Clinical, Humanistic, and Economic Outcomes of Next-Generation Sequencing Tests in Cancer Management of Patients with Advanced Cancer in the United States: Systematic Literature Review

Gibbs SN[1], Dalglish H[1], Campos C[1], Thakkar S[2], Palomares M[2], Yermilov I[1], Cuyún Carter G[3]

[1] Partnership for Health Analytic Research (PHAR), LLC, Beverly Hills, CA, USA. [2] Exact Sciences Corporation, Redwood City, CA, USA. [3] Exact Sciences Corporation, Madison, WI, USA

Background & Objective

- In oncology, next generation sequencing (NGS) tests are used to identify biomarkers to inform the selection of targeted therapy as directed by clinical guidelines and/or regulatory approvals, and to inform eligibility for clinical trials.
- Understanding the clinical, humanistic, and economic benefits of NGS testing across cancer types is critical.
- **Objective:** To perform a comprehensive systematic literature review and summarize the published evidence on the clinical, humanistic, and economic outcomes of using NGS testing to guide advanced cancer management (i.e., treatment selection or enrollment in clinical trials) of adult patients in the United States (US).

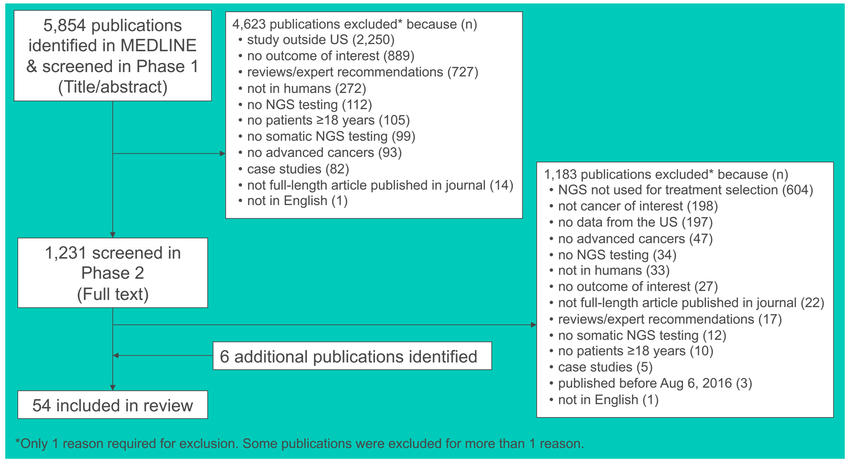
Methods

- Pre-defined search strategy to search MEDLINE (via PubMed) on Aug 6, 2021, to identify publications that were:
  - Written in English
  - Primary research (reviews, editorials, and case reports were excluded) published in peer-reviewed scientific journals in the last 5 years
  - Included US adult patients with advanced, metastatic, refractory, or recurrent cancer receiving somatic-focused NGS tests to guide treatment selection or enrollment in clinical trials
  - Included ≥1 clinical (progression-free survival [PFS], overall survival [OS], tumor response), humanistic (morbidity, quality of life), or economic (healthcare costs, utilization) outcome
- Search was limited to the following cancers: Non-small cell lung (NSCLC), prostate, colorectal, breast, cholangiocarcinoma, ovarian, hepatobiliary, pancreatic, urothelial, melanoma, central nervous system, sarcoma, hematologic (leukemias, lymphomas).
- Publications reporting on multiple (≥2) tumor types (pan-cancer) were included if ≥1 cancer type of interest was included.
- Screening occurred in 2 phases (Phase 1: title/abstract; Phase 2: full-text). Additional publications found outside the search were added.

Results

- 5,854 publications initially identified.
- 54 publications (including 6 identified beyond the search) met the inclusion criteria (Figure 1, supplementary file).
- Most publications described retrospective observational designs (Figure 2) including several cancers (Figure 3).
- Most publications reported on clinical outcomes (n=48) and/or economic outcomes (n=10). Only 1 publication reported on humanistic outcomes.

Figure 1. Publication Screening Flow Chart

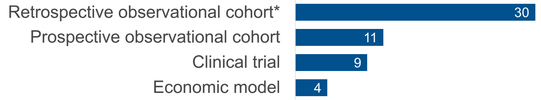


*Only 1 reason required for exclusion. Some publications were excluded for more than 1 reason.

References are available in the supplementary file.

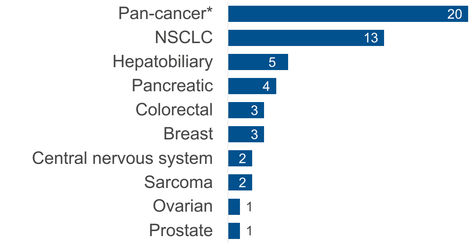
Results

Figure 2. Number of Publications by Study Design



*Includes 24 medical record reviews, 6 healthcare claims analyses

Figure 3. Number of Publications by Tumor Type



*Publications reporting ≥2 tumor types were classified as pan-cancer. Cancers included are listed in the supplementary file.

Table 1. Publications Reporting Both PFS and OS in Matched vs Non-Matched Therapy Groups

Study Ref	Study Design	Number of Patients	Cancer Type	PFS (median months, unless noted)	OS (median months, unless noted)
14	Retrospective observational cohort study - medical record review	122 (40 matched)	Pan-cancer	Matched: 5.3 Previous treatment: 2.9 HR 0.44 (95% CI 0.26-0.77), p=0.0006	Matched: 18.6 Non-matched: 10.9 HR 0.60 (95% CI 0.34-1.06), p=0.07
24	Prospective observational cohort study	715 (125 matching score ≥50%; 304 matching score <50%)	Pan-cancer	HR=0.62 (95% CI: 0.47-0.81), p<0.001 in patients who received therapies with high ≥50% vs low <50% matching score	HR=0.67 (95% CI: 0.50-0.90), p=0.007 in patients who received therapies with high ≥50% vs low <50% matching score
26	Prospective observational cohort study	2,457 (25 matching score ≥50%; 15 matching score <50%)	Pan-cancer	Matching score ≥50%: 6.2 (95% CI: 3.6-8.8) Matching score <50%: 2.0 (95% CI: 0.7-3.3) HR 0.24 (95% CI 0.11-0.51), p<0.001	Matching score ≥50%: 8.3 (95% CI: 3.3-13.3) Matching score <50%: 5.3 (95% CI: 4.2-6.4) p=0.15
42	Clinical trial	149 (60 matched for PFS; 73 matched for OS; 9 non-matched for PFS; 10 non-matched for OS)	Pan-cancer	Matched: 3.67 (95% CI: 3.34-4.00) Non-matched: 1.93 (95% CI: 1.62-2.24) HR 0.65 (95% CI 0.31-1.38), p=0.253	Matched: 11.80 (95% CI: 7.20-16.40) Non-matched not reached (after a median follow-up of 6.80 months, 95% CI 3.9-13.2) HR 1.24 (95% CI 0.38-4.06), p=0.727
49	Retrospective observational cohort study - medical record review	1,307 (711 matched; 596 non-matched)	Pan-cancer	Matched: 4.0 (95% CI 3.7-4.4) Non-matched: 2.8 (95% CI 2.4-3.0) HR 0.67, p<0.001	Matched: 9.3 (95% CI 8.4-10.5) Non-matched: 7.3 (95% CI 6.5-8.0) HR 0.72, p<0.001
37	Clinical trial	1,790 (143 targeted; 315 immunotherapy [non-matched]; 56 docetaxel [non-matched])	Lung - squamous NSCLC	Targeted: 2.5 (95% CI: 1.7-2.8) Immunotherapy: 3.0 (95% CI: 2.7-3.9) Docetaxel: 2.7 (95% CI: 1.9-2.9)	Targeted: 5.9 (95% CI: 4.8-7.8) Immunotherapy: 10.8 (95% CI: 9.4-12.3) Docetaxel: 7.7 (95% CI: 6.7-9.2)
27	Retrospective observational cohort study - medical record review	94 (17 matched; 18 non-matched)	Colorectal	Matched: 6.1 (95% CI: 3.8-8.7) Non-matched: 2.3 (95% CI: 0.5-4.1) p=0.08	Matched: Not reached at 11.1 Non-matched: 9.4 p=0.146
31	Prospective observational cohort study	121 (34 matched; 46 non-matched)	Biliary tract	Matched: 4.3 (95% CI: 2.7-5.9) Non-matched: 3.0 (95% CI: 2.4-3.6) HR 0.61 (95% CI 0.37-0.99), p=0.04	Matched: 11.9 (95% CI: 5.8-18.0) Non-matched: 7.9 (95% CI: 5.9-9.9) Not statistically significant
35	Retrospective observational cohort study - medical record review	1,082 (46 matched; 146 non-matched)	Pancreatic	Matched: 10.93 (95% CI: 7.89-not reached) Non-matched: 4.53 (95% CI: 4.03-6.33) HR 0.50 (95% CI 0.29-0.86), p=0.0124	Matched: 30.96 (95% CI: 28.68-not reached) Non-matched: 18.12 (95% CI: 15.96-22.44) HR 0.42 (95% CI 0.26-0.68), p=0.0004

Reference numbers correspond to references in the supplementary file.
CI=confidence interval, HR=hazard ratio, NSCLC=non-small cell lung cancer, OS=overall survival, PFS=progression free survival

Clinical Outcomes

48 publications reported on clinical outcomes. 31 compared PFS and/or OS across subgroups of patients receiving NGS-informed cancer management vs not.

- 5 PFS only, 17 OS only, 9 both PFS and OS (Table 1), and 9 included tumor response.

PFS was significantly longer among patients who received an NGS-informed/aligned cancer management approach (e.g., matched therapy vs non-matched therapy) in 11 publications and OS significantly longer in 16 publications across tumor types.

Among publications on the same tumor type, survival increase ranged as follows:

- Colorectal cancer: OS 2-3 months longer in patients who received matched therapies.[7,27]
- Pancreatic cancer: PFS 1-6 months longer[34,35] and OS 5-22 months longer[32,35] in patients who received matched therapies.

Humanistic Outcomes

1 publication[46] reported on patients with metastatic breast cancer perceptions of treatment after NGS testing and found patients were less confident in their treatment after receiving their results, especially those whose therapy decision did not change.

- Prior to NGS testing, 36 (65.5%) of 55 patients agreed they would feel more confident in their treatment's success vs 12 (30.8%) of 39 patients after testing.

Economic Outcomes

10 publications reported on economic outcomes and 7 (4 retrospective observational cohorts, 2 economic models, 1 clinical trial) of these compared costs of NGS testing or NGS-informed management to non-NGS approaches.

- Total annual cost-benefit of NGS was estimated to be $25,000 per patient in diverted drug costs as a result of enrollment in clinical trials.[38]
- NGS-matched therapies were associated with higher overall costs:
  - Total drug and administration costs $68,729 vs $30,664, mostly driven by longer survival.[9]
  - Mean total costs $91,790 vs $40,782, mostly driven by drug costs; resulted in lower cost per week due to longer PFS.[18]
- Overall costs associated with NGS testing were higher than single-marker testing ($67,110 vs $58,297, incremental cost-effectiveness ratio was $148,478 per life-year gained[45]) but less expensive than sequential, exclusionary, or hotspot testing.[12,33]
  - NGS testing was also associated with cost savings and shorter time-to-test results compared to sequential, exclusionary, or hotspot testing.[33]
- Budget impact to the health plan of using NGS instead of single-gene testing in NSCLC over 5 years was $432,554, which represents $0.0072 per member per month.[53]

Limitations of this study include: 8 individual reviewers screened publications and abstracted data; publications were not evaluated for quality or author bias.

Conclusions

- In this review, 31 publications compared PFS and/or OS among patients who received NGS-informed cancer management (e.g., targeted or matched therapies) vs not. In 11 and 16 publications across tumor types, PFS and OS were significantly longer respectively among patients who received targeted or matched therapies.
- Publications presenting data on economic outcomes reported higher overall costs associated with NGS testing (e.g., total drug costs and costs of testing) in part because of costs associated with the targeted therapy, longer survival, and time-on-treatment, although there is the potential for cost offsets due to enrollment in clinical trials.
- There is a significant gap in the literature on humanistic outcomes. Only 1 publication reported on patient perception of NGS testing outcomes.

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