CANCER GENOMICS

review articles

Comprehensive Review on the Clinical Impact of Next-Generation Sequencing Tests for the Management of Advanced Cancer

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abstract

PURPOSE This review summarizes the published evidence on the clinical impact of using next-generation sequencing (NGS) tests to guide management of patients with cancer in the United States.

METHODS We performed a comprehensive literature review to identify recent English language publications that presented progression-free survival (PFS) and overall survival (OS) of patients with advanced cancer receiving NGS testing.

RESULTS Among 6,475 publications identified, 31 evaluated PFS and OS among subgroups of patients who received NGS-informed cancer management. PFS and OS were significantly longer among patients who were matched to targeted treatment in 11 and 16 publications across tumor types, respectively.

CONCLUSION Our review indicates that NGS-informed treatment can have an impact on survival across tumor types.

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INTRODUCTION

Next-generation sequencing (NGS) assays are rapidly becoming standard in the management of patients with advanced cancer. NGS assays use high-throughput DNA sequencing technology to sequence the entire genome, the whole exome, or exons of selected genes (targeted panels).[1] Some NGS assays use tumor tissue, whereas others use blood; some sequence RNA in addition to DNA; some compare DNA from tumor cells with normal germline cells to identify somatic mutations; and some are targeted for a specific class of tumors, whereas other larger gene panels may be used for multiple tumor types.[1]

The introduction of NGS assays has allowed the cancer genome to be systematically studied, providing oncologists with more comprehensive, precise, predictive, prognostic, and diagnostic information.[2] NGS-based gene panel tests have successfully identified driver mutations in lung cancers,[3,4] colorectal cancer,[5] and breast cancer,[3] which in turn has resulted in the development and use of targeted treatments that are associated with improved outcomes.[6-8] Other studies have demonstrated that genomically guided therapy is associated with increased survival across cancer types[6,7] although basket clinical trials (which enroll patients with the same mutation expressed in different tumor types) show that response to targeted therapies may vary by tumor type.[9]

NGS tests are increasingly used to inform targeted therapy in oncology.[10-14] In 2020, 28 targeted therapies identified via NGS were Food and Drug Administration (FDA)–approved,[2,10,15] and many clinical trials now use NGS to define patient eligibility.[16,17] ASCO recently released a Provisional Clinical Opinion (2022) outlining recommendations for genomic testing in patients with metastatic or advanced cancers.[10] These include recommending multigene panels and/or testing to identify gene fusions when the results could identify targets matched to approved therapeutic agents. However, the clinical utility of NGS assays has not yet been broadly summarized in the literature.

In this study, we sought to identify and summarize recent evidence on the potential impact of NGS testing and NGS-informed cancer management in adult patients with advanced cancer in the United States. We present evidence on the clinical outcomes of NGS testing by comparing progression-free survival (PFS) and/or overall survival (OS) in patients who received targeted therapy on the basis of NGS testing versus patients who did not receive targeted therapy.

METHODS

We conducted a single screen comprehensive review to identify literature on PFS and OS of adult (18 years and older) patients with advanced (stages III or IV), metastatic, refractory, or recurrent cancer in the United States

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Cancer is caused by mutations to genes. However, the mutations that are present differ across patients, even for the same type of cancer. Identification of the specific mutations present in an individual's cancer allows for the use of treatments that are specifically matched to those mutations.

Knowledge Generated

In this project, we ask whether identifying actionable mutations and using matched therapies improve cancer patient outcomes, specifically prolonging the time until the cancer progresses (progression-free survival) and/or increasing overall survival. We examined studies that compared patients with advanced cancers in the United States who received treatments selected using next-generation sequencing tests (which allow identification of mutations) with those who did not receive matched treatments.

Relevance

Overall, we found that patients with cancer who were matched to targeted treatment had more time before their cancer returned and lived longer.

receiving somatic NGS testing to guide treatment selection or enrollment in clinical trials. We searched PubMed on August 6, 2021, to identify English language articles published over a 5-year span (August 7, 2016 through August 6, 2021). We also searched Embase on November 29, 2021, to identify relevant conference abstracts presented in 2020 and 2021 at the following conferences: ASCO Annual Meeting, European Society for Medical Oncology (ESMO) Congress, and International Association for the Study of Lung Cancer World Conference on Lung Cancer. Search terms were developed with support from a medical librarian and are available in the Appendix.

Eight reviewers independently screened publications in two phases (an initial title and abstract screen followed by a full-text screen) using DistillerSR (version 2.35),[18] a systematic review program (Evidence Partners, Ottawa, Canada). We included articles that compared PFS and OS in adult patients in the United States (even if pooled with data from patients outside the United States) who received NGS-informed cancer management (ie, matched to targeted therapies or enrolled in clinical trials on the basis of NGS test results) versus who did not (ie, definition varied by article or was not specific; may include patients who did not receive NGS testing, in whom no identifiable mutations were identified, or who refused matched treatment) for the following cancers: breast, central nervous system (including brain, spinal cord), cholangiocarcinoma, colorectal, hematologic (including leukemias, lymphomas), hepatobiliary (including gallbladder, liver), melanoma, non–small-cell lung cancer (NSCLC), ovarian, pancreatic, prostate, sarcoma, and urothelial (including bladder). Publications that presented data on multiple (two or more) tumor types (pan-cancer) were included if at least one of these cancer types of interest was included. We excluded case studies, review articles, and editorials/opinion articles. We reviewed included abstracts and papers to confirm that there were no overlapping studies.

We abstracted the following: study design, study population, lines of therapy received before NGS testing, clinical trial enrollment, number of patients who received NGS testing and targeted therapies, OS, PFS, tumor response, type of NGS test received, and NGS test characteristics (eg, number of genes sequenced and source type). Mean or median PFS and OS in days, weeks, or years were converted to months (by dividing days by 30.5, dividing weeks by 4.5, and multiplying years by 12). Hazard ratios (HRs), 95% CI, and other effect size measures were abstracted when available. Statistical significance was defined as $P < .05$. We did not abstract information on tumor histology or grade.

The original intent of our study was descriptive, and by including multiple cancer types, we recognized comparisons that would be difficult to make. Therefore, we did not conduct any statistical data synthesis (no meta-analysis, exploration of heterogeneity, nor sensitivity analyses) and no analytic code was generated. No bias or certainty assessments were conducted. We did not register this review. An internal protocol was developed (including information outlined above and a data abstraction form), which is not publicly available. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[19]

RESULTS

Bibliometric Results

We identified 5,854 unique journal articles (Fig 1) and 621 conference abstracts (Fig 2). After two screening phases and data abstraction, 29 journal publications[20-48] and two nonoverlapping conference abstracts[49,50] fit the criteria and were included.

Twenty-one publications (68%) used retrospective observational cohort designs (Table 1). Five (16%) used prospective observational cohort designs, and five (16%) were nonrandomized clinical trials. A mean of 804 and median of 185 patients were included (range, 35-5,688). Eighteen

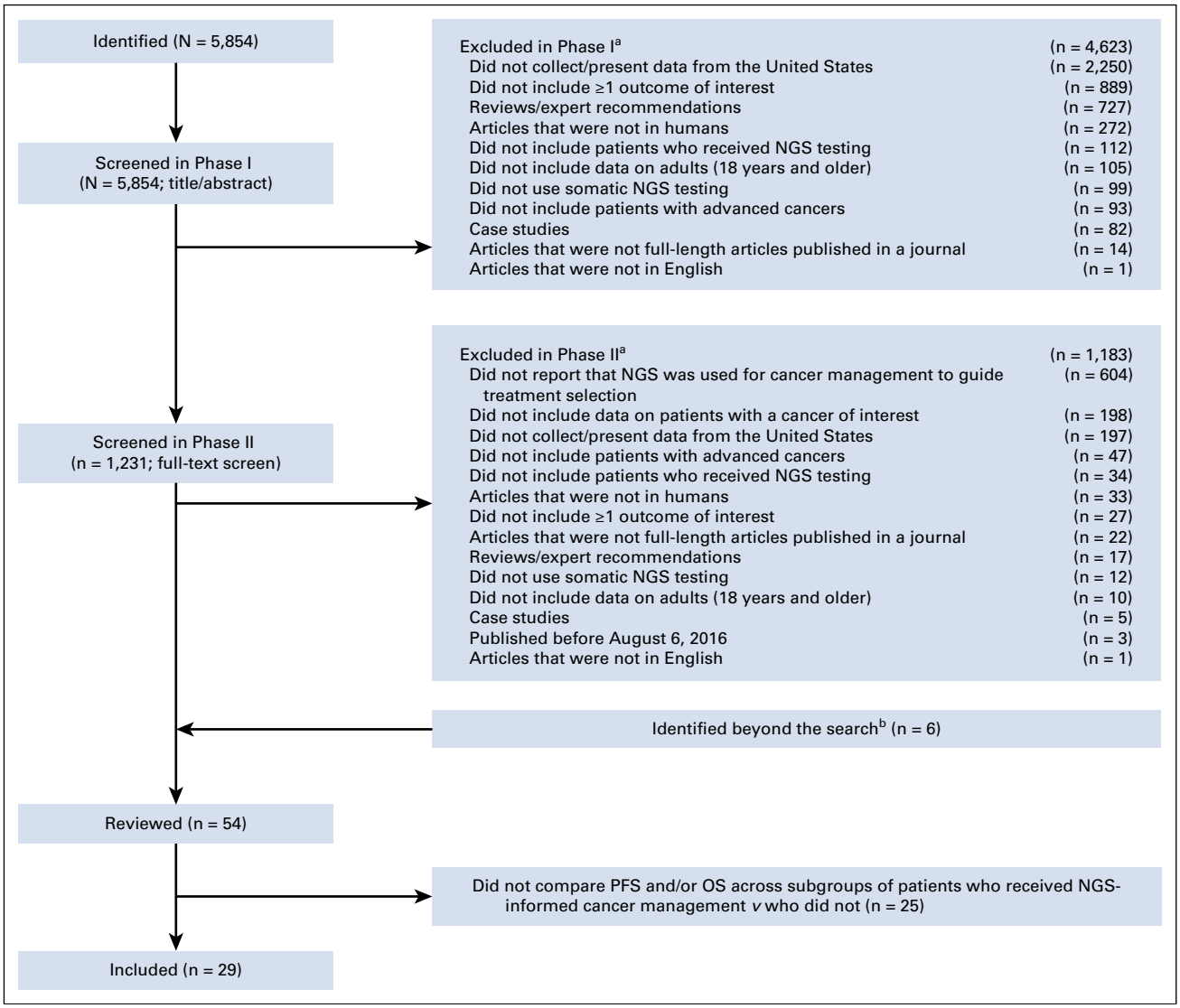

FIG 1. Flow diagram (journal publications). [a] Only one reason for exclusion was required to exclude a study during the screening process although more than one reason could be selected. Therefore, reasons for exclusion do not sum to the number excluded. [b] Refs. 38, 39, 62-65. NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival.

publications presented data on two or more tumor types. The other 13 reported on single cancers: three NSCLC, two breast, two pancreatic, two biliary tract, two colorectal, one sarcoma, and one liver/hepatocellular. Sixteen publications reported the lines of therapy that patients received before NGS testing, only eight of which reported a median number of lines of therapy (range, 0-4).

Seven publications[24,27,32,36-38,46] reported on patients enrolled in clinical trials as the recommended cancer management per NGS testing (Table 1). In one study,[37] all patients who were matched to targeted treatment on the basis of NGS were enrolled in a clinical trial. In the remaining, only a minority of patients (mean, 14%; range, 2%-29%) were enrolled in clinical trials informed by NGS test results.

Survival Results

The number of patients who received NGS testing and were matched to targeted treatment (ie, therapy or clinical trial) as a result is reported in Table 2. In 24 publications, the proportion of patients who were matched to targeted treatment could be calculated. Among these, a mean of 29% and a median of 25% (range, 2%-66%) of patients who received NGS testing were matched to targeted treatment. The number of patients matched to targeted treatment ranged from 7 to 711 (mean, 143; median, 40). Reasons for not receiving matched treatment are reported in Appendix Table A3 and included no therapies available, physician chose alternate treatment, patient progressed or died, patient declined treatment, or patient was lost to

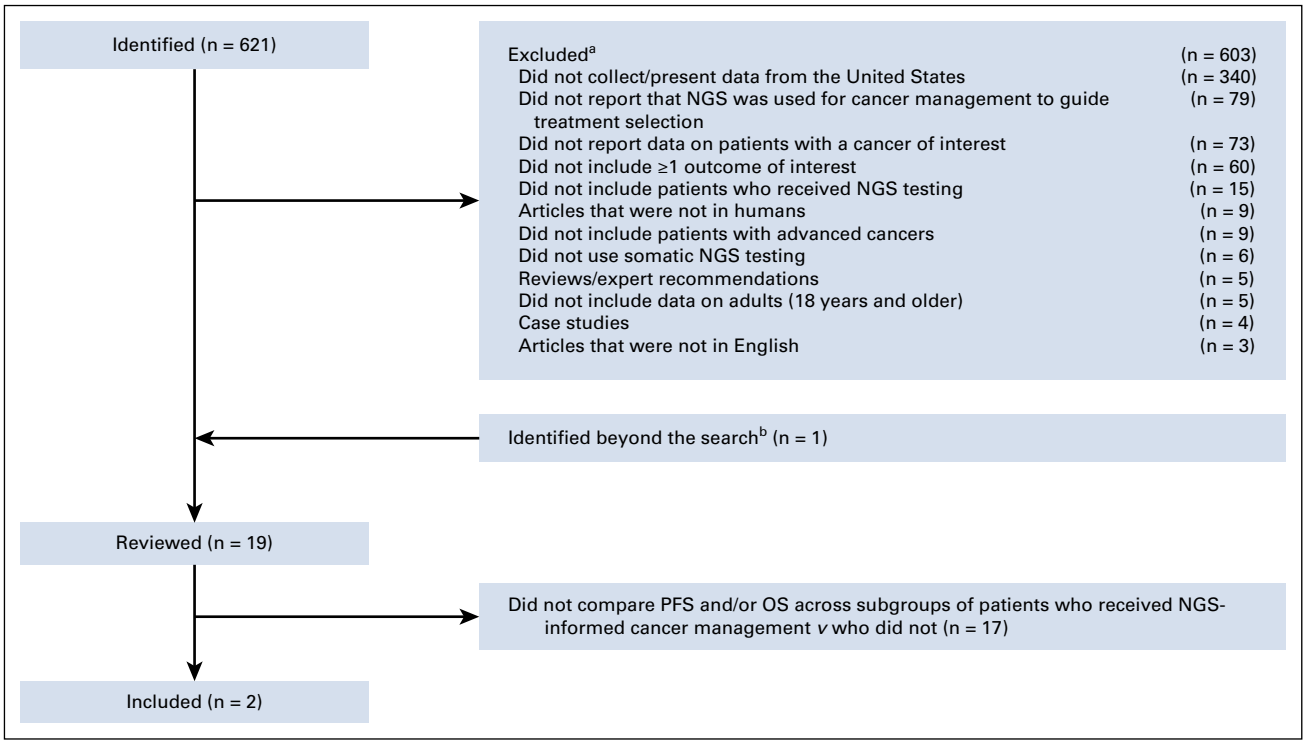

FIG 2. Flow diagram (conference abstracts). [a] Only one reason for exclusion was required to exclude a study during the screening process although more than one reason could be selected. Therefore, reasons for exclusion do not sum to the number excluded. [b] Ref. 66. NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival.

follow-up, among others. Twelve publications named the targeted therapies used (Appendix). Three publications provided a matching score definition (ie, the number of alterations targeted by therapies over the total number of alterations identified).[28,30,33]

OS and PFS by subgroups of patients who were/were not matched to targeted treatment on the basis of NGS test results are reported in Table 2. Fourteen publications compared PFS among subgroups (either in survival time or via a HR). In one publication,[41] PFS was longer, but the difference was not statistically significant. Two publications did not report significance tests.[24,37] Among the remaining 11 publications, the differences in PFS were statistically significantly longer for those who received matched therapies. Ten of these (nine pan-cancer[25,26,28-30,33,45-47] and one biliary tract cancer[45]) reported a statistically significant PFS HR in favor of those receiving matched therapies (range of HRs reported 0.24-0.67, mean of HRs reported 0.47, median of HRs reported 0.47).

Twenty-six publications compared OS among subgroups. Six publications reported that OS was longer, but the difference was not statistically significant.[25,27,30,41,45,50] Three publications did not report significance tests.[32,37,39] One publication[43] descriptively noted that there were no differences in OS without reporting survival times. Sixteen reported statistically significantly longer OS among patients receiving matched treatment. Seven of these (all pan-cancer[22,28,31,33,35,47]) reported a statistically significant OS HR in favor of those receiving matched therapies (range of HRs reported 0.34-0.84, mean of HRs reported 0.56, median of HRs reported 0.47); one publication[25] reported a nonstatistically significant OS HR (HR, 0.60 [95% CI, 0.34 to 1.06]; $P = .07$).

Few publications reported on the same outcome in the same cancer type. Among publications that reported on a single cancer type (rather than ≥2), only five tumor types were reported by more than one publication (three NSCLC, two breast, two pancreatic, two biliary tract, two colorectal) and only the publications on biliary tract[44,45] and pancreatic tumors[46,47] reported on the same outcome.

Ten publications reported tumor response rates[22,25,28-30,33-35,37,41] (Table 2). Eight compared response rates between subgroups of patients who were/were not matched to targeted treatment on the basis of NGS test results. Among these eight, three[28,30,35] reported significantly higher response among patients who received targeted treatment, one reported a higher response that was not statistically significant, and the remaining four did not report significance tests. Two publications did not compare response rates by subgroups.

NGS Test Characteristics

Twenty-one publications reported on the number and types of NGS tests used. A single test was used in eight, and more than one test was used in 13 publications. Sixteen

TABLE 1. Publications Included in This Review (n = 31)

Short Reference	Study Research Design	No. of Patients Included in the Study	Cancer Type	No. of Previous Lines of Therapy Received (mean; median; range; %)[a]
Carter et al[20]	Retrospective observational cohort study—health care claims review	841	Pan-cancer	NR
Carter et al[21]	Retrospective observational cohort study—registry (Caris CODE)	112	Pan-cancer	NR
Charo et al[22]	Retrospective observational cohort study—medical record review	105	Pan-cancer	Median, 2; range, 0-13
Chawla et al[23]	Clinical trial, phase I	188	Pan-cancer	NR
Dalton et al[24]	Retrospective observational cohort study—medical record review	155	Pan-cancer	Mean, 2; range, 0-11
Dumbrava et al[25]	Retrospective observational cohort study—medical record review	122	Pan-cancer	Median, 2; range, 0-7
Haslem et al[26]	Retrospective observational cohort study—medical record review	72	Pan-cancer	Median, 3.1 (matched), 2.9 (nonmatched); range, 1-7 (for both)
Jones et al[27]	Retrospective observational cohort study—medical record review	108	Pan-cancer	NR
Kato et al[28]	Prospective observational cohort study	715	Pan-cancer	NR
Kato et al[29]	Prospective observational cohort study	40	Pan-cancer	Median, 2; range, 0-7
Kato et al[30]	Prospective observational cohort study	2,457	Pan-cancer	NR
Kopetz et al[31]	Prospective observational cohort study	521	Pan-cancer	NR
Madhira et al[49]	Retrospective observational cohort study—medical record review	194	Pan-cancer	NR
Reitsma et al[32]	Retrospective observational cohort study—medical record review	96	Pan-cancer	Median, 0; range, 0-6
Sicklick et al[33]	Clinical trial, phase NR	149	Pan-cancer	Median, 2; IQR, 1-3
Tsimberidou et al[34]	Retrospective observational cohort study—medical record review	1,307	Pan-cancer	Median, 4; range, 0-16
Tsimberidou et al[35]	Retrospective observational cohort study—medical record review	1,179	Pan-cancer	≤3 lines, 55% >3 lines, 45%[b]
Watson et al[36]	Retrospective observational cohort study—medical record review	185	Pan-cancer	0 or 1 line, 50% 2 lines, 24% ≥3 lines, 26%
Redman et al[37]	Clinical trial, phase NR	1,790	Squamous NSCLC	0 or 1 line, 79% 2 lines, 14% ≥3 lines, 7%
Presley et al[38]	Retrospective observational cohort study—medical record review	5,688	NSCLC	≥1 line, 100%
Steuten et al[39]	Retrospective observational cohort study—medical record review	5,688	NSCLC	NR
Carter et al[40]	Retrospective observational cohort study—registry (Caris CODE)	95	Colorectal	Mean, 3.92
Kato et al[41]	Retrospective observational cohort study—medical record review	94	Colorectal	Median, 1; range, 0-5
Carter et al[42]	Retrospective observational cohort study—registry (Caris CODE)	92	Breast	NR
Stover et al[43]	Clinical trial, phase I	142	Breast	NR
Javle et al[44]	Retrospective observational cohort study—medical record review	321	Liver/ hepatocellular	NR
Okamura et al[45]	Prospective observational cohort study	121	Biliary tract	Median, 0

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TABLE 1. Publications Included in This Review (n = 31) (Continued)

Short Reference	Study Research Design	No. of Patients Included in the Study	Cancer Type	No. of Previous Lines of Therapy Received (mean; median; range; %)[a]
Shahid et al[50]	Retrospective observational cohort study—medical record review	35	Biliary tract	NR
Pishvaian et al[46]	Retrospective observational cohort study—medical record review	1,245	Pancreatic	NR
Pishvaian et al[47]	Retrospective observational cohort study—medical record review	677[c]	Pancreatic	1 line, 39% ≥2 lines, 61%
Hay et al[48]	Clinical trial, phase NR	392	Sarcoma	NR

Abbreviations: NR, not reported; NSCLC, non–small-cell lung cancer.
[a]Mean, median, range, or percentage reported on the basis of statistics available in publication.
[b]Percentage calculated out of 637 patients with identified mutations.
[c]Included in the analysis cohort.

publications reported the number of genes sequenced. The smallest panel used included 11 genes,[35] and the largest included 596.[28] Nineteen publications reported the type of sample sequenced (10 tissue only,[27,30,31,35,37,43,44,46-48] nine tissue and blood/liquid[22,24,25,28,29,33,41,45,49]), and two tests sequenced RNA in addition to DNA.[33,48]

DISCUSSION

Several clinical trials have demonstrated the utility of targeted therapies, resulting in 28 FDA-approved targeted therapies in 2020.[2,10,15] In turn, clinical cancer guidelines (eg, National Comprehensive Cancer Network,[51] ESMO,[52] ASCO[53]) now recommend biomarker testing, including NGS assays, for some cancers. In this review, we sought to determine whether matched therapies and clinical trials identified by NGS testing improve PFS and OS.

This review indicates that NGS testing to identify matched therapies can have an impact on PFS and OS. More than half of publications report that patients who receive NGS testing and are subsequently matched to targeted treatments have longer PFS and OS. Twenty-nine articles and two conference abstracts compared PFS and/or OS across subgroups of patients who received NGS-informed cancer management versus patients who did not. Among patients who were matched to targeted treatment, PFS was significantly longer in 11 (of 14) publications across tumor types and a significant HR was reported in 10 publications (range of HRs 0.24-0.67; mean of HRs 0.47; median of HRs 0.47). OS was significantly longer in 16 (of 26) publications, and a significant HR was reported in seven publications (range of HRs 0.34-0.84, mean of HRs 0.56, median of HRs 0.47).

Although previous reviews have demonstrated the clinical and economic value of NGS tests in specific settings, we have not found other comprehensive reviews that summarize PFS and OS of patients across multiple tumor types receiving NGS-informed targeted treatments. Zheng et al[54] reported that NGS testing in NSCLC can lead to increased survival while being cost neutral or cost saving. Morash et al[55] and Zimmer et al[56] reviewed prospective studies across tumor types, and Del Vecchio et al[5] reviewed studies on colorectal cancer and summarized the clinical benefits of NGS (in terms of increased response rates, PFS, and OS). However, none of these studies took a comprehensive approach. Tan et al[57] systematically reviewed the clinical and cost-effectiveness of NGS, but defined clinical benefit as mutation detection rate rather than benefits with respect to PFS or OS.

Although matched therapies are beneficial and the number of approved targeted therapies is increasing, NGS testing to identify actionable mutations has not yet been fully incorporated into clinical practice. In a survey of oncologists treating breast cancer, only three quarters of respondents reported using NGS tests to guide treatment decisions (eg, selecting therapies, guiding enrollment in clinical trials).[58] Adopters of NGS testing tended to be younger oncologists with genomics training who see more patients. Furthermore, in a large real-world study, fewer than 50% of patients with lung cancer were found to have received all five guideline-recommended biomarker tests.[59]

Although not the focus of this study, our search identified 12 publications (including two conference abstracts) that presented economic outcomes on NGS testing. For example, total annual cost-savings of NGS was estimated to be $25,000 in US dollars (USD) per patient in diverted drug costs as a result of enrollment in clinical trials.[32] NGS-matched therapies were associated with higher overall costs mostly because of longer survival.[23,26] The budget impact of using NGS instead of single-gene testing in NSCLC in a health plan over 5 years was $432,554 (USD), which represents $0.0072 (USD) per member per month.[60] In gastrointestinal stromal tumors, an economic model showed that therapy informed by NGS was associated with an incremental cost-effectiveness ratio of $92,100 (USD), compared with the standard of care.[61] Our

TABLE 2. PFS/OS for Patients Receiving NGS-Informed Cancer Management Versus Those Not Receiving It (n = 31)

Short Reference	No. of Patients Who Received NGS Testing, No. of Patients Who Received NGS-Informed Cancer Management (%)[a]	No. of Patients Enrolled in Clinical Trials as a Result of NGS Testing, No. (%)[b]	PFS (median/mean months[c]; HRs/ORs; *P* values; 95% CI; other relevant statistics comparing matched *v* nonmatched patients)	OS (median/mean months[d]; HRs/ORs; *P* values, 95% CI, other relevant statistics comparing matched *v* nonmatched patients)	RR, Including PR, CR, and SD, No. (%)
Carter et al[20]	NR, 438	NR	NR	Matched: 16.8 (mean; 512 days) Nonmatched: 15.3 (mean; 468 days; *P* = .07) Mortality at the end of monitoring: 34% matched *v* 47% nonmatched (***P* = .0001***)	NR
Carter et al[21]	112, 64 (57)	NR	NR	Matched: 19.4 (mean) Nonmatched: 14.7 (mean; ***P* = .0265***) Mortality at the end of monitoring: 30% matched *v* 40% nonmatched	NR
Charo et al[22]	105, 33 (31)	NR	NR	Matched: 20.0 (median) Nonmatched: 5.3 (median; ***P* = .005***) HR, 0.34 (95% CI, 0.16 to 0.75; ***P* = .007***)	NR
Chawla et al[23]	188, 122 (65)	NR	NR	Matched: 8.2 (mean) Nonmatched: 5.9 (mean; ***P* ≤ .002***)	NR
Dalton et al[24]	153, 24 (16)	13 (10)[e]	Matched: 5.0 (median; 95% CI, 2.9 to not reached) Nonmatched: 2.97 (median; 95% CI, 2.4 to 5.13)	NR	NR
Dumbrava et al[25]	122, 40 (33)	NR	Matched: 5.3 (median; 24 weeks) Nonmatched: 2.9 (median; 13 weeks) HR, 0.44 (95% CI, 0.26 to 0.77; ***P* = .0006***)	Matched: 18.6 (median) Nonmatched: 10.9 (median) HR, 0.60 (95% CI, 0.34 to 1.06; *P* = .07)	12 (30%) achieved CR/PR
Haslem et al[26]	72, 36 (50)	NR	Matched: 5.1 (mean; 22.9 weeks) Nonmatched: 2.7 (mean; 12.0 weeks; ***P* = .002***) HR, 0.47 (95% CI, 0.29 to 0.75; ***P* = .002***)	NR	NR
Jones et al[27]	108, 30 (28)	NR (5)[f]	NR	Full sample: 8.4 (median) Matched: 12.8 (median) Nonmatched: 6.6 (median) No actionable results: 7.9 (median; *P* = .5160)	NR
Kato et al[28]	429, 265 (62)	NR	High matching score:[g] 6.0 (median) Low matching score: 4.0 (median) HR, 0.62 (95% CI, 0.47 to 0.81; ***P* = .001***)	High matching score: 17.0 (median) Low matching score: 10.0 (median) HR, 0.67 (95% CI, 0.50 to 0.90; ***P* = .007***)	High *v* low matching score SD ≥6 months/PR/CR OR = 0.40 (95% CI, 0.24 to 0.67; ***P* < .001***)

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TABLE 2. PFS/OS for Patients Receiving NGS-Informed Cancer Management Versus Those Not Receiving It (n = 31) (Continued)

Short Reference	No. of Patients Who Received NGS Testing, No. of Patients Who Received NGS-Informed Cancer Management (%)[a]	No. of Patients Enrolled in Clinical Trials as a Result of NGS Testing, No. (%)[b]	PFS (median/mean months[c]; HRs/ORs; *P* values; 95% CI; other relevant statistics comparing matched *v* nonmatched patients)	OS (median/mean months[d]; HRs/ORs; *P* values, 95% CI, other relevant statistics comparing matched *v* nonmatched patients)	RR, Including PR, CR, and SD, No. (%)
Kato et al[29]	NR, 21	NR	Matched: 19.7 (median) Nonmatched: 3.5 (median) HR, 0.26 (95% CI, 0.10 to 0.71; ***P* = .008***)	NR	SD ≥6 months/PR/CR: 21 (52.4) SD ≥6 months: 3 (14.3%) PR: 6 (28.6%) CR: 2 (9.5%)
Kato et al[30]	2457, 40 (2)	NR	High matching score:[g] 6.2 (median; 95% CI, 3.6 to 8.8) Low matching score: 2.0 (median; 95% CI, 0.7 to 3.3; ***P* = .001***) HR, 0.24 (95% CI, 0.11 to 0.51; ***P* ≤ .001***)	High matching score: 8.3 (median; 95% CI, 3.3 to 13.3) Low matching score: 5.3 (median; 95% CI, 4.2 to 6.4; *P* = .15)	SD ≥6 months/PR High matching score: 13 (57%) Low matching score: 3 (21%), ***P* = .048***
Kopetz et al[31]	507, 40 (8)	NR	NR	HR, 0.47 (95% CI, 0.25 to 0.89; ***P* = .0172***)	NR
Madhira et al[49]	194, 129 (66)	NR	NR	Matched: 26.6 (mean; 810 days) Nonmatched: 24.6 (mean; 750 days; ***P* = .0056***)	NR
Reitsma et al[32]	96, 21 (22)	6 (29)	NR	Full sample: 4.8 (median; range, 0-31) Matched: 9.5 (median; range, 1.1-24.2) Nonmatched: 4.6 (median; range, 0.30-9)	NR
Sicklick et al[33]	NR, 73	NR	High matching score:[g] 6.5 (median; 95% CI, 3.2 to 9.9) Low matching score: 3.1 (median; 95% CI, 2.5 to 3.8) HR, 0.40 (95% CI, 0.23 to 0.71; ***P* = .001***)	High matching score: median not reached after 8.5 months follow-up Low matching score: 10.2 (median; 95% CI, 4.3 to 16.0) HR, 0.44 (95% CI, 0.19 to 1.01; ***P* = .046***)	SD ≥6 months/PR/CR Matched: 20 (33.3%) Nonmatched: 1 (11.1%)
Tsimberidou et al[34]	NR, 711	NR	Matched: 4.0 (median; 95% CI, 3.7 to 4.4) Nonmatched: 2.8 (median; 95% CI, 2.4 to 3.0; ***P* < .0001***) HR, 0.67 (***P* < .001***)	Matched: 9.3 (median; 95% CI, 8.4 to 10.5) Nonmatched: 7.3 (median; 95% CI, 6.5 to 8.0; ***P* < .0001***) HR, 0.72 (***P* < .001***)	Matched: CR 19 (2.8%), PR 94 (13.6%), SD ≥6 months 130 (18.9%) Nonmatched: CR 3 (0.5%), PR 28 (4.9%), SD ≥6 months 84 (14.8%)
Tsimberidou et al[35]	1,179, 390 (33)	NR	NR	Matched: 8.4 (median) Nonmatched: 7.3 (median) HR, 0.84 (95% CI, 0.71 to 0.99; ***P* = .041***)	CR/PR Matched: 43 (11%) Nonmatched: 12 (5%) OR, 2.4 (95% CI, 1.2 to 4.6; ***P* = .0099***)
Watson et al[36]	185, 27 (15)	5 (19)	NR	Ovarian: no difference in OS according to molecular alteration (*P* = .56) Uterine: significant difference according to molecular alteration (***P* = .013***)	NR

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TABLE 2. PFS/OS for Patients Receiving NGS-Informed Cancer Management Versus Those Not Receiving It (n = 31) (Continued)

Short Reference	No. of Patients Who Received NGS Testing, No. of Patients Who Received NGS-Informed Cancer Management (%)[a]	No. of Patients Enrolled in Clinical Trials as a Result of NGS Testing, No. (%)[b]	PFS (median/mean months[c]; HRs/ORs; *P* values; 95% CI; other relevant statistics comparing matched *v* nonmatched patients)	OS (median/mean months[d]; HRs/ORs; *P* values, 95% CI, other relevant statistics comparing matched *v* nonmatched patients)	RR, Including PR, CR, and SD, No. (%)
Redman et al[37]	1,404, 655 (47)	655 (100)	Matched: 2.5 (median; 95% CI: 1.7 to 2.8) Immunotherapy nonmatched: 3.0 (median; 95% CI: 2.7 to 3.9) Docetaxel nonmatched: 2.7 (median; 95% CI, 1.9 to 2.9)	Matched: 5.9 (median; 95% CI, 4.8 to 7.8) Immunotherapy nonmatched: 10.8 (median; 95% CI, 9.4 to 12.3) Docetaxel nonmatched: 7.7 (median; 95% CI, 6.7 to 9.2)	CR/PR Matched: 10 (7.0%) Immunotherapy nonmatched: 53 (16.8%) Docetaxel nonmatched: 3 (5.4%)
Presley et al[38]	875, 201 (23)	5 (2)[h]	NR	Unadjusted survival at 12 months: Broad-based genomic sequencing: 69.5% Routine testing: 50.8% (***P* ≤ .001***)	NR
Steuten et al[39]	875, 183 (21)[i]	NR	NR	Matched: 27.72 (95% CI, 3.72 to 49.44; mean) Nonmatched: 20.76 (95% CI, 3.36 to 43.08; mean)	NR
Carter et al[40]	NR, 42	NR	NR	Matched: 14.5 (mean; 442 days) Nonmatched: 17.7 (mean; 541 days; *P* = .1773) Mortality at the end of monitoring: 19% matched *v* 49% nonmatched (***P* = .0022***)	NR
Kato et al[41]	76, 17 (22)	NR	Matched: 6.1 (median; 95% CI, 3.8 to 8.7) Nonmatched: 2.3 (median; 95% CI, 0.5 to 4.1; *P* = .08)	Matched: not reached at 11.1 months (median) Nonmatched: 9.4 (median; *P* = .146)	PR/SD ≥6 months Matched: 11 (65%) Nonmatched: 5 (31%)
Carter et al[42]	NR, 43	NR	NR	Matched: 21.9 (mean; 667 days) Nonmatched: 16.7 (mean; 510 days; ***P* = .0316***) Mortality at the end of monitoring: 26% matched *v* 41% nonmatched (*P* = .1257)	NR
Stover et al[43]	100, 10[h] (10)	NR	NR	No significant difference in OS by FoundationOne CDx-supported treatment change (*P* = .71)	NR
Javle et al[44]	321, 94 (29)	NR	NR	Gallbladder carcinoma Matched: 45.3 (median) Nonmatched: 40.0 (median; *P* = .90) Extrahepatic cholangiocarcinoma Matched: 34.7 (median) Nonmatched: 51.1 (median; *P* = .78) Intrahepatic cholangiocarcinoma Matched: 53.6 (median) Nonmatched: 41.3 (median; ***P* = .07***)	NR
Okamura et al[45]	121, 34 (28)	NR	Matched: 4.3 (95% CI, 2.7 to 5.9) Nonmatched: 3.0 (95% CI, 2.4 to 3.6) HR, 0.61 (95% CI, 0.37 to 0.99; ***P* = .04***)	Matched: 11.9 (median; 95% CI, 5.8 to 18.0) Nonmatched: 7.9 (median; 95% CI, 5.9 to 9.9) Not statistically significant	PR Matched: 8 (24%) Nonmatched: 2 (4.7%), *P* = .2

(Continued on following page)

TABLE 2. PFS/OS for Patients Receiving NGS-Informed Cancer Management Versus Those Not Receiving It (n = 31) (Continued)

Short Reference	No. of Patients Who Received NGS Testing, No. of Patients Who Received NGS-Informed Cancer Management (%)[a]	No. of Patients Enrolled in Clinical Trials as a Result of NGS Testing, No. (%)[b]	PFS (median/mean months[c]; HRs/ORs; *P* values; 95% CI; other relevant statistics comparing matched *v* nonmatched patients)	OS (median/mean months[d]; HRs/ORs; *P* values, 95% CI, other relevant statistics comparing matched *v* nonmatched patients)	RR, Including PR, CR, and SD, No. (%)
Shahid et al[50]	35, NR	NR	NR	Matched: 19 (median) Nonmatched: 10.5 (median; *P* = .051)	NR
Pishvaian et al[46]	737, 126 (17)	26 (21)	Matched (highly actionable + matched): 4.1 Nonmatched (highly actionable + nonmatched): 1.9 Not highly actionable: 2.8 HR: 0.47 (95% CI, 0.24 to 0.94; ***P* = .03***)	NR	NR
Pishvaian et al[47]	1,082, 46 (4)	NR	Matched: 10.93 (95% CI, 7.89 to not reached) Nonmatched: 4.53 (95% CI, 4.03 to 6.33) HR, 0.50 (95% CI, 0.29 to 0.86; ***P* = .0124***)	Matched: 30.96 (median; 95% CI, 28.68 to not reached) Nonmatched: 18.12 (median; 95% CI, 15.96 to 22.44) HR, 0.42 (95% CI, 0.26 to 0.68; ***P* = .0004***)	NR
Hay et al[48]	392, 7 (2)	NR	Matched: 4.1 (median; 124 days) Nonmatched: 1.8 (median; 54 days; ***P* = .03***)	NR	NR

NOTE. *P* values in bold with asterisk indicate statistical significance.

Abbreviations: CR, complete response; HR, hazard ratio; NGS, next-generation sequencing; NR, not reported; OR, odds ratio; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate; SD, stable disease.

[a]The number of patients who received NGS-informed therapy (ie, matched to targeted therapy or clinical trial) aligns with the number included in PFS/OS/RR analysis. Percentage is calculated from the number of patients who received NGS-informed therapy out of the number of patients who received NGS testing. The number of patients may not align with total sample size listed in Table 1.

[b]Unless otherwise noted, percentage is either reported in the article or calculated on the basis of the number of patients matched to treatment.

[c]Months are calculated if only days or weeks are reported on in the publication; in these cases, days and weeks are also presented in parentheses.

[d]Months are calculated if only days or weeks are reported on in the publication; in these cases, days and weeks are also presented in parentheses.

[e]Percentage calculated out of 129 eligible patients.

[f]Publication states that 5% were enrolled in clinical trials but does not specify whether this is of 30 patients who received matched treatment or 79 patients with clinical action identified.

[g]Matching score defined as the number of alterations targeted by drugs over the total number of alterations found. Categorized as ≥50% (high matching score) and <50% (low matching score).

[h]Patients enrolled for first-line treatment.

[i]Number of patients who received NGS-informed therapy estimated manually; article included percentage only.

[j]Ten patients had a treatment change as a result of NGS test results and were included in OS analysis.

search also found only one journal publication and no conference abstracts on humanistic outcomes. These small numbers represent a significant gap in the literature and an opportunity for future research.

Our goal was to examine the clinical impact of NGS testing across cancer types. However, the publications we found made it difficult to aggregate and compare the impact across cancer types. We only found 13 publications that reported on a single tumor type, and most reported on different tumor types (biliary tract, breast, colorectal, liver/hepatocellular, NSCLC, pancreatic, and sarcoma). In all but two cancers, there was at most a single publication that reported on median PFS or OS stratified by NGS-informed cancer management. Although this demonstrates that there is evidence of the impact of NGS across tumor types, given the different combinations of cancer types in these studies, it is difficult to present aggregate survival estimates across studies.

In only 16 publications did all patients receive NGS testing. A mean of 29% (median, 25%) of tested patients were matched to targeted treatment or clinical trial, resulting in relatively small sample sizes on which to base survival data (mean, 143; median, 40; range, 7-711). Additional, potential qualitative studies that explore why only a fraction of patients receive targeted therapies are warranted. Furthermore, only seven publications reported on patients enrolled in clinical trials, limiting our conclusions about the impact of NGS testing to support clinical trial enrollment. Our study also included mostly observational studies (26 publications); despite our comprehensive review, we did not identify any prospective randomized controlled trials. Thus, the conclusions we draw are based only on observational data and nonrandomized clinical trials, and so we cannot assume causality. Randomized trials would be needed to assess the clinical impact more accurately.

Few publications described the NGS tests used in detail, and no publications presented survival by test characteristics (eg, blood *v* tissue, size of gene panel) or by the number of previous lines of therapy patients received, making it difficult to draw conclusions about the impact of different types of tests. Finally, many included publications did not present important information on the use of NGS results such as clear matching scores, the proportion of patients eligible to receive NGS-informed cancer management, or why some patients eligible for matched treatments did not receive them. A recent publication not included in our review does present some of this information,[62] citing deteriorating health as a major reason for not receiving matched therapies and suggesting the need for NGS-informed treatment selection earlier in a patient's disease course.

Our methodology had limitations. Systematic dual screening and abstraction were not conducted; unknown and untested individual biases may be present. Publications were not evaluated for quality, author, or nonreporting bias. As the original intent of the study was descriptive, no statistical syntheses or sensitivity analyses were conducted. Although we confirmed that there were no overlapping abstracts and manuscripts, publications might have used overlapping cohorts of patients, which could confound results in unknown and untested directions. Many different terms are used to describe NGS panels. Our search terms were very broad, yet we missed publications that did not use these terms. For example, six publications were identified outside of the PubMed search,[38,39,63-67] and we might have missed others. Many conferences that we did not screen are publishing abstracts on this topic, such as the American Association for Cancer Research, possibly resulting in missed studies. Furthermore, our search results did not include publications from ASCO's Targeted Agent and Profiling Utilization Registry or the National Cancer Institute Molecular Analysis for Therapy Choice trials, which are large, ongoing trials of patients receiving matched therapies. Relevant publications from these trials might have been missed, or they were identified but did not meet our inclusion criteria (eg, reporting response rate rather than PFS or OS). Finally, the field of cancer genomics is evolving quickly. Our search was conducted on August 6, 2021. Repeating the search in PubMed on August 25, 2022 (after the current study was completed), resulted in close to 2,000 new publications released in the past year alone. Among these were several relevant publications that could have been included in this review.[68-70]

A large body of mainly retrospective real-world evidence exists that supports the use of NGS testing in oncology, including studies that demonstrate increased survival in patients matched to targeted treatments on the basis of NGS tests. However, few clinical trials (and no randomized trials) exist to demonstrate its clinical utility. We also found no studies on the impact of NGS testing on quality of life nor any studies comparing outcomes from tests that use different methodologies (eg, blood *v* tissue, size of the gene panel). Studies incorporating patient-reported outcomes are needed to better understand the patient perspective, and ones that combine NGS test characteristics with survival data (such as those that compare outcomes among patients who receive small *v* large panel tests) are also needed to evaluate the performance of different types of tests. The science around NGS testing is rapidly advancing, and future reviews should revisit the clinical, economic, and humanistic impact of these tests.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

TABLE A1. PubMed and Embase Search Strategy

Topic of Interest	PubMed Search String	Embase Search String
Population: adults 18 years and older (human) in the United States	NA (characteristics to screen)	NA (characteristics to screen)
Disease: stage III or IV, metastatic, refractory, recurrent cancer	("Neoplasms"[Mesh] OR "neoplasm*"[tw] OR "cancer*"[tw] OR "carcinoma*"[tw] OR "Carcinoma"[Mesh] OR "malignan*"[tw] OR "tumour*"[tw] OR "tumor*"[tw])	('neoplasm'/exp OR 'neoplasm*' OR 'cancer*' OR 'carcinoma*' OR 'carcinoma'/exp OR 'malignan*' OR 'tumour*' OR 'tumor*')
Exposure: received NGS testing to guide cancer management	(next generation sequencing OR "next gen sequencing"[tw] OR "High-Throughput Nucleotide Sequencing"[Mesh] OR "high throughput sequencing"[tw] OR "whole transcriptome"[tw] OR "comprehensive genomic profiling"[tw] OR "molecular profiling"[tw] OR "whole exome sequencing"[tw] OR "whole genome sequencing"[tw] OR "genomic panel"[tw] OR "gene panel"[tw] OR "tumor profiling"[tw])	('next generation sequencing' OR 'next gen sequencing' OR 'high throughput sequencing'/exp OR 'high throughput sequencing' OR 'whole transcriptome' OR 'comprehensive genomic profiling' OR 'molecular profiling' OR 'whole exome sequencing' OR 'whole genome sequencing' OR 'genomic panel' OR 'gene panel' OR 'tumor profiling')
Clinical outcomes: progression-free survival, overall survival	("Survival"[Mesh] OR "survival"[tw] OR "survive"[tw] OR "mortalit*"[tw] OR "Mortality"[Mesh] OR "Recurrence"[Mesh] OR "recurrence"[tw] OR "tumor response"[tw] OR "Neoplasm Recurrence, Local"[Mesh] OR "remission"[tw])	('survival'/exp OR 'survival' OR 'survive' OR 'mortalit*' OR 'mortality'/exp OR 'recurrent risk'/exp OR 'recurrence' OR 'tumor response' OR 'tumor recurrence'/exp OR 'remission')
Humanistic outcomes: morbidity, quality of life	("Morbidity"[Mesh] OR "morbidit*"[tw] OR "burden of illness"[tw] OR "illness burden*"[tw] OR "Quality of Life"[Mesh] OR "quality of life"[tw] OR "QOL"[tw] OR "HRQOL"[tw] OR "life quality"[tw] OR "clinical burden"[tw] OR "disease burden*"[tw] OR "burden of disease*"[tw])	('morbidity'/exp OR 'morbidit*' OR 'burden of illness' OR 'illness burden*' OR 'quality of life'/exp OR 'quality of life' OR 'QOL' OR 'HRQOL' OR 'life quality' OR 'clinical burden' OR 'disease burden*' OR 'burden of disease*')

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TABLE A1. PubMed and Embase Search Strategy (Continued)

Topic of Interest	PubMed Search String	Embase Search String
Economic outcomes: health care costs, health care utilization	("Cost of Illness"[Mesh] OR "economic disease burden"[tw] OR "economic burden of disease"[tw] OR "Patient Acceptance of Health Care"[Mesh] OR "healthcare utilization"[tw] OR "health care utilization"[tw] OR "Health Care Costs"[Mesh] OR "health care cost*"[tw] OR "healthcare cost*"[tw] OR "medical care cost*"[tw] OR "medical cost*"[tw] OR "Health Care Economics and Organizations"[Mesh] OR "health care economics"[tw] OR "healthcare economics"[tw] OR "health economics"[tw] OR "budget impact"[tw] OR cost effectiveness)	('cost of illness'/exp OR 'economic disease burden' OR 'economic burden of disease' OR 'patient attitude'/exp OR 'healthcare utilization' OR 'health care utilization' OR 'health care cost'/exp OR 'health care cost*' OR 'healthcare cost*' OR 'medical care cost*' OR 'medical cost*' OR 'health care economics' OR 'healthcare economics' OR 'health economics' OR 'budget impact' OR 'cost effectiveness')
Others: not case studies, English language, published within the past 5 years in medical journals	NOT (Case Reports[ptyp]) NA (add publication year and English language filters within the search and screen for journal)	('case report'/exp)

Abbreviations: NA, not available; NGS, next-generation sequencing.

TABLE A2. Targeted Therapies Listed in Publications

Short Reference	Type of Matched Therapy[a]
Carter et al[20]	Bevacizumab, capecitabine, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin hydrochloride, fluorouracil, gemcitabine hydrochloride, irinotecan hydrochloride, leucovorin calcium, oxaliplatin, paclitaxel, pegylated liposomal, doxorubicin hydrochloride
Carter et al[21]	NR
Charo et al[22]	NR
Chawla et al[23]	NR
Dalton et al[24]	NR
Dumbrava et al[25]	Antibody drug conjugates bispecific antibody, small-molecule HER2 inhibitor, trastuzumab, trastuzumab + chemotherapy or + targeted therapy
Haslem et al[26]	Ado-trastuzumab, erlotinib, everolimus, imatinib, MEK inhibitor, pazopanib, trametinib
Jones et al[27]	Lucitanib, mTOR inhibitor, neratinib, olaparib
Kato et al[28]	NR
Kato et al[29]	NR
Kato et al[30]	Customized combination therapies (eg, CDK4/6 inhibitor–based)
Kopetz et al[31]	NR
Madhira et al[49]	NR
Reitsma et al[32]	NR
Sicklick et al[33]	Customized combination therapies (eg, MEK inhibitors, VEGF/VEGFR)
Tsimberidou et al[34]	AKT, anti-EGFR, BRAF, EGFR, KIT, MEK, MET respective kinase inhibitors, mTOR, PIK3CA, RET
Tsimberidou et al[35]	AKT, anti-EGFR, BRAF inhibitors, MEK, mTOR, PI3K, various kinase inhibitors, VEGF/VEGRF inhibitors
Watson et al[36]	NR
Redman et al[37]	NR
Presley et al[38]	NR
Steuten et al[39]	NR
Carter et al[40]	Bevacizumab, capecitabine, fluorouracil, irinotecan hydrochloride, oxaliplatin
Kato et al[41]	NR
Carter et al[42]	Doxorubicin hydrochloride, docetaxel, letrozole, trastuzumab
Stover et al[43]	NR
Javle et al[44]	Alisertib/MLN8237, AMG337, bevacizumab, BGJ398 + dovitinib/TKI258, binimetinib/MEK162, buparlisib/BKM120, CEP-37250/KHK2804, dabrafenib + GSK/trametinib, erlotinib + bevacizumab, erlotinib + panitumumab + cetuximab, everolimus + sirolimus, LEE001, LOXO-101, MLN9708/IXAZOMIB, pazopanib, pazopanib + GSK/trametinib, pembrolizumab/MK-3475 + MPDL3280A, RXDX-101, talazoparib/BMN673, trastuzumab, vemurafenib
Okamura et al[45]	NR
Shahid et al[50]	NR
Pishvaian et al[46]	NR
Pishvaian et al[47]	NR
Hay et al[48]	Doxorubicin, ipilimumab + nivolumab, nivolumab, olaparib, palbociclib, pazopanib

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TABLE A2. Targeted Therapies Listed in Publications (Continued)

Abbreviations: AKT, protein kinase B; BRAF, proto-oncogene B-Raf; CDK4/6, cyclin-dependent kinase 4/6; EGFR, epidermal growth factor receptor; GSK, glycogen synthase kinase; HER2, human epidermal growth factor receptor 2; KIT, cluster of differentiation 117; MEK, mitogen-activated protein kinase kinase; MET, mesenchymal-epithelial transition factor; mTOR, mammalian target of rapamycin; NGS, next-generation sequencing; NR, not reported; PIK3CA, phosphoinositide 3-kinase; RET, ret proto-oncogene; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor.

[a]Medications matched to mutations identified via NGS provided if included in publication.

TABLE A3. Reason(s) Patients Did Receive NGS-Informed Cancer Management

Short Reference	Reason(s) Patients Did Not Receive NGS-Informed Cancer Management
Carter et al[20]	NR
Carter et al[21]	NR
Charo et al[22]	No ctDNA detected; preferentially matched by tissue-based molecular profile; no actionable mutation; received unmatched immunotherapy; received standard cytotoxic therapy; enrolled in a secondary unmatched clinical trial; hospice/health deterioration/death; lost to follow-up; treatment not indicated at this time
Chawla et al[23]	Never received a new evaluable treatment after providing consent; had received previous immunotherapy; received a drug with an unclear action; underwent stem-cell transplantation
Dalton et al[24]	Lack of available clinical trials; higher threshold for recommending off-label use of targeted therapies
Dumbrava et al[25]	Noneligibility for a HER2-targeted trial; equivocal HER2 amplification results; insurance denial; clinical issues such as poor performance status, chronic tumor–related bleeding, or inadequate organ function
Haslem et al[26]	Did not receive a match
Jones et al[27]	NR
Kato et al[28]	NR
Kato et al[29]	NR
Kato et al[30]	Other medical issue that precluded systemic therapy; not metastatic lesion; lost to follow-up; no information on treatment; regimen before NGS was continued; treated with radiation and/or surgery

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TABLE A3. Reason(s) Patients Did Receive NGS-Informed Cancer Management (Continued)

Short Reference	Reason(s) Patients Did Not Receive NGS-Informed Cancer Management
Kopetz et al[31]	Deceased; decline in performance status; declined trial/elected local treatment; ineligible for matched trial; insurance denial; no matched trials available; patient did not progress; physician chose radiation; physician did not consider mutation actionable; physician missed alteration on report and follow-up alert; pathway previously targeted
Madhira et al[49]	NR
Reitsma et al[32]	NR
Sicklick et al[33]	Deterioration or died before treatment could be initiated
Tsimberidou et al[34]	No available clinical trial; patient did not agree to comply with study requirements
Tsimberidou et al[35]	No targetable mutation; patient denied treatment; patient was not medically fit enough; lack of access to treatment
Watson et al[36]	Provider/patient elected alternate treatment; patient declined; hospice or death before discussion; no actionable mutation identified; no evidence of disease
Redman et al[37]	Death; no progression; no substudies available; exclusion on the basis of ALK/EGFR
Presley et al[38]	NR
Steuten et al[39]	NR
Carter et al[40]	NR
Kato et al[41]	NR
Carter et al[42]	NR
Stover et al[43]	No available tissue; insufficient tissue; poor DNA quality; died before FoundationOne CDx report was released; did not receive FoundationOne CDx report within 10 weeks; lost to follow-up; withdrew consent

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TABLE A3. Reason(s) Patients Did Receive NGS-Informed Cancer Management (Continued)

Short Reference	Reason(s) Patients Did Not Receive NGS-Informed Cancer Management
Javle et al[44]	NR
Okamura et al[45]	NR
Shahid et al[50]	NR
Pishvaian et al[46]	NR
Pishvaian et al[47]	Treating physician chose not to use therapy; access to therapies was insufficient; patients were unable or unwilling to travel to enroll in a clinical trial
Hay et al[48]	Progression; patient preference; progression on imaging; stable disease; patient expired; no new treatment; lost to follow-up; utility discontinued; unclear

Abbreviations: ALK, anaplastic lymphoma kinase; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NGS, next-generation sequencing; NR, not reported.