JNCI: Journal of the National Cancer Institute, 2025, 117(6), 1117–1124
https://doi.org/10.1093/jnci/djaf015
Advance Access Publication Date: January 22, 2025
Review

Comprehensive genome profiling for treatment decisions in patients with metastatic tumors: real-world evidence meta-analysis and registry data implementation

Ioannis Zerdes, MD, PhD[1,2], Panagiotis Filis, MD[3,4], Georgios Fountoukidis, MD[5,6], Ali Inan El-Naggar, MD[5,6], Foteini Kalofonou, MD, PhD[7], Antonio D'Alessio, MD[8,9], Athanasios Pouptsis, MD[10], Theodoros Foukakis, MD, PhD[1,2], George Pentheroudakis, MD, PhD[3], Johan Ahlgren, MD, PhD[11], Daniel Smith, PhD[12], Antonios Valachis, MD, PhD*[,5,6]

[1]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden
[2]Theme Cancer, Karolinska University Hospital and Comprehensive Cancer Center, Stockholm, Sweden
[3]Department of Medical Oncology, Medical School, University of Ioannina, Ioannina, Greece
[4]Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece
[5]Department of Oncology, Faculty of Medicine and Health, Örebro University, 7018 Örebro, Sweden
[6]Department of Oncology, Örebro University Hospital, Örebro, Sweden
[7]Department of Medical Oncology, The Royal Marsden Hospital NHS Trust, London, United Kingdom
[8]Department of Surgery and Cancer, Hammersmith Hospital Campus, Imperial College London, London, United Kingdom
[9]Department of Translational Medicine, Università Del Piemonte Orientale "A. Avogadro", Novara, Italy
[10]Department of Medical Oncology, Hospital Universitari de la Ribera, Valencia, Spain
[11]Regional Cancer Centre, Mid-Sweden Health Care Region, Uppsala, Sweden
[12]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden

*Corresponding author: Antonios Valachis, MD, PhD, Department of Oncology, Faculty of Medicine and Health, Örebro University Hospital, Örebro University, Örebro, Sweden (antonios.valachis@oru.se).

Author Contributions: D. Smith and A. Valachis share the co-last authorship and jointly supervised the work.

Abstract

Background: Although precision oncology has rapidly been developed in recent years, its real-world impact and challenges in health care implementation remain underexplored. Through a meta-analysis of real-world evidence (RWE), we aimed at investigating the applicability and clinical impact of comprehensive genome profiling (CGP) in cancer patients with metastatic solid tumors.

Methods: We systematically searched Medline, Embase, and Web of Science for RWE studies on CGP and matched therapies in metastatic solid tumors (publication period: 2012-2023). Pooled proportions of actionable genomic alterations, patients treated with matched targeted therapies, treatment, and survival outcomes were calculated. Data from Swedish cancer registries were used as a case study for nationwide CGP implementation.

Results: Out of the 7218 identified studies, 144 were included in our analysis; 59.8% of CGP-tested patients had actionable genomic alterations, with 15.6% (95% CI = 13.4% to 18.2%) of them having received targeted therapy. Objective response was seen in 23.9% (95% CI = 20.8% to 27.3%). Overall, CGP-guided treatment was correlated with prolonged progression-free survival (pooled hazard ratio [HR] = 0.63; 95% CI = 0.56 to 0.70; 18 studies) and overall survival (pooled HR = 0.60; 95% CI = 0.51 to 0.70; 21 studies) when compared to conventional treatment. Meta-regression time projections analyses showed that these rates will steadily increase by 2030.

Conclusions: Pooled analyses of RWE studies indicate that approximately one-fourth of the patients receiving CGP-matched treatment have an objective response. By utilizing meta-regression projections, our nationwide cancer registry case study offers insights into the potential of precision oncology for patients with metastatic cancer and to inform future health care strategies.

Introduction

Precision oncology, defined by the molecular profiling analysis of tumors to identify genetic alterations where a matched targeted treatment can be assigned, has revolutionized the management of cancer patients and disease outcomes.[1,2] An essential step in order to understand the impact and challenges of such clinical implementation is to be able to estimate the number of patients who are potentially eligible for comprehensive genome profiling (CGP), as well the anticipated clinical benefit of CGP-based targeted therapy in a real-world setting. The aim of the present study was to perform a systematic review and meta-analysis of contemporary real-world evidence (RWE) to estimate: (1) the proportion of cancer patients with metastatic solid tumors where CGP resulted in identification of actionable alterations and (2) the proportion of patients who received a targeted

Received: October 02, 2024. Revised: December 09, 2024. Accepted: January 13, 2025

therapy based on these alterations. Using a meta-regression model, we project the clinical benefit of this personalized approach to 2030.

Of note, the field of precision oncology is rapidly evolving owing to the advances in next-generation sequencing (NGS) technologies including multigene panel and whole exome/genome sequencing (WES/WGS) analysis, enabling the detection of actionable or targetable genomic alterations.[3,4] Currently, many standard therapeutic approaches in oncology rely on companion diagnostics and on the routine evaluation of various biomarkers (single/multiple genes or proteins) to support the choice of treatment in many tumor types (eg, nonsmall-cell lung cancer, ovarian, colorectal).[1,5,6] In addition, several tissue-agnostic immune and targeted therapies have received regulatory approval, based on relevant biomarkers such as microsatellite instability-high, tumor mutational burden-high, Neurotrophic tyrosine receptor kinase (NTRK) fusions, thus posing challenges for reliable and accurate identification, given the inherent limitations and capacity of multigene sequencing.[7,8] To this end, the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) have launched a set of recommendations for the use of genomic testing and CGP in patients with metastatic cancer.[4,9] Furthermore, ESMO has developed a framework called ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) to rank genomic alterations according to the level of clinical evidence for molecular targets in a 6-tier scale, from targets ready for implementation (tier I) to preclinical-only or those with lack of evidence.[10]

Following the results of pivotal randomized trials demonstrating a substantial clinical benefit of CGP-matched treatment in patients with metastatic cancer,[2] many centers worldwide have launched initiatives for integrating CGP toward detection of genomic drivers in clinical routine and assessing its clinical utility using CGP-guided treatments. Considering the emerging role of real-world data (RWD) in clinical cancer research and in complementing the traditional clinical trial-based strategies,[11] as well as the multigene panel-based testing on treatment decision-making in cancer patients with metastatic disease in the real-world setting, health care systems should be prepared to meet the resource and public policy challenges of a broad implementation of these technologies in clinical practice. Therefore, the RWE-based information from the current meta-analysis was also applied to Sweden's nationwide cancer registries data from selected solid tumors, with the aim to estimate the actual number of patients expected to receive benefit from CGP at a national level, serving as a paradigm for future health care planning and implementation strategies.

Methods

Search strategy and study selection criteria

A literature search was performed in Medline, Embase, and Web of Science databases and the last search was conducted in June 2023. The search strategy was developed in Medline (Ovid) in collaboration with librarians at the Karolinska Institutet University Library. Key search terms included: "neoplasms," "metastasis," "gene expression profiling," "whole genome sequencing," "whole exome sequencing," "molecular targeted therapy," "molecular tumor board," "precision medicine." For each search concept, Medical Subject Headings terms and free text terms were identified. The search was then translated, in part using Polyglot Search Translator,[12] into the other databases. The detailed search strategy and algorithm are provided in Methods S1. The searching was restricted to studies published in English language and articles published before 2012 were not reviewed, considering the recent evolution in NGS technologies. The search strategies were peer reviewed by another librarian prior to execution. Deduplication was done using the method described by Bramer et al.[13] One final, extra step was added to compare Digital Object Identifiers (DOIs). The systematic review and meta-analysis protocol was registered in PROSPERO repository (CRD42023463314) and was reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist[14] (Table S1).

Title, abstract, and full-text screening was performed by 4 independent reviewers (I.Z., P.F., G.F., A.V.), who agreed upon study selection. Eligible studies were identified and included in our meta-analysis if they fulfilled the following PICOS elements/framework: (1) P (Population): included patients with advanced or metastatic solid tumors apart from non small cell lung cancer (NSCLC) (due to the established role of CGP testing in this cancer type); (2) I (Intervention): performed CGP-based genomic testing to identify predictive biomarkers for targeted therapies; (3) C (Comparator): included patients treated with conventional therapy without CGP testing; (4) O (Outcome): reported success rate, actionable alteration rate, actionable alteration of ESCAT I-II level rate; recommended targeted therapy rate, recommended off-label targeted therapy rate, objective response rate (ORR) in patients treated with targeted therapy, progression-free survival (PFS) and overall survival (OS) in patients treated with targeted therapy; (5) S (Study): retrospective or prospective cohort studies as well as nonrandomized phase II studies with a setting resembling clinical practice. Only studies that led to an NGS-guided targeted therapy were included. Studies including less than 30 patients, pediatric populations, more than 15% NSCLC, randomized phase II and phase III trials, basket or umbrella trials, studies including in vitro and/or in vivo experiments, case reports, (systematic) reviews, or previous meta-analyses were excluded.

Data extraction, outcome definitions, and quality assessment

Data extraction of the selected studies was performed independently by 8 reviewers (I.Z., P.F., G.F., A.E.-N., F.K., A.D., A.P., A.V.) using a predefined form in Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). All studies were checked in duplicates by 2 reviewers (I.Z., A.V.) through comparison of the databases and any discrepancies were resolved after discussion between the 2 reviewers. Variables included name of the first author, journal, year of publication, country of the principal investigator, multicenter or single-center study, study type (prospective/retrospective), number of patients tested with NGS were collected from each record. Data on the main and secondary outcomes of interest were also retrieved from each eligible study according to the following definitions:

Main outcomes included metrics related to applicability of CGP in clinical practice: (1) success rate, that is, proportion of patients where CGP resulted in a reliable result; (2) actionable alteration rate, that is, proportion of patients where an actionable genomic alteration was identified through CGP; (3) rate of actionable alteration of clinical significance, that is, proportion of patients where an actionable genomic alteration of ESCAT I/II level—according to the latest ESMO recommendations or similar—was identified through CGP; (4) recommended targeted therapy rate, that is, proportion of patients where a targeted therapy was used based on CGP results; (5) recommended off-label

targeted therapy rate, that is, proportion of patients where an off-label targeted therapy was used based on CGP results.

Secondary outcomes included metrics related to clinical effectiveness of CGP-based treatment: (1) ORR, that is, proportion of patients treated with targeted therapy based on CGP results achieving complete or partial response; (2) PFS in patients treated with targeted therapy; (3) OS in patients treated with targeted therapy; (4) ORR, PFS, and OS for patients received CGP-guided treatment vs those received conventional therapy without multigene testing (comparator arm). For the treatment and survival outcomes (ORR, PFS, OS), we accepted the definition used in each study, thus not performing any separate alignment for the definitions. Moreover, for studies with a comparator arm, the Newcastle-Ottawa Scale (NOS) was applied for quality assessment of the eligible studies by 8 independent reviewers (I.Z., P.F., G.F., A.E.-N., F.K., A.D., A.P., A.V.), as previously described.[15] Newcastle-Ottawa Scale comprised 9 items grouped in 3 broad perspectives: (1) selection and (2) comparability of the different study groups as well as (3) ascertainment of the outcome of interest, with studies receiving a score of more than equal to 7 being of high quality. However, the quality of each study did not impact its inclusion in the meta-analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was utilized to grade the certainty of evidence among outcomes derived from studies with comparator arm.[16]

Nationwide data and description of the patient population

The total number of incident and prevalent cases of metastatic cancer in 2 selected cancer types with complete pooled analyses for all relevant outcomes, as identified in the systematic review, that is, breast cancer and biliary tract malignancies, were retrieved from the corresponding Swedish national cancer registries. The total number of patients with each of the selected diagnoses within 1 year (2022) in Sweden were used to estimate the actual number of patients expected to receive benefit from CGP implementation at a national level.

Statistical analysis

Statistical analysis was performed in R version 4.4.0 relying heavily on the packages; *metafor*, *clubSandwich*, *emmeans*, and the *tidyverse* suite.[17-20] Our assembled data comprised of subset combinations of outcome types (ie, proportions, medians, ratios) and cancer types (the latter including an "any" category, where effects were to be pooled across all cancers). We computed the logarithm of the outcome type, and its variance using information collected from primary studies (numerators and denominators for proportion outcomes, and Confidence Intervals for medians and ratio measures).

Univariate meta-analyses

We used random effects univariate meta-analytic models to compute pooled metrics and 95% Confidence Intervals, for each of the aforementioned subsets containing at least 5 estimates from primary studies. We report several measures of heterogeneity, including I^2, H^2, and τ^2.

Multivariate meta-analysis of proportions

Several metrics were each divided by the number of patients tested with NGS in order to compute proportions for analyses. These included the number patients with: (1) reliable NGS results; (2) actionable genomic alterations, (3) actionable genomic alterations of clinical significance, (4) any targeted therapy, and (5) objective response. For the latter, we also computed a proportion with the denominator being the number of patients treated with any targeted therapy. We hereafter refer to these 6 computed metrics as proportion "outcome." We fitted a multivariate meta-analytic mixed model of the log proportion. This model included outcome and the interaction between outcome and year of inclusion period as moderator (ie, explanatory) variables. Using this model, we estimated the mean proportion and 90% Confidence Intervals conditional on outcome type and year of inclusion period. For the latter, we extrapolated to 2030, yielding model-based projections. A detailed description of statistical analyses is provided in Methods S1.

Results

Study selection process and characteristics

The initial search identified 13 930 records (Medline: 4656, Embase: 5485, Web of Science: 3789) and following deduplication, 7218 records were screened. Upon the exclusion of 6851 studies based on title and/or abstract, 367 records were retrieved and screened in full-text and a total of 144 studies fulfilled the eligibility criteria and included in the meta-analysis. The PRISMA flow diagram of search and study selection is presented in Figure 1.

The majority of the studies were published between 2020 and 2023 (62.5%), conducted in Europe (42.4%) and in single centers (75%). Most of the studies used commercially available gene panels (47.8%), while approximately 10% used WES/WGS approaches. The majority of the studies reported data on multiple cancer types (40.1%), with most frequent types being breast (9.3%), biliary tract (8.6%), gastrointestinal (8%), and gynecological (7.4%) malignancies (Table 1). A detailed description of each eligible study is provided in Table S2.

Pooled proportions of actionable alterations, matched targeted therapies, and treatment response

Based on the studies including any cancer type, nearly all of the patients who were tested with CGP had reliable results (98.3%, 95% CI = 97.50 to 98.82; $n = 42\,728$ patients; 124 studies); approximately two-thirds of the patients presented with actionable genomic alterations (59.8%, 95% CI = 54.98 to 64.42; 127 studies); about one-fifth (22.4%, 95% CI = 16 to 30.3; 38 studies) had genomic alterations of clinical significance and 15.6% (95% CI = 13.4 to 18.2; $n = 54\,739$; 139 studies) received targeted CGP-based treatment. Although the rates of objective response were low in the whole CGP-tested population (pooled ORR: 3.87%; 95% CI = 3.06 to 4.89), 23.9% (95% CI = 20.8 to 27.3) of the patients receiving CGP-guided treatment achieved an objective response (Table 2). When WGS/WGS approaches were applied, the pooled proportion of patients with actionable genomic alterations detected and received any NGS-based targeted therapy were higher compared to multigene panel-based strategies 74.75% vs 59.79% for the actionable alteration and 19.98% vs 15.61% who received treatment. However, fewer objective responses were observed in the treated patients with extended genomic testing (Table S4).

Regarding specific cancer types, 75.3% of patients with breast cancer, 58.7% with biliary tract/liver cancer, 55.6% with sarcoma had actionable genomic alterations, while 22.3%, 17.3%, and 8.8% received targeted therapy, respectively. Furthermore, out of the aforementioned patients who received targeted treatment, approximately one-fifth experienced an objective response

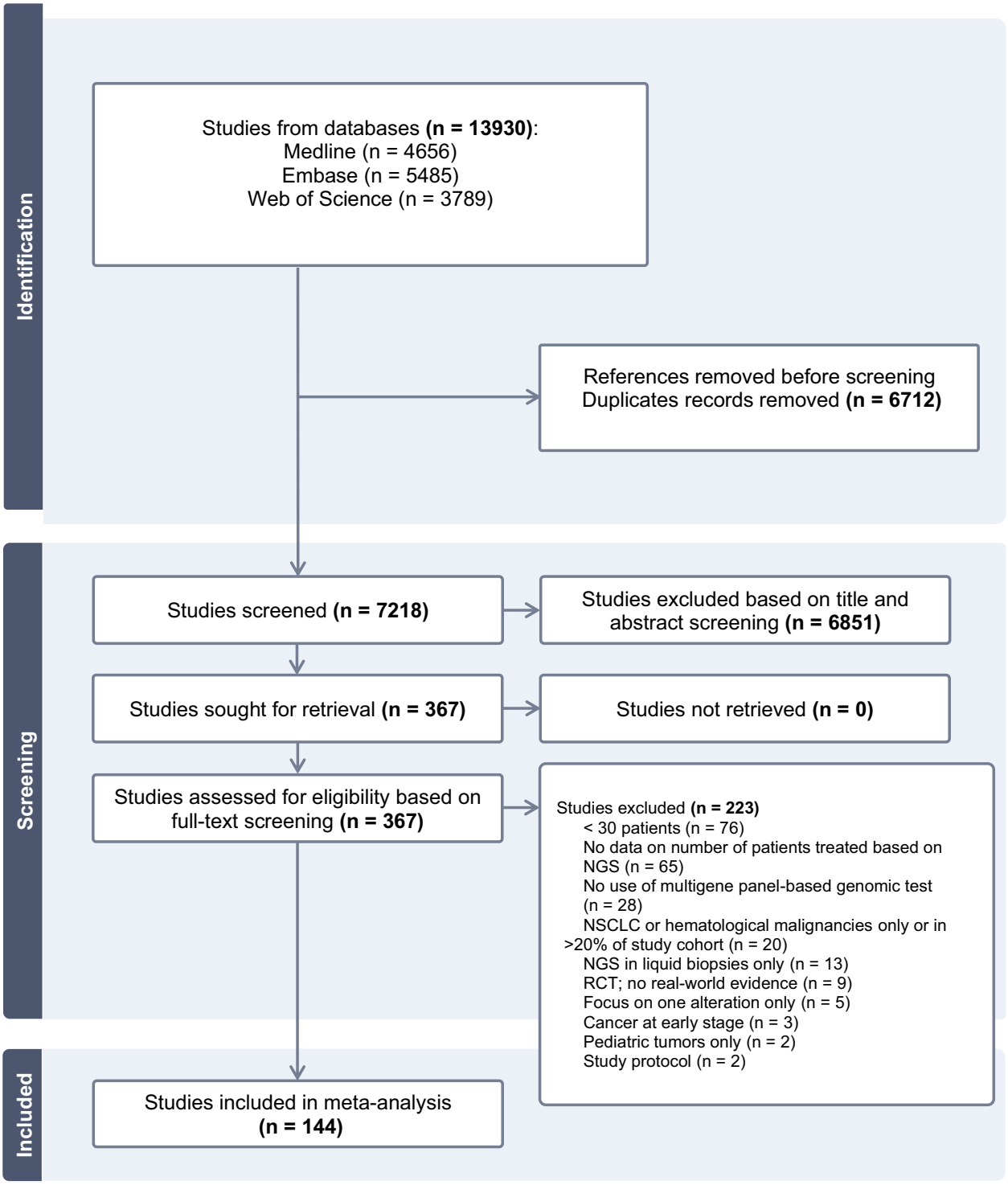

Figure 1. PRISMA flowchart of search and study selection. Abbreviation: NGS = next generation sequencing; NSCLC, non small cell lung cancer; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

(breast cancer: 20.2%; biliary tract/liver cancer: 25.1%, sarcoma: 18.8%) (Table S3). Substantial statistical heterogeneity ($I^2 > 50\%$) was observed among the included studies in the majority of the pooled proportion analyses.

For patients treated with NGS-guided therapy, the pooled median PFS was 4.41 months (95% CI = 3.71 to 5.24; 35 studies) and OS was 13.14 months (95% CI = 9.56 to 18.06; 16 studies) for all cancer types (Table S5). Regarding the effect of CGP-guided treatment ($n = 40$ studies, median NOS overall score of 5.5 [IQR: 4.0-6.5]) (Table S6), statistically significantly increased ORR (Odds Ratio = 2.75; 95% CI = 1.84 to 4.13; 16 studies, $n = 1109$; Figure S1A), longer PFS (HR = 0.63; 95% CI = 0.56 to 0.70; 18 studies, $n = 3269$; Figure S1B), and OS (HR = 0.60; 95% CI = 0.51 to 0.70; 21 studies, $n = 2772$; Figure S1C; Table S7) were observed compared

Table 1. Summary of characteristics of the eligible studies.

Characteristics	*n* (%)
Total number of included studies	144
Country	
USA or Canada	52 (36.1%)
Europe	61 (42.4%)
Asia	29 (20.1%)
Oceania	2 (1.4%)
Publication year	
2010-2014	2 (1.4%)
2015-2019	52 (36.1%)
2020-2023	90 (62.5%)
Multicentric	36 (25%)
Cancer type	
Multiple	65 (40.1%)
Breast	15 (9.3%)
Biliary tract	14 (8.6%)
Pancreatic	10 (6.2%)
Gynecological malignancies	12 (7.4%)
Sarcoma	9 (5.6%)
CUP	5 (3.1%)
CNS	5 (3.1%)
Gastrointestinal	13 (8%)
Genitourinary	8 (4.9%)
Other (head and neck, thyroid, ocular)	6 (3.7%)
NGS assay	
FoundationOne	33 (23.2%)
Other commercially available assay	35 (24.6%)
In-house gene panel	22 (15.5%)
Various	37 (26.1%)
WES/WGS	13 (9.2%)
Not reported/specified	2 (1.4%)

Abbreviations: CUP = Cancer unknown primary; CNS = Central nervous system; NGS = next-generation sequencing; WES/WGS = whole exome/genome sequencing.

to conventional treatment, although with a very low to low certainty of evidence (Table S8).

Projections of pooled proportions over time

We used our multivariate meta-analytic model to estimate the aforementioned different pooled proportions and to project them over time. Accordingly, the anticipated proportion of patients with actionable genomic alterations (2025: 66.1%, 2030: 68.3%), CGP-guided treatments (2025: 17.9%, 2030: 19.3%), and objective responses (2025: 29.1%, 2030: 32.5%) are expected to gradually rise toward 2030 (Figure 2, Table S9).

Nationwide CGP data implementation: a cancer registry real-world case study

In order to provide estimations on the potential of CGP implementation at a national level, we applied the aforementioned projections to patient data from the Swedish cancer registries for selected diagnoses in 2022, in order to estimate the expected number of patients and 90% confidence limits. Regarding biliary tract cancer patients planned for noncurative treatment for advanced disease ($n = 383$), the number of patients with identified actionable mutations of clinical significance could rise from 109 (95% CI = 56 to 163) to 146 (95% CI = 37 to 299), with objective responses increasing from 18 (95% CI = 8 to 37) to 23 (95% CI = 5 to 89) patients by 2030. Among patients with breast cancer and de novo or recurrent metastatic disease ($n = 1414$), the number of patients with actionable mutations would rise from 402 (95% CI = 208 to 676) to 541 (95% CI = 137 to 1106) with objective responses anticipating to be increased from 65 (95% CI = 30 to 138) to 83 (95% CI = 18 to 328) patients by 2030.

Discussion

This is—to the best of our knowledge—the first meta-analysis evaluating the impact of CGP for treatment decision-making in patients with metastatic solid tumors in the real-world setting. Among 144 eligible studies, a total of 54 739 patients underwent CGP, with approximately 15% of the CGP-tested patients receiving matched treatment and one-fourth of them experiencing an objective response. These results mirror the mounting knowledge on molecular mechanisms and treatment resistance, the development of more potent drugs and the growing arsenal of tumor-agnostic drug approvals.

When comparative efficacy data were considered, CGP-guided targeted therapy was implied to be associated with improved outcomes compared to traditional treatment strategies, although with a low certainty of evidence, mainly due to clinical heterogeneity and the low internal validity of eligible studies. On the other hand, one could argue that the rates of patients who received matched CGP-based therapy and had objective responses remain low. Regarding the former, inadequate, insensitive, or narrow CGP testing techniques could lead to lower rates of detectable actionable alterations, while the limited availability of targeted treatments and early phase clinical trial programs as well as cost-reimbursement issues could impact the access to CGP-matched therapies.[21] The observed discrepancy between the patients with identified actionable mutations and the proportion of patients receiving matched treatment could also be attributed to patient-related factors, that is, aggressive disease and heavily pretreated patients that could not receive the recommended therapy due to clinical deterioration. Moreover, even for patients receiving a CGP-matched treatment, the presence of intrapatient/tumoral heterogeneity as well as the impact of the genomic context could affect the therapeutic response.[22]

Interestingly, although the majority of the studies reported data based on the use of commercially available gene panels—indicating the lower cost and increased availability of targeted sequencing approaches—10% of the studies reported results on WES/WGS platforms. This observation is reflecting the advances of sequencing technologies, the potential for implementation of wide-genome testing, thus paving the way for the integration of additional diagnostic modalities to standard DNA testing (ie, transcriptomics, proteomics), thus enhancing the precision cancer treatment options.[1,23]

In order to provide a real-world case study and exemplify the implementation of our time projection analyses, we used data from the national cancer registries to estimate the actual number of patients who might derive benefit by CGP implementation. These projections could be a valuable tool for future health care strategies and policy making, with a view to project, design, and execute precision oncology initiatives in other countries using data from nationwide cancer registries. Considering the high completeness of the Swedish National Cancer Registries, such implementation in other countries would imply similar coverage and patient demographics. Given that the proportion of patients with actionable genomic alterations and those with potential clinical benefit are expected to rise during the coming 5 years, our results could be, therefore, utilized as a framework to quantify the impact of implementing NGS-based treatment approach into national health care systems. Hence, based on the expected number of patients to be treated, each country or region could adapt and utilize the health economic resources for the optimal use of broad NGS-based panels and accessibility to new targeted therapies. We argue that the results of our pooled analyses could

Table 2. Pooled proportions of reliable NGS results, actionable genomic alterations, actionable genomic alterations of clinical significance, treated with matched treatment based on NGS, objective responses for all eligible studies of any cancer type.

Numerator	Denominator	*n* estimates	*n* studies	*n* numerator	*n* denominator	Pooled proportion (%) (95% CI)	I^2 (%)	H^2	τ^2
Any cancer type									
n patients treated with any NGS-based targeted therapy	*n* patients tested with NGS	146	139	6355	54 739	15.61 (13.36 to 18.16)	97.33	37.45	1.12
n patients with actionable genomic alterations	*n* patients tested with NGS	148	127	24 642	53 385	59.79 (54.98 to 64.42)	98.81	83.72	1.23
n patients with actionable genomic alterations of clinical significance	*n* patients tested with NGS	40	38	5437	23 278	22.36 (16.01 to 30.32)	99.09	110.49	1.47
n patients with reliable NGS results	*n* patients tested with NGS	138	124	42 728	46 654	98.28 (97.50 to 98.82)	98.25	57.24	2.96
n patients with objective responses	*n* patients treated with any NGS-based targeted therapy	83	78	845	3960	23.90 (20.80 to 27.30)	69.94	3.33	0.33
n patients with objective responses	*n* patients tested with NGS	84	78	846	25 823	3.87 (3.06 to 4.89)	89.16	9.23	0.91

Abbreviation: NGS = next-generation sequencing.

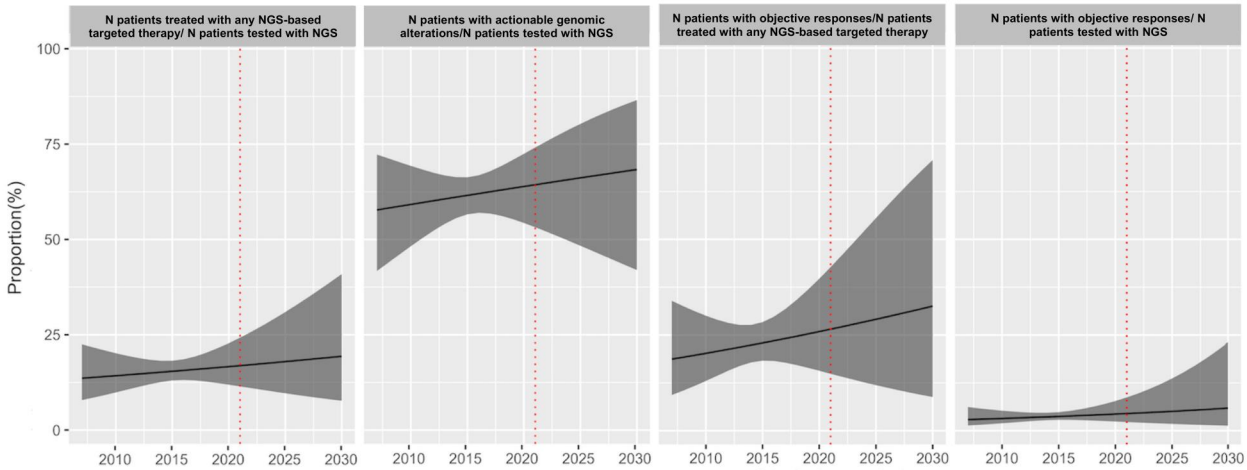

Figure 2. Time series meta-regression projections of pooled proportions of (1) patients treated with NGS-based therapy, (2) patients with actionable genomic alterations, (3) objective responses among patients treated with NGS-based therapy, and (4) objective responses among patients with NGS analysis up to 2030. Abbreviation: NGS = next-generation sequencing.

also be used as health care indicators before the establishment of a precision oncology program and the resource allocation strategies and estimation of patients needed to be tested and eventual clinical benefit. Moreover, the focus on RWE could also inform the design of future precision oncology clinical trials and drug repurposing studies.

Nonetheless, the implementation of such precision medicine platforms might be challenging and quite heterogeneous, mainly due to geographical and health care system disparities in availability and accessibility of biomolecular technologies, biomarker testing and access to targeted treatments in Europe and in other countries in the world.[24,25] In order to surpass these barriers and promote standardization of the decision-making process, the development of machine learning-based tools carries the potential to significantly facilitate the inclusion of patients in precision oncology programs.[26,27]

Although our findings could be considered supportive for the implementation of CGP in clinical practice, several challenges remain to be addressed, such as the complexity of interpretation and reporting of the genomic results using various available tools,[28] the infrastructure and expertise needed for the establishment of the fundamental multidisciplinary molecular tumor boards,[29,30] the unacceptably long turnaround time of the genomic testing results and the overall treatment recommendations, the educational resources for health care professionals, and the ongoing need for qualified clinician-scientists.[31] Of note, the adaptation of a common framework for the scaling clinical actionability[9,10] is of utmost importance, as it is reflected in the relatively low rates of genomic alterations of clinical significance in the reported studies. Furthermore, the need of international collaboration remains of high priority, especially in the case of rare tumor types where the comprehensive characterization of molecular landscape in a prospective manner could enhance therapeutic opportunities for these patients.[32-34]

In terms of implementation of CGP in clinical practice, our findings should be interpreted with caution as several limitations do exist. Although we mostly focused on CGP RWD, we chose to include phase II nonrandomized clinical trials that aimed to match patients to CGP-guided treatments as well, given that many clinical centers' precision oncology programs were

incorporated only within single arm phase II clinical trials (resembling the rest of RWE initiatives). An additional limitation was the exclusion of studies reporting less than 30 patients; this could have led to underrepresentation of patients with rare cancers and the inability to perform further subgroup analyses of potential interest and within specific tumor subtypes. Furthermore, the fact that this is not an individual patient data meta-analysis precludes any in-depth analysis based on specific tumor- or patient-related characteristics. Considering that our pooled results mostly relied on RWD analyses, various methodological drawbacks of the eligible studies as selection bias (for all eligible studies), confounding by indication bias, and immortal-time bias (primarily for comparative studies) as well as publication bias could impact the validity of study results. This is the reason why the use of GRADE approach was specifically applied to reveal the certainty of evidence in the analyses related to comparative studies, thus facilitating a more balanced interpretation of study results. Moreover, the clinical heterogeneity among the eligible studies (various cancer types, various treatment lines, various treatment strategies as comparators) could also affect the validity of study results. Finally, the follow-up was not reported for the vast majority (78.4%) of the comparative studies and as a result, it was not possible to assess the adequacy of follow-up or any imbalance in the follow-up strategies between the different treatment strategies. Besides, given the uncertainty of the meta-regression model estimates of over time (due the assumption that the effect of time is linear on the log proportion and that this effect remains so over the extrapolation period), we chose not to extrapolate beyond 2030. Hence, these shortcomings highlight the need for improving the quality of RWD reporting, also in studies including molecular oncology analyses.[35]

In conclusion, the results of the present study revealed that approximately one-fourth of the patients receiving matched treatment-based CGP will have an objective response and that CGP-guided therapeutic decisions could be correlated with improved outcomes in the real-world setting, though with very low to low certainty of evidence. Our nationwide CGP cancer registry case study could represent a valuable framework for future health care precision oncology implementation strategies.

Acknowledgments

The authors would like to acknowledge the contribution of Sabina Gillsund, librarian at the Karolinska Institutet University Library during the preparation of this manuscript.

Author contributions

Ioannis Zerdes (Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Supervision, Writing—original draft), Panagiotis Filis (Data curation, Investigation, Validation, Writing—review & editing), Georgios Fountoukidis (Data curation, Investigation, Validation, Writing—review & editing), Ali Inan El-Naggar (Data curation, Investigation, Validation, Writing—review & editing), Foteini Kalofonou (Data curation, Investigation, Validation, Writing—review & editing), Antonio D'Alessio (Data curation, Investigation, Validation, Writing—review & editing), Athanasios Pouptsis (Data curation, Investigation, Validation, Writing—review & editing), Theodoros Foukakis (Methodology, Supervision, Writing—review & editing), George Pentheroudakis (Methodology, Supervision, Writing—review & editing), Johan Ahlgren (Conceptualization, Methodology, Supervision, Writing—review & editing), Daniel Smith (Data curation, Formal analysis, Methodology, Software, Visualization, Writing—original draft, Writing—review & editing), and Antonios Valachis (Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing—original draft, Writing—review & editing).

Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

Funding

I.Z. is supported by the Region Stockholm (clinical postdoctorial appointment, FoUI-977295). A.D. is supported by the National Institute for Health Research (NIHR) Imperial BRC, by grant funding from the European Association for the Study of the Liver (2021 Andrew Burroughs Fellowship) and from Cancer Research UK (RCCPDB-Nov21/100008).

Conflicts of interest

I.Z.: financial interests, institutional, invited speaker: Novartis. Financial interests (institutional), research grant: Gilead. A.D. received educational support for congress attendance from Roche, and consultancy fees from Roche, AstraZeneca, and Chugai. A.P. received educational support for congress attendance from Novartis, and consultancy fees from GSK and Astellas. T.F.: financial interests, institutional, invited speaker: Roche, AstraZeneca, Gilead Sciences; financial interests, personal, advisory board: Novartis, Veracyte, Exact Sciences, Affibody; financial interests, personal, invited speaker: Pfizer; financial interests, personal, royalties, authorship of 2 chapters in UpToDate: Wolters Kluwer; financial interests, institutional, coordinating PI, clinical trial support (research grant and study drug): Pfizer; financial interests, institutional, sponsor and coordinating PI, international co-PI of academic trial ARIADNE (EU CT: 2022-501504-95-00): AstraZeneca, Novartis, Veracyte. G.P. declares employment by ESMO; nonrenumerated membership of ASCO, Hellenic Cooperative Oncology Group, and Hellenic Society of Medical Oncology. A.V.: financial interests (institutional), unrestrictive research grant Roche and MSD; invited speaker (institutional): Daiichi Sankyo, MSD, Novartis, Pfizer, Roche, Seagen. All other authors have declared no conflicts of interest.

Data availability

The datasets and R code used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

1. Aldea M, Friboulet L, Apcher S, et al. Precision medicine in the era of multi-omics: can the data tsunami guide rational treatment decision? *ESMO Open*. 2023;8:101642.
2. Schwaederle M, Zhao M, Lee JJ, et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. *J Clin Oncol*. 2015;33:3817-3825.

3. Schwartzberg L, Kim ES, Liu D, Schrag D. Precision oncology: who, how, what, when, and when not? *Am Soc Clin Oncol Educ Book*. 2017;37:160-169.
4. Mosele MF, Westphalen CB, Stenzinger A, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. *Ann Oncol*. 2024;35:588-606.
5. Jørgensen JT. The current landscape of the FDA approved companion diagnostics. *Transl Oncol*. 2021;14:101063.
6. Hendriks LE, Kerr KM, Menis J, et al.; ESMO Guidelines Committee. Electronic address: Clinicalguidelines@esmo.org. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:339-357.
7. Adashek JJ, Kato S, Sicklick JK, Lippman SM, Kurzrock R. If it's a target, it's a pan-cancer target: tissue is not the issue. *Cancer Treat Rev*. 2024;125:102721.
8. Westphalen CB, Martins-Branco D, Beal JR, et al. The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. *Ann Oncol*. 2024;35:936-953.,
9. Chakravarty D, Johnson A, Sklar J, et al. Somatic genomic testing in patients with metastatic or advanced cancer: ASCO provisional clinical opinion. *J Clin Oncol*. 2022;40:1231-1258.
10. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29:1895-1902.
11. Saesen R, Van Hemelrijck M, Bogaerts J, et al. Defining the role of real-world data in cancer clinical research: the position of the European Organisation for Research and Treatment of Cancer. *Eur J Cancer*. 2023;186:52-61.
12. Clark JM, Sanders S, Carter M, et al. Improving the translation of search strategies using the Polyglot Search Translator: a randomized controlled trial. *J Med Libr Assoc*. 2020;108:195-207.
13. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc*. 2016;104:240-243.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
15. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Accessed October 10, 2024. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
16. Guyatt GH, Oxman AD, Vist GE, et al.; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
17. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Soft*. 2010;36:1-48.
18. Pustojevsky J. clubSandwich: cluster-robust (sandwich) variance estimators with small-sample corrections. 058 [R Package]; 2022.
19. Lenth R. Emmeans: estimated marginal means, aka least-squares means. R package version 1.9.0.2023. 2024.
20. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *J Open Source Softw*. 2019;4:1686.
21. Hernando-Calvo A, Nguyen P, Bedard PL, et al. Impact on costs and outcomes of multi-gene panel testing for advanced solid malignancies: a cost-consequence analysis using linked administrative data. *EClinicalMedicine*. 2024;69:102443.
22. Fulton-Ward T, Middleton G. The impact of genomic context on outcomes of solid cancer patients treated with genotype-matched targeted therapies: a comprehensive review. *Ann Oncol*. 2023;34:1113-1130.
23. Pleasance E, Bohm A, Williamson LM, et al. Whole-genome and transcriptome analysis enhances precision cancer treatment options. *Ann Oncol*. 2022;33:939-949.
24. Bayle A, Bonastre J, Chaltiel D, et al. ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe. *Ann Oncol*. 2023;34:934-945.
25. Normanno N, Apostolidis K, Wolf A, et al. Access and quality of biomarker testing for precision oncology in Europe. *Eur J Cancer*. 2022;176:70-77.
26. Kasprzak J, Westphalen CB, Frey S, et al. Supporting the decision to perform molecular profiling for cancer patients based on routinely collected data through the use of machine learning. *Clin Exp Med*. 2024;24:73.
27. Aldea M, Ghigna MR, Lacroix-Triki M, Andre F. Unlocking the potential of AI-assisted pathology for molecular alteration screening. *Eur J Cancer*. 2024;197:113467.
28. Tamborero D, Dienstmann R, Rachid MH, et al.; Cancer Core Europe Consortium. The Molecular Tumor Board Portal supports clinical decisions and automated reporting for precision oncology. *Nat Cancer*. 2022;3:251-261.
29. Di Pilla A, Cozzolino MR, Mannocci A, et al. The impact of tumor boards on breast cancer care: evidence from a systematic literature review and meta-analysis. *Int J Environ Res Public Health*. 2022;19:14990.
30. Tamborero D, Dienstmann R, Rachid MH, et al.; Cancer Core Europe Consortium. Support systems to guide clinical decision-making in precision oncology: the Cancer Core Europe Molecular Tumor Board Portal. *Nat Med*. 2020;26:992-994.
31. Lim KHJ, Westphalen CB, Berghoff AS, et al. Young oncologists' perspective on the role and future of the clinician-scientist in oncology. *ESMO Open*. 2023;8:101625.
32. Morfouace M, Horak P, Kreutzfeldt S, et al. Comprehensive molecular profiling of sarcomas in adolescent and young adult patients: results of the EORTC SPECTA-AYA international proof-of-concept study. *Eur J Cancer*. 2023;178:216-226.
33. Morfouace M, Stevovic A, Vinches M, et al. First results of the EORTC-SPECTA/Arcagen study exploring the genomics of rare cancers in collaboration with the European reference network EURACAN. *ESMO Open*. 2020;5:e001075.
34. Tagliamento M, Morfouace M, Loizides C, et al. EORTC-SPECTA Arcagen study, comprehensive genomic profiling and treatment adaptation of rare thoracic cancers. *NPJ Precis Oncol*. 2024;8:37.
35. Castelo-Branco L, Pellat A, Martins-Branco D, et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW). *Ann Oncol*. 2023;34:1097-1112.

JNCI: Journal of the National Cancer Institute, 2025, 117, 1117–1124
https://doi.org/10.1093/jnci/djaf015
Review