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Original Article

Supporting Biomarker-Driven Therapies in Oncology: A Genomic Testing Cost Calculator

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Abstract

Background: Adoption of high-throughput, gene panel-based, next-generation sequencing (NGS) into routine cancer care is widely supported, but hampered by concerns about cost. To inform policies regarding genomic testing strategies, we propose a simple metric, cost per correctly identified patient (CCIP), that compares sequential single-gene testing (SGT) vs. multiplex NGS in different tumor types.

Materials and Methods: A genomic testing cost calculator was developed based on clinically actionable genomic alterations identified in the European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets. Using sensitivity/specificity data for SGTs (immunohistochemistry, polymerase chain reaction, and fluorescence in situ hybridization) and NGS and marker prevalence, the number needed to predict metric was monetarized to estimate CCIP.

Results: At base case, CCIP was lower with NGS than sequential SGT for advanced/metastatic non-squamous non-small cell lung cancer (NSCLC), breast, colorectal, gastric cancers, and cholangiocarcinoma. CCIP with NGS was also favorable for squamous NSCLC, pancreatic, and hepatic cancers, but with overlapping confidence intervals. CCIP favored SGT for prostate cancer. Alternate scenarios using different price estimates for each test showed similar trends, but with incremental changes in the magnitude of difference between NGS and SGT, depending on price estimates for each test.

Conclusions: The cost to correctly identify clinically actionable genomic alterations was lower for NGS than sequential SGT in most cancer types evaluated. Decreasing price estimates for NGS and the rapid expansion of targeted therapies and accompanying biomarkers are anticipated to further support NGS as a preferred diagnostic standard for precision oncology.

Key words: precision oncology; next-generation sequencing; calculator; biomarker.

Implications for Practice

With the rapid development and approval of targeted therapies and accompanying clinically actionable genomic alterations, the genomic testing cost calculator described herein demonstrates the case for using next-generation sequencing (NGS) and other multiplex diagnostic advances over that of sequential single-gene testing (SGT). By providing an analytical framework that informs local and national policymakers on the value of investing in a transition from sequential SGT to diagnostic, multiplex NGS, patients will benefit from early identification of matched therapies that have proven clinical benefit, leading to improved clinical outcomes and quality of life, while offsetting the incremental costs of sequential SGTs.

Introduction

Rapid progress in identifying oncogenic driver mutations, along with advances in molecular diagnostics, has paved the way for precision oncology, contributing to growing opportunities to develop new therapies targeted against "clinically actionable" genomic alterations (eg, trastuzumab for HER2-positive breast cancer, EGFR inhibitors for *EGFR* mutation-positive non-small cell lung cancer [NSCLC], and Philadelphia chromosome [BCR-ABL fusion] in chronic myelogenous leukemia).[1] The introduction of tumor-agnostic therapies that target genomic driver alterations independent of histology (eg, *NTRK* gene fusions, microsatellite

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instability-high [MSI-H]/deficient mismatch repair [dMMR], tumor mutational burden-high [TMB-H]) has expanded the number of vulnerable tumors with genomic targets.[2–4] Improving patient outcomes has compelled widespread adoption of precision oncology, including some real-world studies that suggest improvement in survival with genomically matched vs. unmatched therapies.[5–8]

The growing compendium of genomic biomarkers has led to guideline recommendations regarding biomarker-guided diagnostics and treatment by the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology, including recommendations on sequencing for approved biomarkers in advanced/metastatic cancers.[9,10]

Next-generation sequencing (NGS) is a high-throughput DNA sequencing technology that offers the advantage of simultaneous analysis of multiple targets from a single-tissue sample, providing comprehensive genomic profiles.[11–13] It is the only method for identifying multigene molecular signatures (eg, TMB,[14] homologous recombination deficiency[15]). With the expected advances in genomic science, targeted panel NGS is poised to become the preferred approach for optimizing time to correct diagnosis and treatment.[16–18] In 2020, ESMO's Precision Medicine Working Group recommended the use of NGS for lung adenocarcinomas and prostate cancers and its consideration for colorectal carcinoma (CRC), cholangiocarcinoma, and ovarian cancers, but not squamous cell lung, breast, gastric, pancreatic, or liver cancers.[19]

Implementation of routine NGS testing has been hindered by the lack of harmonization of clinical infrastructure and insufficient guidance and clinical standardization, while entangled with challenges to equitable reimbursement and the lack of value assessment processes.[20] For many countries, the lack of investment in infrastructure and inadequate reimbursement have hampered its access. Although NGS has demonstrated better cost-effectiveness than single-gene testing (SGT) in NSCLC and CRC,[21,22] data from other tumors are lacking.

For analyses to be meaningful, they must account for factors that affect both costs and probability of a correct diagnosis in a given laboratory, healthcare system, or region. Analyses should be specific to: (1) the tumor, (2) prices and test performance characteristics of selected tests, and (3) a specific set of genomic alterations whose prevalence may vary across regions or treatment settings. To ensure that economic data are appropriately tailored, we developed a novel metric—cost per correctly identified patient (CCIP)—and tested it in a newly developed genomic testing cost calculator that enables stakeholders (eg, clinicians, pathologists, and pathology advisory groups) to compare the cost of targeted panel NGS with the standard practice of sequential SGT in achieving an accurate diagnosis of a patient's genomic alterations. To evaluate the clinical utility of this approach—defined as the net benefit to patients and health systems with regard to clinical outcomes, patient access, and shared decision-making[23,24]—we evaluated the applicability of the calculator based on ESMO–issued NGS recommendations in 2020 for approved targeted therapies.[19]

Materials and Methods

Targeted Literature Review

The scope of the calculator was determined based on ESMO guidelines for selecting tumor types (advanced/metastatic non-squamous NSCLC, squamous NSCLC, breast cancer [mBC], metastatic colorectal carcinoma [mCRC], prostate, gastric [mGC], pancreatic ductal [PDAC], hepatocellular cancers, and cholangiocarcinoma) and genomic alterations of the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) Tier 1 (ie, genomic alterations for which there is an approved targeted therapy).[19] Sensitivity and specificity values were identified using a targeted PubMed search and supplemented by Google searches of gray scientific literature (through December 2021). Relevant citations were reviewed for outcomes relating to sensitivity/specificity of relevant diagnostic tests (fluorescence or chromogenic in situ hybridization [FISH/CISH], PCR, Sanger, small/large-targeted panel NGS, and quantitative PCR [qPCR]) for 34 genetic targets (ESCAT I & II genomic alterations). Raw numbers for each true positive (TP), false positive (FP), true negative (TN), and false negative (FN) were extracted from the literature search and summed to calculate a single sensitivity and specificity measure for each SGT: IHC, PCR/qPCR, FISH, and NGS.

Sensitivity was defined as probability of true positive, and specificity was defined as probability of a true negative, with probability conditioned on being truly positive or truly negative, respectively. Prevalence data were collected from Mosele et al.[19] except for that of *NTRK* fusions and MSI-H. For *NTRK*, prevalence data were collected from Forsythe et al.[25] a meta–analysis that synthesized all prevalence data on *NTRK* derived from a systematic literature review. It also included uncertainty estimates against each prevalence estimate, thus, is believed to provide a more robust estimate. Bonneville et al. was used for prevalence rates of MSI-H.[26] Normanno et al. was used for price estimates for SGTs.[27] Prevalence data are shown in Table 1.

Cost calculations were made for a "base case" scenario using the published prices for each test, with "cost" defined as direct cost of NGS or sequential SGT, and "price" referring to published price estimates for each test. Given that prices can vary between different countries and health systems, calculations were also made using a range of prices that spanned the base case price for each test.

Calculation of Sensitivity and Specificity

Data for sensitivity and specificity, such as TP, FP, TN, and FN, were extracted from eligible papers. Summed TP, FP, TN, and FN values were used to calculate an aggregate sensitivity and specificity parameter for each SGT and NGS. In cases where the first genetic test was a screening test, followed by a confirmatory test, we used a serial testing approach proposed by Parikh et al[29] using the following formulas:

$$\text{Sensitivity}\,[\text{SGT1}] * \text{Sensitivity}\,[\text{SGT2}] = \text{Sensitivity}$$

$$\text{Specificity}\,[\text{SGT1}] + \text{Specificity}\,[1 - \text{SGT1}] * \text{Specificity}\,[\text{SGT2}] = \text{Specificity}$$

Table 1 shows the sequential SGTs used in this study by tumor type.

Definitions and Equations

Assuming that the objective is to maximize the overall predictive accuracy of a test, it was important to identify a metric that accounts for both positive predictive value (PPV) and negative predictive value (NPV) in a target population.[30] When comparing tests, those associated with higher false-positive

Table 1. Prevalence and sequential SGT for select tumor types.[19,25,26,28]

Marker	Prevalence (%)	SGT1	SGT2
Advanced non–squamous NSCLC			
EGFR	15.0	PCR	
ALK fusions	5.0	IHC	FISH
MET exon 14 skipping	3.0	PCR	
BRAF mutations	2.0	PCR	
NTRK fusions	0.17	FISH	
	25.17		
Advanced squamous NSCLC			
NTRK fusions	0.05	FISH	
	0.05		
Metastatic breast cancer			
PIK3CA hotspot mutations	30.0	PCR	
ERBB2 amplifications	17.5	IHC	FISH
MSI-H	1.5	IHC	PCR
NTRK fusions	0.14	FISH	
	49.14		
Metastatic colorectal carcinoma			
BRAF mutations	8.5	PCR	
MSI-H	19.7	IHC	PCR
NTRK fusions	0.26	FISH	
	28.46		
Advanced prostate cancer			
MSI-H	0.6	IHC	PCR
	0.6		
Metastatic gastric cancer			
ERBB2 amplifications	16.0	IHC	FISH
MSI-H	19.1	IHC	PCR
NTRK fusions	0.1	FISH	
	35.20		
Advanced pancreatic ductal adenocarcinoma			
MSI-H	0.1	IHC	PCR
NTRK fusions	0.31	FISH	
	0.41		
Advanced hepatocellular carcinoma			
NTRK fusions	0.05	FISH	
MSI-H	0.8	IHC	PCR
	0.85		
Advanced cholangiocarcinoma			
IDH1 mutations	20.0	PCR	
FGFR2 fusions	15.0	FISH	
MSI-H	1.35	IHC	PCR
NTRK fusions	0.2	FISH	
	36.55		

Note: Values in bold represent the total, combined prevalence of biomarkers for each tumor type.
Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MSI-H, microsatellite instability-high; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; SGT, single-gene testing.

and false-negative rates would be "penalized," while those associated with lower false-positive and false-negative rates would be considered as having better value. These considerations led to use of a metric based on number needed to predict (NNP: number of patients that need to be examined within the patient population in order to correctly predict the diagnosis of 1 person[31]), which was monetarized to create the metric of CCIP.

The input data required to calculate NNP include the following: test sensitivity, specificity, and prevalence/yield in a patient population.[31] Prices can be customized or adapted to a particular lab, healthcare system, or country.

Predictive summary index (PSI) is a metric for measuring test performance for persons who test positive or negative, defined as a total net gain in certainty from a diagnostic test which may be of interest to clinicians, patients, and policy makers/economists.[30] Comparisons of SGT and NGS were conducted using CCIP such that lower values reflect lower total costs to achieve one correctly identified patient.

The following equations were used:

$$\text{CCIP} = \text{NNP cost per patient}$$

$$\text{Cost per patient} = \text{NNP} * \text{cumulative test cost across genomic alteration by tumor type}$$

$$\text{Diagnostic yield} = \text{Sum of FP} + \text{TP across genomic alteration/total test } (N)$$

$$\text{NNP} = \frac{1}{\text{PSI}}$$

$$\text{PSI} = \text{PPV} + \text{NPV1}$$

$$\text{PPV} = \text{true-positive}/\left(\text{true-positive} + \text{false-positive}\right)$$

$$\text{NPV} = \text{true-negative}/\left(\text{true-negative} + \text{false-negative}\right)$$

Calculations of NNP, CCIP, and PSI

We ran a simulation of 1000 lab tests (N). Starting with the most prevalent gene alteration, we generated an algorithm, using the prevalence, recommended test, and its associated sensitivity and specificity. To align with standard laboratory workflow, if the first test was a screening test (eg, IHC), a second (confirmatory) test (eg, PCR/qPCR) was performed on individuals with a positive test result. The matrices were readjusted using the sensitivity and specificity of the serial testing approach. While evaluating each gene alteration sequentially in order of highest to lowest prevalence, all positives (TP + FP) were subtracted from N (total lab tests), and the above procedure was repeated for individuals with a negative test result until the list of ESCAT 1 category genomic alterations was exhausted. A tumor–specific algorithm was then generated to calculate PPV, NPV, PSI, NNP, and consequently, CCIP. CCIP estimates are deterministic; smaller or larger lab cohort sizes will only impact estimates of uncertainty (95% CIs) and can be easily tailored within the model. The diagnostic yield for each tumor was calculated as the sum of positives (TP + FP) over the total number of lab tests (N).

The same process was repeated for NGS, but without repeating procedures used for sequential SGT. The prevalence

across the ESCAT 1 category was summed, and using the relevant sensitivity and specificity, an algorithm was similarly created to calculate the same parameters as SGT.

Parameter uncertainty was assessed by conducting a probabilistic sensitivity analysis (PSA), where probability distributions were used to reflect individual parameter uncertainty and analyzed using 1000 Monte Carlo simulations. For model inputs that varied in PSA, data for sensitivity and specificity were varied using a random draw from a binomial distribution. With each iteration, sensitivity and specificity were calculated. Test price was not varied in the PSA because it is expected to be a lab–specific, fixed parameter with a user-modifiable input. For *NTRK* prevalence, we calculated a standard error using the reported CI in Forsythe et al.[25] and a random draw from a beta distribution was used in the PSA. For other prevalence proportions, we assumed 20% of the mean as a measure of standard error and repeated the above procedure. PSA results were used to generate 95% uncertainty intervals by calculating the 2.5th and 97.5th percentiles across the PSA iterations.

Results

Test Costs, Sensitivity, and Specificity

The objective for the genomic testing cost calculator was to estimate the CCIP using NGS vs. sequential SGT. A targeted literature search was conducted to identify publications on sensitivity and specificity of IHC, PCR/qPCR, FISH, and NGS (Table 2). Normanno et al was used for estimating the price of each test.[27]

For IHC, sensitivity was estimated at 92.54%, and specificity at 86.45%. The price of IHC screening was estimated at €242 per test. Alternate scenarios were calculated at €200, €300, and €350. When IHC was followed by PCR, test sensitivity was 86.26% and specificity was 99.49%. When IHC was followed by FISH, test sensitivity was 82.90% and specificity was 99.98%.

For FISH, sensitivity was estimated at 89.58% and specificity at 97.67%. The price of FISH was estimated at €664 per test.[27] Alternate scenarios were calculated at €600, €700, and €750.

For PCR/qPCR, sensitivity was estimated at 93.41% and specificity at 94.79%. The price of PCR/qPCR was estimated at €218 per test.[27] Alternate scenarios were calculated at €200, €250, and €300.

For NGS, sensitivity was estimated at 84.98% and specificity at 98.50%. Estimates from studies suggest much higher sensitivity rates for NGS.[75–78] The effect of assuming higher sensitivity for NGS tests would improve CCIP relative to SGT. The price of NGS testing was estimated at €593 for an up to 50-gene panel.[27] Alternate scenarios were calculated at €500, €800, and €1000.

Impact of Test Specificity and Prevalence on Number Needed to Predict a Correctly Identified Patient

Figure 1 shows the impact of test specificity, sensitivity, and prevalence of a given genomic alteration on the NNP. At the highest sensitivity and specificity levels for a given test, the NNP remains low, independent of mutational prevalence. However, as specificity of a test decreases, the NNP becomes inversely proportional to the mutational prevalence, such that NNP is higher for low prevalence alterations and vice versa. For tests with low specificity, NNP is also inversely proportional to the test sensitivity, such that at a given mutational prevalence, NNP increases as test sensitivity decreases. At low mutational prevalence (eg, 1%), NNP is high, while at high prevalence (eg, 20%), NNP remains low, regardless of sensitivity or specificity of the test.

CCIP Using Sequential SGT vs. NGS

Using the base case estimates, a more favorable CCIP was observed using NGS vs. SGT, for advanced non-squamous NSCLC (€1983 for sequential SGT vs. €658 for NGS), mBC (€1202 vs. €695), mCRC (€1226 vs. €659), mGC (€1202 vs. €695), and cholangiocarcinoma (€1661 vs. €667) (Fig. 2; Table 3). Cost differences between sequential SGT and NGS were greatest in non–squamous NSCLC, which had the highest number of clinically actionable mutations.

Lower costs were also observed at base case for advanced squamous NSCLC (€35 259 vs. €21 637), hepatocellular carcinoma (€4596 vs. €1825), and PDAC (€8190 vs. €3153), but with overlap in CIs (Table 3). The high relative costs for squamous NSCLC for either sequential SGT or NGS can be attributed to the low prevalence (0.17%, Table 1) of *NTRK* gene fusions found in this cancer type, which drives the NNP higher (Fig. 1).

CCIP at base case was lower for sequential SGT than NGS in advanced prostate cancer (€540 vs. €2340), for which MSI-H was the only actionable marker. The cost difference

Table 2. Summary of baseline inputs into the genomic testing cost calculator by Tier 1 (A, B, or C) by tumor.

Test strategy	Gene test	Price per test (€)	Sensitivity (%)	Specificity (%)	Sources
Sequential SGT	Initial IHC	242	92.54	86.45	32–44
	IHC followed by PCR		86.26	99.49	29
	IHC followed by FISH		82.90	99.98	29
Sequential SGT	FISH	664	89.58	97.67	45–49
Sequential SGT	PCR/qPCR	218	93.41	94.79	33,45,50–62
NGS	NGS Panel (up to 50 genes)	593	84.98	98.50	54,60,61,63–74

Note: Sensitivity and specificity were taken from published, multi-tumor studies. Given the small sample sizes in specific tumors, the overall study test characteristics were used in this analysis.
Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction; qPCR, quantitative polymerase chain reaction; SGT, single-gene testing.

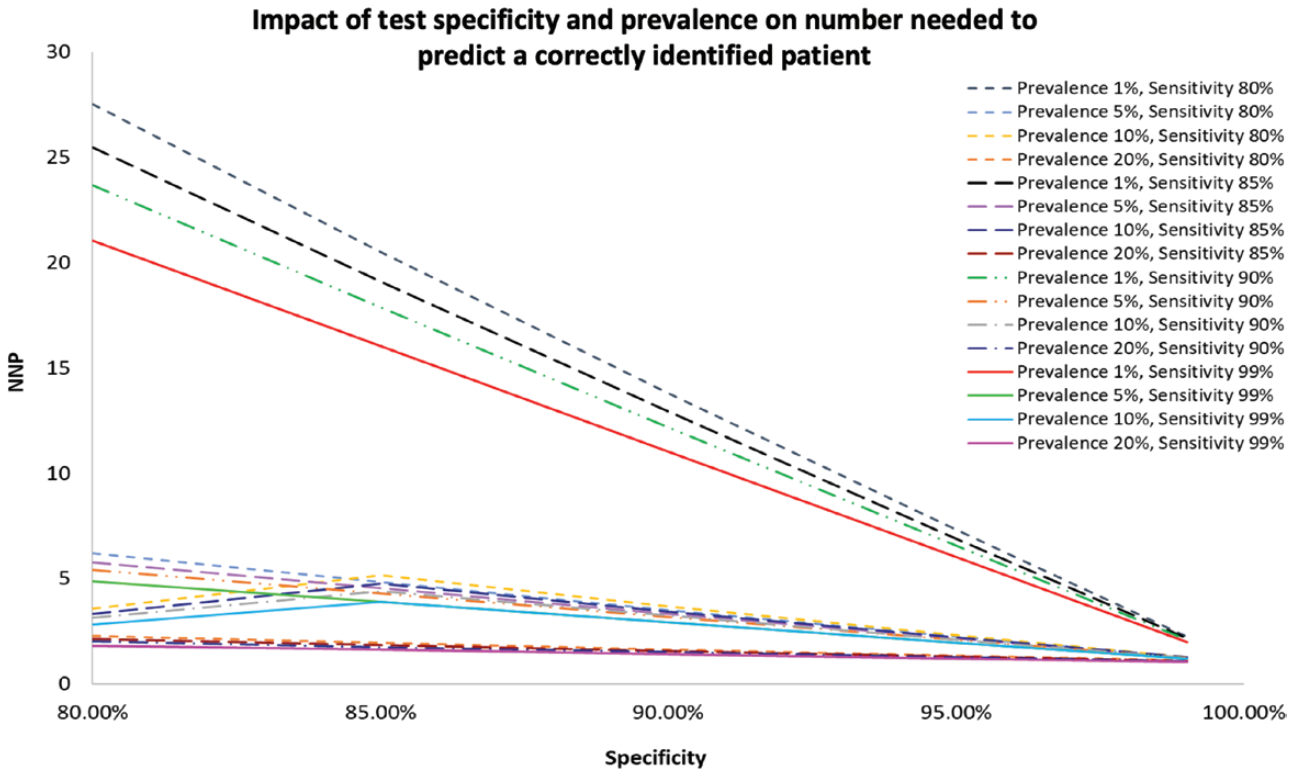

Figure 1. Impact of test specificity and prevalence on number needed to predict a correctly identified patient.

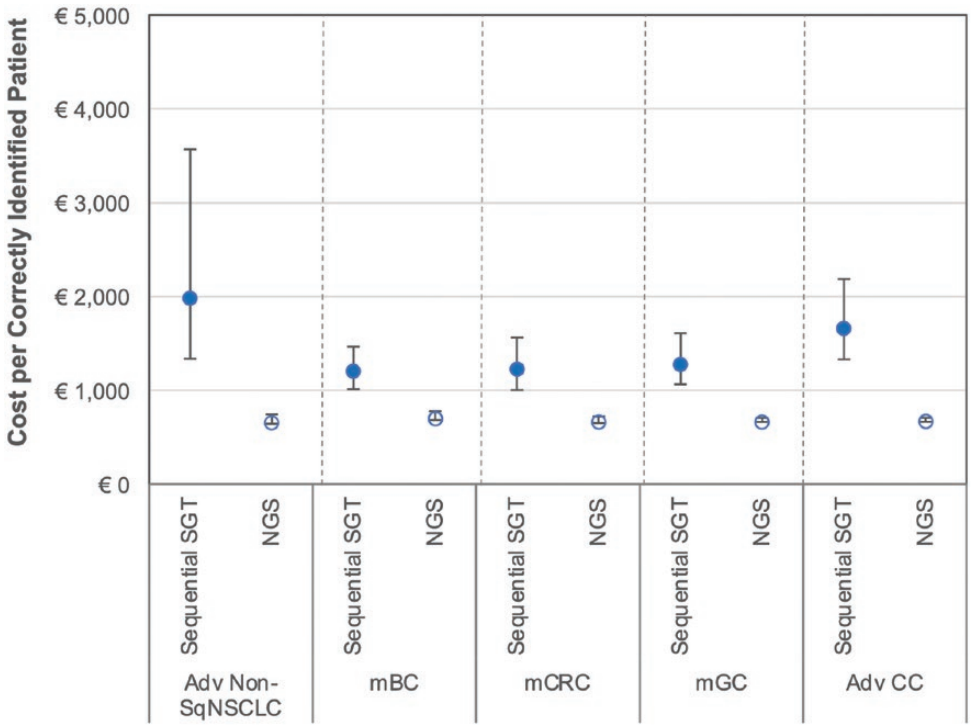

Figure 2. Tumor types favoring next-generation sequencing (NGS) over sequential single gene testing (SGT) in cost per correctly identified patient. Error bars, 95% CI. Adv, advanced; CC, cholangiocarcinoma; mBC, metastatic breast cancer; mCRC, metastatic colorectal carcinoma; mGC, metastatic gastric cancer; sqNSCLC, squamous non–small cell lung cancer.

for this cancer type would become negligible if the diagnostic yield was increased, for example, if both ESCAT 1 and 2 were to be included. When genomic alterations from the ESCAT 2 category are included, the CCIP with NGS further decreases, such that it becomes lower than sequential SGT for advanced prostate cancer (data not shown).

Table 3. Cost per correctly identified patient using a sequential SGT or NGS to achieve a comprehensive genomic profile in Europe.

Tumor	Diagnostic yield (%)	PSI (%)	Number needed to predict	Cost per patient (€)	Cost per correctly identified patient (€)	95% CI (lower, upper)
Advanced non–squamous NSCLC						
Sequential SGT	31.59	66.34	1.51	1315.43	1982.79	[1332.26-3462.41]
NGS	22.52	90.12	1.11	593.00	658.00	[643.62-729.6]
Advanced squamous NSCLC						
Sequential SGT	2.37	1.88	53.10	664.00	35 259.42	[4205.33-21248]
NGS	1.55	2.74	36.49	593.00	21 636.63	[1284.83-8895]
Metastatic breast						
Sequential SGT	43.16	88.32	1.13	1061.64	1202.10	[1010.36-1452.98]
NGS	42.52	85.36	1.17	593.00	694.71	[683.01-779.17]
Metastatic colorectal						
Sequential SGT	28.65	79.52	1.26	974.92	1225.95	[1001-1548.42]
NGS	25.26	90.02	1.11	593.00	658.74	[650.16-720.71]
Advanced prostate						
Sequential SGT	1.02	50.48	1.98	272.58	539.98	[214.05-2495.9]
NGS	2.01	25.34	3.95	593.00	2340.47	[NE-12725.98]
Metastatic gastric						
Sequential SGT	29.67	90.90	1.10	1158.50	1274.47	[1060.29-1601.48]
NGS	30.89	89.19	1.12	593.00	664.84	[663.15-702.48]
Advanced pancreatic ductal						
Sequential SGT	3.18	11.38	8.79	931.77	8189.74	[NE-32623.53]
NGS	1.85	18.81	5.32	593.00	3153.24	[NE-11860]
Advanced hepatocellular						
Sequential SGT	3.54	20.25	4.94	930.45	4595.59	[1906.64-28453.55]
NGS	2.21	32.50	3.08	593.00	1824.75	[741.25-13967.82]
Advanced cholangiocarcinoma						
Sequential SGT	36.46	81.45	1.23	1352.50	1660.61	[1336.78-2165.45]
NGS	32.02	88.94	1.12	593.00	666.71	[664.91-702.24]

Note: Diagnostic yield is the expected percentage of all ESCAT Tier 1 genetic alterations within the tumor category as found in the ESMO NGS guideline recommendations.
Abbreviations: NE, not estimable; NGS, next-generation sequencing; NSCLC,non-small cell lung cancer; SGT, single-gene testing.

Alternate scenarios considering a range of prices showed the same general trends across all scenarios, with incremental changes in the magnitude of difference between NGS and SGT related to the incremental change in the price estimate of each test (Table 4). For example, when NGS price was increased to €1000, CCIP for squamous NSCLC became higher with NGS than sequential SGT (€36 487 vs. €35 259, respectively) and differences between sequential SGT and NGS became negligible (~€31) for metastatic breast cancer. Table 4 illustrates hypothetical examples of cost differentials at various price estimates for each test, compared with the base case scenario.

Discussion

The need for NGS or other multiplex diagnostics in routine cancer care is widely recognized, but impeded by concerns about cost. We propose the use of a simple metric and analytic framework to inform national policies regarding genomic testing strategies, illustrating the methodology in a comparison of a sequential SGT algorithm vs. NGS. To demonstrate use of the calculator, we applied NGS recommendations from ESCAT 1 to compare sequential SGT vs. NGS and showed that CCIP favored NGS in advanced/metastatic non-squamous NSCLC, mBC, mCRC, mGC, and cholangiocarcinoma. CCIP also favored NGS for advanced squamous NSCLC, PDAC, and hepatocellular carcinoma, but with overlapping CIs. For prostate cancer, CCIP favored sequential SGT over NGS.

Development of the genomic testing cost calculator was based on previously reported prevalence and cost.[19,25–27] Mosele et al. was selected to provide a EU perspective on NGS, based on ESMO recommendations.[19] Forsythe et al. was a systemic literature review and meta–analysis that provided the most robust estimate of *NTRK* prevalence to date.[25] For price estimates, Normanno et al. was chosen for providing representative European estimates that would facilitate comparisons for this study,[27] but estimates for comparisons may be adapted by the user to reflect individual cases or support lab practices. We developed the calculator to allow full cost comparisons involving initial setup and maintenance costs for a given diagnostic test (eg, purchasing of equipment,

Table 4. A model of CCIP differences from use of sequential SGT vs. NGS, based on different price estimates for each test.

		Advanced non–squamous NSCLC	Advanced squamous NSCLC	Metastatic breast cancer	Metastatic colorectal carcinoma	Advanced prostate cancer	Metastatic gastric cancer	Advanced pancreatic ductal adenocarcinoma	Advanced hepatocellular carcinoma	Advanced cholangio-carcinoma
		CCIP differential (€) between sequential SGT vs. NGS (= total cost of NGS—cost of sequential SGT)								
Base case vs. NGS[a]		−1324.79	−13 622.79	−507.39	−567.22	1800.50	−609.64	−5036.50	−2770.84	−993.90
PCR price estimate (€)	200	−1255.97	−13 622.79	−485.23	−538.74	1805.50	−604.72	−5014.93	−2758.52	−969.66
	250	−1447.13	−13 622.79	−546.79	−617.84	1791.60	−618.38	−5074.84	−2792.73	−1036.99
	300	−1638.29	−13 622.79	−608.36	−696.94	1777.71	−632.04	−5134.75	−2826.93	−1104.33
IHC price estimate (€)	150	−1209.93	−13 622.79	−373.28	−464.67	1982.75	−420.66	−4227.87	−2327.22	−919.04
	200	−1272.35	−13 622.79	−446.17	−520.40	1883.70	−523.36	−4667.34	−2568.32	−959.72
	300	−1397.20	−13 622.79	−591.94	−631.86	1685.60	−728.77	−5546.29	−3050.51	−1041.09
	350	−1459.62	−13 622.79	−664.82	−687.60	1586.55	−831.48	−5985.76	−3291.61	−1081.78
FISH price estimate (€)	300	−860.36	5706.17	−188.94	−232.09	1800.50	−216.14	−1856.17	−973.01	−352.46
	400	−987.95	396.01	−276.43	−324.16	1800.50	−324.24	−2729.89	−1466.92	−528.68
	600	−1243.13	−10 224.29	−451.40	−508.29	1800.50	−540.45	−4477.32	−2454.73	−881.12
	700	−1370.72	−15 534.45	−538.89	−600.36	1800.50	−648.55	−5351.04	−2948.64	−1057.34
	750	−1434.51	−18 189.52	−582.63	−646.39	1800.50	−702.61	−5787.89	−3195.6	−1145.45
NGS price estimate (€)	500	−1427.98	−17 016.06	−616.34	−670.52	1433.44	−713.90	−5531.02	−3057.01	−1098.46
	700	−1206.06	−9718.71	−382.04	−448.35	2222.81	−489.67	−4467.53	−2441.58	−873.6
	800	−1095.10	−6070.04	−264.89	−337.27	2617.49	−377.56	−3935.79	−2133.87	−761.17
	1000	−873.18	1227.31	−30.59	−115.10	3406.86	−153.33	−2872.3	−1518.44	−536.31
	1300	−540.29	12 173.32	320.87	218.16	4590.91	183.01	−1277.07	−595.29	−199.02
	1500	−318.37	19 470.67	555.17	440.33	5380.28	407.24	−213.58	20.14	25.84
	1800	14.51	30 416.68	906.62	773.59	6564.33	743.58	1381.65	943.28	363.13

[a]For base case estimates: €218 for PCR, €242 for IHC, €664 for FISH, and €593 for large panel NGS.
Abbreviations: CCIP, cost per correctly identified patient; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next–generation sequencing; NSCLC, non–small cell lung cancer; PCR, polymerase chain reaction; SGT, single–gene testing.

laboratory and IT infrastructure, personnel, validation, etc), as well as the ongoing costs (eg, sequencing kits and flow cells) of validated, genomic tests. Of note, labor costs, initial infrastructure, and ongoing genomic testing costs vary significantly across countries, and the calculator allows individual labs and hospitals to use comprehensive local costs as input source. As such, these results compare the costs of validated diagnostic tests with an approach consistent with prior cost-effectiveness analyses of genomic tests. To illustrate this point, CCIPs were calculated using a range of published prices for each test. While some variability was observed at the different SGT cost estimates, the same general trends were seen as base case. At the higher cost estimates for NGS, the cost differential from SGTs became smaller, and vice versa.

As testing strategies have shifted in favor of NGS, its perceived high cost has raised concerns about its value and sustainability, particularly its budget impact compared to SGT.[22] Our results are largely consistent with previous cost-effectiveness studies on NGS and SGT. In a study investigating costs of different diagnostic approaches in 3 Italian hospitals, Pruneri et al. applied several different scenarios (eg, current testing pathway, minimum set per local guidelines, and anticipated future mutational load) for patients with advanced NSCLC or mCRC and found that the NGS-based strategy was cost-saving in all scenarios except one, where the additional cost for NGS was modest.[22] Savings per patient were higher in scenarios where NGS encompassed a more comprehensive set of mutations, attributed both to the volume of detectable alterations via NGS and to the reduction in personnel time needed. In another analysis from the perspective of the US Centers for Medicare & Medicaid Services (CMS) or US commercial payers, an economic impact model showed that, compared with SGT, NGS for metastatic NSCLC was associated with cost savings for both CMS and commercial payers, while also providing shorter time-to-test results by 2-3 weeks.[21]

In contrast, despite the importance in advancing national policies regarding optimal use of NGS in routine cancer care, some cost-effectiveness analyses for genomic testing approaches have been limited and/or lacked gravitas to decision makers because of the nature of rapidly changing key parameters, such as test prices, test performance characteristics (eg, sensitivity and specificity), and the number and type of clinically actionable biomarkers.[79–81] For example, a 2020 analysis in Brazil of cost-effectiveness of SGT vs. NGS for *EGFR*, *ALK*, and *ROS1* in NSCLC concluded that NGS-facilitated identification was not cost-effective due to an incremental $3479 per correct case detected;[82] however, the limited number of biomarkers included in that study was insufficient to accurately estimate the cost differential between diagnostic methods. On the other hand, a study in Singapore found that use of a targeted NGS panel for DNA alterations (29 selected genes including *BRAF*, *EGFR*, *ERBB2*, and *TP53*) and an RNA fusion panel (*ALK*, *ROS1*, and *RET*) resulted in identification of an additional 1% of patients with actionable alterations, without significant added costs.[83]

The development of our genomic testing cost calculator and findings from its initial application have important implications for the oncology community, not only in terms of economic value but also for informing policy and how physicians approach diagnostics, both in clinical practice and in clinical trial design. Within the current clinical landscape, where there is a drive to develop companion diagnostics in parallel with clinical trials, offering a model that can estimate cost differentials in trials will facilitate adoption and access to both drug and diagnostic approaches following marketing authorization. As illustrated in the cancer types selected for our analysis, NGS provided favorable CCIP for some but not all cancers, with the differences related to the number of biomarkers tested, their prevalence within a given cancer type, and the sensitivity and selectivity of each test. In the US, NGS testing has increased to 48% for advanced NSCLC, but remains <20% for mCRC, mBC, and advanced melanoma. For those who remain skeptical about value of NGS, the genomic testing cost calculator makes comparative cost calculations accessible to clinicians, guideline developers, and other decision makers who otherwise may not have specialized health economics training. Pruneri et al. has suggested that the increased adoption of NGS over SGT can lead to cost reduction, particularly at a given threshold of patient numbers or molecular alterations.[22] Furthermore, the anticipated growing number of molecular alterations will also increase the potential savings generated by NGS.[22] Indeed, prevalence data collected from Mosele et al. in this study are conservative and perhaps outdated, given the growing availability of targeted therapies and potential for increased yield via NGS.[19]

Recent years have seen a growing number of clinically actionable biomarkers: 58% of 62 cancer drugs approved by FDA and 59% of 46 cancer drugs authorized by EMA in the last 5 years have been granted pharmacogenomic labels.[84–86] This rapid expansion of biomarker-guided therapies is apparent even in the short timeframe from when the ESCAT rankings were published in August 2020.[19] For example, at time of the ESMO NGS publication, there were 5 genomic alterations (*EGFR*, *ALK*, *MET*, *BRAF*^{V600E}, and *NTRK*) for which targeted therapies had been approved for NSCLC by FDA and/or EMA. Over the last 2 years, at least 11 new therapies have been approved that depend on testing of genomic/molecular alterations, 7 of which target ESCAT 1 markers, 3 which target non-ESCAT 1 markers, and 1 indicated for NSCLC without certain genomic alterations.[87,88] Given the pace and volume of emerging new therapies that target genomic alterations, we believe the CCIP differences between NGS and single SGTs presented in our analysis are conservative and will increase in favor of NGS over time.

Along with the expansion in biomarker-specific labels, the treatment landscape has shifted towards use of precision oncology agents that target specific actionable genomic alterations operating in many cancer types ("tumor agnostic"; eg, tumor–agnostic therapies for *NTRK* gene fusions, MSI-H/dMMR, TMB-H, BRAF^{V600E}) rather than the classic one cancer type—one alteration—one drug approach. Furthermore, the number of late stage, multi–indication trials has increased, along with the potential for increased use of pan–tumor therapies.[89] The interest in genomic–based diagnostics is also evident in new initiatives, such as Europe's Beating Cancer Plan—which recently invested €4 billion in the Knowledge Centre on Cancer, Genomics for Public Health, and Partnership on Personalized Medicine, among other groups.

Indeed, as the number of clinically actionable biomarkers continues to grow, evolving guidelines and new initiatives have kept pace to accelerate genomics for research, prevention, diagnostics, and treatment. In a consensus report published in 2020 by a panel of international experts from Europe, US, and Asia, *NTRK* fusion testing was suggested for all patients with advanced solid tumors without other known actionable and driver gene mutations, with testing to occur both before

and during standard treatment.[2] MSI/MMR testing was recommended for patients with advanced solid tumors with high incidence of MSI-H/dMMR, and weighing the economic considerations of testing with potential clinical benefit, it was suggested that advanced tumors with low incidence of MSI/dMMR should also be considered to inform treatment decisions. Additional guidance is anticipated following the recent FDA approval of dabrafenib plus trametinib for unresectable or metastatic solid tumors with $BRAF^{V600E}$ mutation.[90] NGS testing has been described as having potential to become the standard-of-care for determining eligibility for treatment with PD-(L)1 inhibitors and for assessing tumor responses.[91,92]

A limitation of the calculator is the assumption that it treats false-positives and false-negatives equally, consequences of each may be different and may include suboptimal or incorrectly assigned treatments to patients, resulting in different outcomes and costs over time. By combining values for TP/FP and TN/FN to calculate a single value for sensitivity and specificity parameters for each SGT, neither differences by tumor type/gene alteration nor uncertainty in PSA are taken into account. While the NNP metric takes these rates into consideration, subsequent treatment decisions and their impact on patients were considered out of scope for the calculation and not taken into account. Further research on such impact is warranted.

Evolving treatment guidelines reflect an unprecedented expansion in precision oncology. Recent approvals of molecularly targeted therapies and expanded use of basket trials are uncovering genomic signatures that can inform treatment decisions and improve prediction of outcomes. This rapid pace of change points toward a new era where NGS will enable more efficient oncology testing with demonstrated value than the multiplicity of tests required for multiple single-gene alterations. Indeed, while the genomic testing cost calculator described herein provides comparative benchmarks from different diagnostic methodologies, it can be expanded or tailored to further substantiate the need for adopting NGS or other multiplex diagnostic advances to optimize individual benefits of biomarker-driven, tumor-agnostic precision oncology. Investing in a transition to NGS offers the opportunity to optimize personalized patient care via early identification of efficacious matched therapies and achieve improvements in patient outcomes and quality of life, and cost offsets through minimizing sequential SGTs and ineffective therapeutic regimens and other treatments.

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Conflict of Interest

Albrecht Stenzinger: member of the advisory board/speaker's bureau for Aignostics, Amgen, AstraZeneca, Bayer, BMS, Eli Lilly, Illumina, Incyte, Janssen, MSD, Novartis, Pfizer, Qlucore, Roche, Seattle Genetics, Takeda, and Thermo Fisher Scientific, and receiving grants from Bayer, BMS, Chugai, and Incyte. Brian Cuffel and Noman Paracha: employees and stockholders of Bayer. Eric Vail: employee and stockholder of LungLife AI, receives honoraria from Thermo Fisher Scientific and Illumina, serves in a consulting/advisory role for Tempus Labs, Inc. and PierianDx, and is a member of the speakers' bureau for Bayer, Eli Lilly, AstraZeneca, and Janssen Oncology. Jesus Garcia-Foncillas: reported consulting/advisory, honoraria, and speaker roles with Abbott, Amgen, Astellas, AstraZeneca, Biocartis, Boehringer Ingelheim, BMS, Bayer, Celgene, Eisai, Foundation Medicine, GSK, Hospira, Janssen, Lilly, Merck Serono, MSD, Novartis, Pharmamar, Pfizer, Roche, Sanofi, Servier, Sysmex, and Tesaro. Clifford Goodman: employee of The Lewin Group, Inc., which is a business unit of Optum, a wholly owned subsidiary of UnitedHealth Group, is a stockholder of UnitedHealth Group, and has consulting/advisory roles as part of employment for The Lewin Group for Bayer, BioMarin, Concert Genetics, Magellan Health, Medtronic, Merck, Sandoz, and Roche. Ulrik Lassen: received research grants from BMS, GSK, Pfizer, and Roche, and serves on the advisory boards for Bayer, Novartis, and Pfizer. Gilles Vassal: advisor to Bayer, BMS, Roche/Genentech, Celgene, Debiopharm, Incyte, Ipsen, Lilly, Pfizer, Servier, and Takeda, without personal remuneration. Sean D. Sullivan: serves on the advisory board for Bayer, Incyte, Novartis Gene Therapy, and Neurocrine, and has received grants from Bayer, Incyte, Novo Nordisk, and Neurocrine.

Author Contributions

Conception/design: A.S., J.G.F., C.G., U.L., G.V. Provision of study material or patients: B.C., N.P. Collection and/or assembly of data: B.C., N.P. Data analysis and interpretation: All authors. Manuscript writing: A.S., B.C., N.P. Final approval of manuscript: All authors.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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