial (90.9% with the OncoExTra test versus 70.4% with single-gene testing). Estimated overall survival was unchanged in TNBC and increased by 0.7 months in NSCLC patients and 3.7 months in CRC (Table 3) with OncoExTra testing.

In the population-based analysis, we found that among a hypothetical health plan with 1 million members, 858 oncology patients would be eligible for genomic testing. Of these patients, nearly 500 were Medicare-eligible, and the most frequent cancer site was NSCLC (535 patients) followed by CRC (212 patients), CRPC (68 patients) and TNBC (44 patients). When considering the 858 patients eligible for testing, an assumed 5% shift in the OncoExTra test utilization implies 43 patients received a different test when comparing with vs. without the OncoExTra test use in the population.

In this assessment and in the absence of the OncoExTra test, projected annual costs were $260,899 per cancer patient, ranging from $192,640 for breast cancer patients to $311,340 for CRC patients. Total costs to a plan for testing and treating all eligible patients was $223.9 million, of which approximately 60% was attributable to NSCLC. When using the OncoExTra test in 5% of the population, per patient costs were $260,852, a decrease of $47 per cancer patient. The difference in costs ranged from a savings of $585 per testing-eligible NSCLC patient to an increase of $1,917 per breast cancer patient. Of note, increased use of the OncoExTra test led to a savings of $407,700 to the plan associated with patients enrolling in clinical trials, of which 88% was attributable to NSCLC patients. On a per-member per-month (PMPM) basis, the use of the OncoExTra test in 5% of patients led to a decrease in costs of $0.0033 per member per month, ranging from a savings of $0.026 for NSCLC patients to an increase of $0.009 for prostate cancer patients.

Table 3. Clinical outcomes per patient when comparing the OncoExTra test with no testing or single gene testing.

	TNBC	CRC	NSCLC	CRPC[a]
Patients with actionable alteration detected (%)[b]				
No test	0.0%	0.0%	0.0%	0.0%
Single gene test	70.4%	67.5%	65.8%	n/a
OncoExTra test	90.9%	91.4%	91.8%	81.9%
Δ (OncoExTra test vs. no test)	90.9%	91.4%	91.8%	81.9%
Δ (OncoExTra test vs. single gene test)	20.5%	23.9%	26.0%	n/a
Patients with actionable alteration detected for which there is an approved therapy (%)				
No test	0.0%	0.0%	0.0%	0.0%
Single gene test	70.4%	67.5%	65.8%	n/a
OncoExTra test	74.2%	81.9%	66.5%	38.9%
Δ (OncoExTra test vs. no test)	74.2%	81.9%	66.5%	38.9%
Δ (OncoExTra test vs. single gene test)	3.8%	14.4%	0.7%	n/a
Patients with actionable alteration detected for which there is no approved therapy (%)				
No test	0.0%	0.0%	0.0%	0.0%
Single gene test	0.0%	0.0%	0.0%	n/a
OncoExTra test	16.7%	9.5%	25.3%	43.0%
Δ (OncoExTra test vs. no test)	16.7%	9.5%	25.3%	43.0%
Δ (OncoExTra test vs. single gene test)	16.7%	9.5%	25.3%	n/a
Overall survival (months)				
No test	16.8	12.9	17.2	18.9
Single gene test	17.7	23.4	20.9	n/a
OncoExTra test	17.7	27.1	21.1	19.5
Δ (OncoExTra test vs. no test)	0.9	14.2	3.9	0.6
Δ (OncoExTra test vs. single gene test)	0.0	3.7	0.2	n/a

Abbreviations. TNBC, Triple-negative breast cancer; CRC, Colorectal cancer; NSCLC, Non-small cell lung cancer; CRPC, Castration-resistant prostate cancer.
[a]Single gene testing not performed within CRPC.
[b]Actionable alterations defined as those for which there is an approved NGS-directed targeted therapy or ongoing clinical trial.

Plan costs by cancer type, separated by cost drivers, are shown in Table 4.

Along with the economic impact associated with an increased use of the OncoExTra test, the model also projected an increase in patients identified with an alteration and improved survival with greater use in the population-based analysis. In the scenario without use of the OncoExTra test, 59.1% of patients were detected with an actionable alteration, including 51.1% who were deemed eligible for an approved NGS-directed targeted therapy and 8.0% who were eligible for clinical trial enrolment. When the OncoExTra test was incorporated into the treatment decision-making paradigm, these rates increased to 63.1%, with 53.9% eligible for approved therapy and 9.2% eligible for clinical trials. Clinical trial eligibility was most common within prostate cancer (14.5%) and least common within CRC (4.0%), while the increase in use of targeted therapies ranged from 1.9% of patients in prostate cancer to 3.5% in CRC. Overall survival increased in each of the four tumour types with use of the OncoExTra test, ranging from 0.03 months within CRPC to 0.60 months in CRC. Comparisons of clinical outcomes with and without the OncoExTra test use are shown in Table 4.

In scenario analyses exploring the impact of varying uptake of the OncoExTra test from 2% to 10% (from a base case value of 5%), the savings associated with adding the test varied from $0.0013 to $0.0067 PMPM respectively. Eligibility for either an NGS-directed approved or investigational targeted therapies, ranged from 59.1% without the OncoExTra test use to 60.3% (assuming 2% uptake) and 65.2% (assuming 10% uptake).

In sensitivity analyses in which each parameter was varied ±20% of the base case value, we found that the model-predicted PMPM cost difference was most impacted by changes in the costs associated with treating CRC patients, with the medical costs having a larger influence than the pharmacy costs. Pharmacy and medical costs within CRC are higher than the other three cancers, such that 20% changes to the base case values led to wider ranges of results in absolute terms compared with other tumour types. Additionally, assumptions around eligibility and enrolment in clinical trials as well as CRPC treatment costs were also influential. The characteristics of the OncoExTra test, including the cost and test sensitivity, were less influential. The parameters with the greatest impact on model results are shown in the Tornado Diagram (Figure 2). In probabilistic sensitivity analyses, we found that use of the OncoExTra test was cost-saving in 49% of model simulations when considering all cancer sites combined. Within individual tumour types, use of the OncoExTra test was cost-saving within NSCLC in 74% of model iterations and cost-savings in CRC in 20% of alterations. Within CRPC and TNBC, the OncoExTra test consistently increased costs across iterations. The probabilistic sensitivity analysis scatterplot, showing the cost and clinical implications to a health plan of using the OncoExTra test in 5% of patients, are found in Figure 3. In the scenario analysis in which drug prices were reduced by 30% to capture potential rebates and discounts, the PMPM impact when using the OncoExTra cost was reduced from a savings of $0.0033 to a savings of $0.0022. This was driven by a reduction in the cost savings attributable to clinical trial enrolment, which was caused by reduced pharmacy costs for those receiving approved targeted therapies.

Discussion

Precision medicine is a rapidly evolving field. Biomarker-based therapies comprised at least 25% of FDA approvals each year 2015–2021, presenting a challenge to physicians and payers intent on remaining current in their

Table 4. Costs and clinical outcomes when using the OncoExTra test in 5% of a hypothetical 1 million member plan population.

	TNBC ($n = 44$)	CRC ($n = 212$)	NSCLC ($n = 535$)	CRPC ($n = 68$)
Testing costs				
With OncoExTra test	$141,145	$658,334	$1,725,089	$196,178
Without OncoExTra test	$137,168	$638,372	$1,682,163	$185,217
Difference	$3,977	$19,962	$42,927	$10,961
Pharmacy costs				
With OncoExTra test	$3,101,659	$22,471,020	$59,383,764	$2,260,053
Without OncoExTra test	$3,024,922	$22,352,844	$59,726,127	$2,159,312
Difference	$76,737	$118,176	−$342,363	$100,741
Other direct medical costs				
With OncoExTra test	$5,200,394	$41,853,938	$71,187,467	$13,814,954
Without OncoExTra test	$5,195,344	$41,900,560	$71,184,625	$13,822,628
Difference	$5,050	−$46,622	$2,842	−$7,674
Productivity losses				
With OncoExTra test	$60,267	$1,058,006	$745,531	$30,617
Without OncoExTra test	$61,420	$1,064,220	$761,794	$31,762
Difference	−$1,153	−$6,214	−$16,263	−$1,145
Total costs				
With OncoExTra test	$8,503,465	$66,041,298	$133,041,851	$16,301,802
Without OncoExTra test	$8,418,854	$65,955,996	$133,354,708	$16,198,920
Difference	$84,612	$85,302	−$312,857	$102,882
Per-member per-month (PMPM) costs				
With OncoExTra test	$0.709	$5.503	$11.087	$1.358
Without OncoExTra test	$0.702	$5.496	$11.113	$1.350
Difference	$0.0071	$0.0071	−$0.0261	$0.0086
Patients with actionable alteration detected (%)[a]				
With OncoExTra test	64.8%	61.4%	64.2%	46.4%
Without OncoExTra test	62.1%	58.5%	61.3%	42.3%
Difference	2.7%	2.9%	2.9%	4.1%
Patients with actionable alteration detected for which there is an approved therapy (%)				
With OncoExTra test	57.8%	57.4%	53.5%	31.9%
Without OncoExTra test	55.8%	54.9%	51.8%	30.0%
Difference	2.0%	2.5%	1.7%	1.9%
Patients with actionable alteration detected for which there is a clinical trial (%)				
With OncoExTra test	7.1%	4.0%	10.7%	14.5%
Without OncoExTra test	6.2%	3.5%	9.4%	12.3%
Difference	0.9%	0.5%	1.3%	2.2%
Overall survival (months)				
With OncoExTra test	17.52	21.97	20.21	19.36
Without OncoExTra test	17.49	21.46	20.11	19.33
Difference	0.03	0.51	0.10	0.03

Abbreviations. TNBC, Triple-negative breast cancer; CRC, Colorectal cancer; NSCLC, Non-small cell lung cancer; CRPC, Castration-resistant prostate cancer.

[a]Actionable alterations defined as those for which there is an NGS-directed approved therapy or ongoing clinical trial.

understanding of the clinical and economic consequences of these new treatments[70]. We developed a cost-consequence model to aid such assessments and provide the first estimate of the outcomes associated with the OncoExTra test. In the current model-based analysis examining pairwise comparisons, use of the OncoExTra test led to an increased cost but a clinical improvement when compared with no testing. When compared with single gene testing, the OncoExTra test both increased survival and reduced costs. In the population-based analysis in which 5% of eligible patients were tested with the OncoExTra test, the proportion of patients deemed eligible for an NGS-directed approved targeted therapy or clinical trial increased while a reduction in costs was observed. In both pairwise and population-level analyses, increasing the number of patients who are identified as being eligible for targeted treatments with the use of OncoExTra testing would improve survival while reducing productivity losses compared to alternative testing methods. These findings reinforce that precision medicine and targeted therapies can provide benefits to patients and testing to increase their use is necessary. Our results are generally consistent with other analyses of NGS tests within NSCLC which consistently found increased identification of actionable alterations with NGS testing while economic outcomes were mixed depending on the comparator selected and input costs included[13,65,71,72].

In assessing the economic and clinical benefits of a diagnostic test, one primary driver will be the treatments that test results direct patients to. While novel targeted therapies are associated with possibly more favourable clinical outcomes, they are generally more expensive than non-targeted therapies on a per-month basis and patients often remain on these therapies for longer. These therapeutic costs are incorporated into economic value assessments and impact the perceived value of tests that increase their utilization, such as the OncoExTra test. In this analysis, we incorporated NCCN-recommended treatments and applied the manufacturer listed wholesale acquisition costs without any discounts or rebates. To the extent that negotiations or legislation such as the Inflation Reduction Act limit the costs of pharmaceutical interventions, a test that directs more patients to improved treatments will appear of higher value. Similarly, clinical outcomes associated with each testing approach were based on trial data for the available therapies. As the landscape for targeted

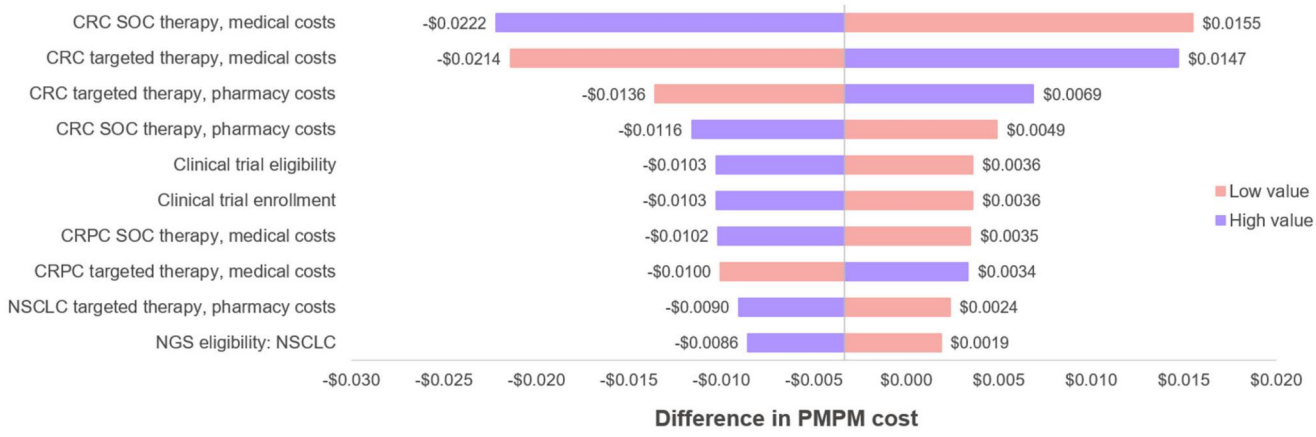

Figure 2. Sensitivity analysis: tornado diagram. Abbreviations. CRC, Colorectal cancer; NSCLC, Non-small cell lung cancer; CRPC, Castration-resistant prostate cancer; SOC, Standard of care; PMPM, Per-member per-month; NGS, Next generation sequencing.

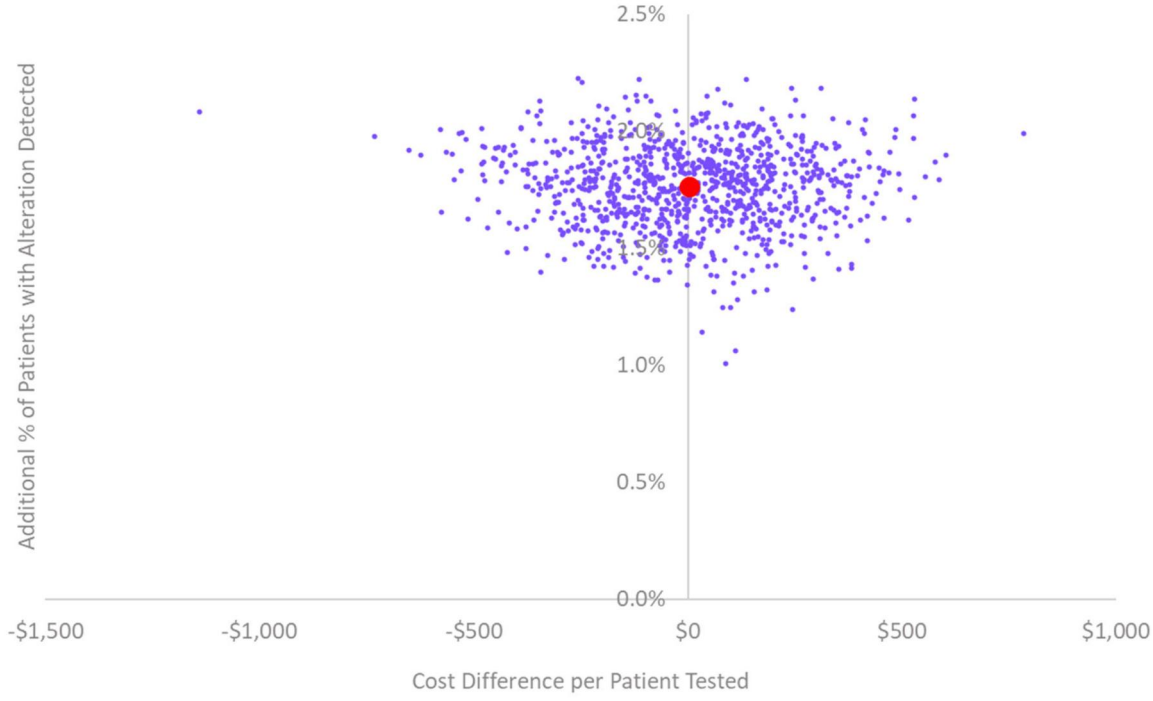

Figure 3. Probabilistic sensitivity analysis: scatterplot.[a] [a]Values reflect combined results across the four tumour types when the OncoExTra test is used in 5% of eligible patients.

therapies is rapidly evolving, the development of new, more efficacious treatments could further highlight the benefits of a test that can be used to determine eligibility. Another factor that can influence the value of testing options is the extent to which they can direct patients to clinical trials. Clinical trials can provide hope to patients who otherwise would not have had treatment alternatives, and can provide clinical benefits to patients earlier, but may also reduce costs to payers. As manufacturers typically provide the therapy to clinical trial investigators without charge, this results in savings to insurers who would otherwise be paying for an approved therapy.

This analysis used recently published inputs and expert opinion to construct a model for projecting the impact of a novel technology and inform decision making. Key differences between tumour types were incorporated, including the epidemiology and available treatment options, and results were presented in a variety of formats to increase the relevance to different stakeholders. While efforts were made to use the best available data and follow best practices in economic modelling, results should be interpreted considering the limitations. Clinical trial enrolment, which was shown to be a highly influential parameter, can vary widely across practice settings. While real world evidence from the literature was used to inform these parameters, they may not reflect the heterogeneity in enrolment rates[73]. In our base case estimate of the costs of treatments following testing, we used list prices without considering any rebates or discounts. In the scenario analysis in which we reduced these prices to capture the impact of discounts and rebates, we found the cost savings associated with increasing use of the OncoExTra test decreased, although overall conclusions remain unchanged. However, this was assuming a consistent rebate across therapies, and based on an assumption as actual rebates typically remain confidential. To the extent

that most prescription drugs are sold below list price, and that price is positively correlated with rebate amount[74], one would expect the more expensive NGS-directed targeted therapies to have deeper discounts than our standard of care regimens. If so, the results presented in this scenario analysis could underestimate the economic value of diagnostic tests that direct more patients to targeted therapies. Additionally, we did not explicitly model the adverse events associated with each oncology treatment or the resulting costs. To the extent that NGS testing is more likely to direct patients to targeted therapies, and targeted therapies may be associated with fewer toxicities than chemotherapy, this omission would lead to an underestimate of the value of NGS testing, The impact of parameter uncertainty was explored in one-way sensitivity analyses in which all cancers were considered together with results reported as the impact on PMPM cost. In future research, we could explore the implications of this uncertainty within each tumour type and on other outcomes such as survival. Uncertainty was also explored in probabilistic sensitivity analyses using 1,000 model iterations. There were few outliers, suggesting that further iterations would be unlikely to alter the results in a meaningful manner. In developing the treatment pathways for patients with each alteration, simplifications needed to be made to allow for representing clinical practice within a model. We relied upon guidelines to inform treatment choices, and expert opinion was used to select a single treatment in cases of multiple recommended therapies. It is unclear what impact this assumption had on model results. In a subsequent study, one could use real-world evidence to assess outcomes for those receiving the OncoExTra test. Such a future analysis could help corroborate these findings or identify key differences between model assumptions and real-world practice. Clinical outcomes associated with each treatment were based on the clinical trials used in approval and reported in the prescribing information, however in some cases these trials were conducted in subgroups that did not exactly match the model population. We limited the scope of the analysis to the first line of therapy where NGS would most likely be considered. To the extent that NGS testing can be used to inform later lines of therapies, this assumption may have underestimated the benefits of testing. However, as patients often progress through multiple lines of therapy, this simplification may have reduced the overall treatment costs for all patients, with the net impact unknown. Similarly, we only considered the first year of costs given turnover often seen in commercial health plans. If patients remain on targeted therapies longer and survival increases, this could lead to higher longer-term costs. As the understanding of the role of genomic alterations in guiding treatment choice is rapidly evolving, our findings are only relevant if the assumptions made at the time the analysis was conducted are valid. To the extent new treatments are approved and additional alterations are identified as being actionable, the value of NGS testing may change. Additionally, we strictly considered NGS testing within solid tumours, but blood-based testing should also be assessed in future models. Tumour profiling approaches currently vary across clinical settings, and we considered only the subset of scenarios in which the decision being made is between no testing or single gene testing versus a comprehensive panel. We did not consider a scenario in which the decision is between WES/WTS testing and targeted panel (<50 genes) testing, which is a limitation of this study. While single-gene testing could be considered an older technology and guidelines suggest against not testing, these practices persist[3,4], therefore there is a need for such an analysis for practitioners who are not conducting tumour profiling. Such evidence will allow clinicians to better understand the trade-offs associated with this current practice compared to using comprehensive panels. Once such analyses are performed, trade-offs across all testing modalities (none, sequential single-gene, targeted panel, and WES/WTS) could be determined.

Conclusions

With an increase in personalized medicine within oncology, there is a need to quickly and efficiently identify patients who are eligible for targeted therapies. Forgoing genomic testing has been shown in this analysis and others to lead to inferior clinical outcomes. The use of single gene testing approaches is more time consuming, may require additional biopsy samples to be taken, and was found in this analysis to increase costs. Key aspects of the OncoExTra test include the ability to detect a wider range of alterations by examining the entire exome, by utilizing RNA and DNA sequencing, and by inclusion of tumour-normal pairing to assure that appropriate patients receive targeted therapies. These benefits should be considered by oncologists when making decisions regarding tumour profiling of, and subsequent therapy recommendations for, their patients, payers when determining reimbursement, and policymakers and clinical associations when making testing recommendations.

Transparency

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