Clinical Benefit of Comprehensive Genomic Profiling for Advanced Cancers in India

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PURPOSE Comprehensive genomic profiling (CGP) assay is increasingly used in low-middle–income countries to detect clinically relevant genomic alterations despite its clinical benefits not being well known. Here, we describe the proportion of patients with advanced cancer in India who received targeted therapy for an actionable genetic alteration identified on CGP assays.

METHODS This was a multicenter, retrospective cohort study in adult patients with advanced nonhematologic malignancies who underwent a CGP test. If patients received a targeted therapy for ≥ 6 months, they were considered to have obtained a clinical benefit from the medication, whereas those continuing for ≥ 12 months were considered to have attained an exceptional response. Descriptive statistics were used to describe the proportion of patients with subsequent targeted therapy.

RESULTS During 2019-2020, 12 medical oncologists provided CGP reports for 297 patients; 221 met the inclusion criteria. Patients received a median of two lines (range: 0-5) of prior systemic therapy. On the basis of the CGP assay, 21 patients (10%) received targeted therapy. Among them, 33% was for human epidermal growth factor receptor 2 (HER2) amplification (nonbreast cancer) and 19% for HER2 or epidermal growth factor receptor exon 20 insertion mutation (lung cancer). After excluding patients with HER2 or epidermal growth factor receptor exon 20 insertions, 8% of 217 patients received targeted therapy. In the overall cohort of 221 patients, clinical benefit was seen in nine patients (4%), of whom two were exceptional responders (1%).

CONCLUSION We observed that in a low-middle–income country setting, 10% of patients received targeted therapy on the basis of CGP assay. Only 4% of patients who underwent CGP testing obtained a clinical benefit.

INTRODUCTION

Cancer arises because of mutations in the human genome, resulting in the development of neoplastic cells. Next-generation sequencing (NGS) techniques provide us with the genetic profile of the patient's cancer, which helps in identifying clinically relevant genetic alterations that can serve as targets for potential therapies. The first molecular targeted therapy on the basis of genetic profiling was trastuzumab in patients with ERBB2-overexpressed breast cancer introduced in 1998. Since then, a large number of novel targeted therapies were discovered including bcr/abl inhibitors in chronic myeloid leukemia, BRAF inhibitors in melanoma, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non–small-cell lung cancer, which yielded robust therapeutic responses. As of 2019, there are 64 Food and Drug Administration–approved molecular targeted therapies used in cancer treatment.

Several comprehensive genomic profiling (CGP) testing platforms such as MedGenome, Caris, and Foundation One are currently available, each assessing different types and numbers of genes. Remarkable antineoplastic activity associated with targeted therapies has led to a rise in the usage of CGP to detect clinically relevant genomic alteration. Although a large number of patients profiled have genomic alterations that could be targeted by molecular therapies, only a very small fraction of them actually receive these sequencing-directed therapies.[1-8] In a recent study by Cobain, 80.5% of the profiled patients had actionable genetic variations but only 16.2% received targeted therapy on the basis of CGP assay.[1] Among those patients who received targeted therapy, only 37.1% (4.82% of total patients profiled) reported clinical benefits.[1] Similar results were also stated by other studies where clinical benefits were seen in only 2%-8% of the total patients profiled.[1,4-6] SHIVA trial, the sole randomized study which assessed the therapeutic benefits of targeted therapy on the basis of CGP assay, reported that treatment with matched molecular therapy did not yield any significant increase in progression-free

CONTEXT

Key Objective

We aimed to study the clinical benefit of comprehensive genomic profiling in advanced cancers in India.

Knowledge Generated

We observed that 10% of patients who underwent testing received a targeted therapy and 4% obtained a clinical benefit, defined as receiving a targeted therapy for at least 6 months.

Relevance

Our findings are unique from the perspective of clinical practice in a low- and middle-income country. It would inform shared decision making on the role of such testing in advanced cancers.

survival of patients with cancer.[9] In contradiction to this, there are other nonrandomized studies that report superior clinical outcomes associated with sequencing-directed molecular therapies.[3,5,8,10-13]

Despite the availability and clinical use of CGP among patients with cancer in low-middle–income countries (LMICs), there is a dearth of systemic studies that assess its clinical utility. This calls for further studies that evaluate the influence of CGP assay on treatment decisions so that its therapeutic benefits could be determined. In our multicenter retrospective study, we describe the proportion of patients with advanced cancers in India who eventually received targeted molecular therapy on the basis of CGP assay. We also estimate the clinical benefit of such a testing and therapeutic strategy.

METHODS

We conducted a multicenter retrospective cohort study conducted among patients with advanced cancer in India. Adult patients (age $\geq$ 18 years) with histologically confirmed nonhematologic advanced malignancies who underwent CGP assay were eligible for enrollment in the study. Patients with any type of tumor, stage of the disease, and undergoing any standard therapy were eligible for inclusion. No restrictions were placed on the number of lines of systemic therapy received by patients before CGP assay. Patients with genetic alterations that have well-validated standardized targeted therapy were excluded (eg; *EGFR* exon 18, 19, 21 mutations for lung cancer, human epidermal growth factor receptor 2 *(HER2)* amplification and *PIK3CA* mutation in breast cancer, *BRAF* mutation in melanoma and lung cancer, *KRAS* mutation in colon cancer, *KIT* mutation in GI stromal tumors, and *HER2* amplification in esophageal adenocarcinoma; Fig 1).

Sequencing-directed therapies was said to be provided only when CGP could identify an actionable mutation in a patient for which either an off-label therapy or clinical trial was available. Institutional Ethics Committee approval was obtained. Data on the eligible patients were collected from 12 participating oncologists from different parts of the country. Data were collected between August 2020 and December 2021. The oncologists provided anonymized information of consecutive CGP test reports along with patient's demographic characteristics through an online data capture form. Details on patient demographics, biopsy type, prior lines of systemic therapy, type and

FIG 1. Study profile. AML, acute myelomonocytic leukemia; CGP, comprehensive genomic profiling; EGFR, epidermal growth factor receptor; GIST, GI stromal tumors; HER2, human epidermal growth factor receptor 2; MDS, myelodysplastic syndrome.
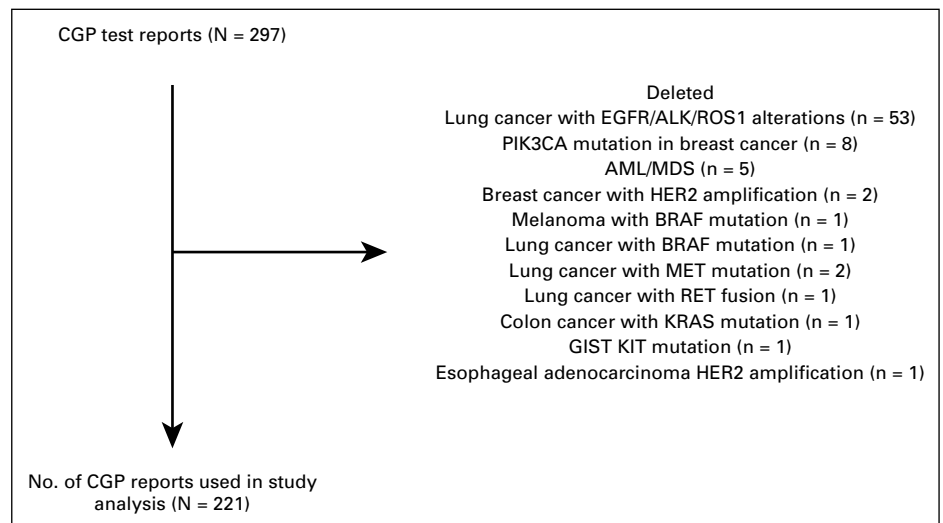
CGP test reports (N = 297)

Deleted
Lung cancer with EGFR/ALK/ROS1 alterations (n = 53)
PIK3CA mutation in breast cancer (n = 8)
AML/MDS (n = 5)
Breast cancer with HER2 amplification (n = 2)
Melanoma with BRAF mutation (n = 1)
Lung cancer with BRAF mutation (n = 1)
Lung cancer with MET mutation (n = 2)
Lung cancer with RET fusion (n = 1)
Colon cancer with KRAS mutation (n = 1)
GIST KIT mutation (n = 1)
Esophageal adenocarcinoma HER2 amplification (n = 1)

No. of CGP reports used in study analysis (N = 221)

TABLE 1. Baseline Characteristics (N = 221)

Characteristic	No.
Sex	
Male	101
Female	120
Type of biopsy	
Tissue	201
Liquid	20
Tumor type	
Lung cancer	39
Breast cancer	34
Pancreatic and pancreatobiliary cancer	21
Colorectal cancer	15
Ovarian cancer	14
Gallbladder cancer	13
Cholangiocarcinoma	12
Endometrial cancer	11
Carcinoma of unknown primary	10
Gastric and gastroesophageal junction cancer	7
Prostate cancer	5
Esophageal cancer	4
Melanoma	4
Sarcoma	4
Hepatocellular carcinoma	3
Glioblastoma	3
Penile cancer	2
Cervical cancer	2
Urachal carcinoma	2
Thyroid carcinoma	2
Kidney cancer	2
Ameloblastic carcinoma	1
Low-grade glioma	1
Head and neck squamous cell cancer	1
Nasopharyngeal carcinoma	1
Vaginal carcinoma	1
Urothelial carcinoma	1
Neuroendocrine tumor	1
Malignant epithelioid hemangioendothelioma	1
Chondrosarcoma	1
Sinonasal carcinoma	1
Adrenocortical carcinoma	1
Rhabdomyosarcoma	1

number of mutations, CGP platform used, genome-directed therapy received, and rationale behind the rejection of sequencing-directed therapies were extracted from data capture forms.

Proportion of profiled patients receiving sequencing-directed therapies and the reasons for declining targeted therapies were then evaluated using descriptive statistics.

Comprehensive Genomic Sequencing

CGP assay could be performed on both tissue and liquid biopsy. Either archived tissue or fresh tissue specimens were used for tissue analysis. The decision to undertake CGP assays was made by the treating oncologist. CGP by NGS techniques could simultaneously detect different types of genetic alterations such as insertion, deletion, fusion, amplification, rearrangement, and mutations of genes. Many different platforms such as MedGenome, Foundation One, and Oncomine Focus assay were used for CGP. Each of these platforms assessed different genes and types of genetic alterations.

Report Interpretation

CGP report identifies all the actionable genetic alterations present in the patient along with possible treatment modalities. Therapeutic intervention on the basis of CGP assay was at the discretion of primary oncologists, which could be in the form of administration of an on-label or off-label drug or enrollment in a clinical trial. If the results were considered ineffective by the treating oncologist, other treatment modalities were explored.

Clinical End Points

The primary end point of the study was to assess the clinical utility of NGS by determining the proportion of patients with advanced cancer in India who eventually receive targeted therapy for an actionable genetic alteration identified on the CGP assay. Secondary objective was to determine the clinical benefit of genome-directed therapy. If patients received a targeted therapy for $\geq$ 6 months, they were considered to have obtained a clinical benefit from the medication. Patients on targeted therapy for $\geq$ 12 months were considered to have obtained an exceptional response from the medication.

Statistical Analysis

Descriptive statistics were used to describe the proportion of patients with subsequent targeted therapy.

RESULTS

We received CGP reports of 297 patients from 12 participating oncologists from different parts of the country. As per our inclusion criteria, 221 patients were included in our study (Table 1). Remaining CGP reports were excluded as they identified genetic alterations that have well-validated Food and Drug Administration–approved standard-of-care therapy. A description of the study profile is given in Figure 1. Fourteen different testing panels were used by the oncologists (Table 2).

Among the study cohort, 46% were male. Ninety-one percent underwent tumor tissue biopsy and 9% had liquid biopsy. The most common cancers were lung (18%),

TABLE 2. Details of Comprehensive Genomic Profiling Testing Platforms

Test Ordered	No. of Genes Tested	Type of Genetic Alterations
Oncomine focus assay	52	35 hotspot genes 19 copy-number variants 23 fusion drivers
Foundation One	324	309 base substitutions, insertion and deletions, copy-number variations 34 gene rearrangements
MedGenome	170	148 single-nucleotide variations, short insertion and deletions 37 fusions and splice variants
Strand	56	NA
Caris	592	150 mutations 442 mutations and copy-number variations 8 gene fusions 2 variant transcripts (RNA)
Datar	409	NA
Oncquest	50	NA
4baseCare target focus	352	NA
Core diagnostics	52	35 hotspot genes 19 copy-number variants 23 fusion drivers
IMPACT	468	NA
Supratech	161	NA
BGI	688	NA
Guardant	73	18 amplifications 6 fusions 22 insertions and deletions 1 alteration in promoter
Lilac insights	56	NA

Abbreviations: BGI, Beijing Genomics Institute; IMPACT, Initiative for Molecular Profiling and Advanced Cancer Therapy; NA, not available.

breast (15%), pancreatobiliary (9%), and colorectal (7%). Patients received a median of two lines (range: 0-5) of prior systemic therapy (Table 1). Ninety-six patients (43%) had a targeted therapy option in the form of an approved drug or the availability of a globally recruiting clinical trial. On the basis of the CGP assay, 21 patients (10%) received targeted therapy (Table 3). Among them, 33% (n = 7) was for HER2 amplification (nonbreast cancer) and 19% for HER2 or EGFR exon 20 insertion mutation (lung cancer; n = 4; Table 4). EGFR mutation was seen in two patients. After excluding patients with HER2 or EGFR exon 20 insertion (four patients), which are emerging targets in lung cancer, 17 patients of 217 (8%) received targeted therapy. Most common reason for patients not receiving targeted therapy was because of availability of a standard-of-care therapy (21%) and declining functional status (18%; Table 5). In the overall cohort of 221 patients, clinical benefit was seen in nine patients (4%), of whom two were exceptional responders (1%). Excluding the emerging targets in lung cancer, clinical benefit was seen in six of 217 patients (3%), of whom two were exceptional responders.

DISCUSSION

Personalized medicine on the basis of alteration in patients' genome is an area of promising development in cancer therapy.[14] Replacing nonselective conventional standard therapies with targeted genomic drugs tailored against a specific mutation on tumor cells is appealing to both doctors as well as the general public. Improved clinical benefits associated with certain specific targeted therapies and the dropping cost of CGP have resulted in a greater demand for the assays. Although there are some studies evaluating the clinical utility of CGP in regular practice, the results are largely contradictory.[1,8,9,15] To the best of our knowledge, there are no similar studies conducted in LMICs. The clinical benefits of CGP must be adequately studied and properly established before it can be integrated into regular clinical practice. This is especially important in a developing country such as India with a resource-constrained health sector where CGP still remains exceedingly expensive for large sections of populations.

NGS is often prescribed for patients when we seek a treatment option in the form of a targeted therapy. Most often, it is done when patients have exhausted all available standard-of-care therapeutic options. However, in some situations, even upfront testing is routinely done—for instance, for patients with adenocarcinoma of the lung. It is also recommended in the context of clinical trial recruitment for studies of novel investigative strategies such as

TABLE 3. Details of Patients Who Received GDT

No.	Age (years)	Cancer Type	Biopsy Type	Test Ordered	Lines of Systemic Therapy Given Before CGP Testing	Mutations Detected	Mutated Genes	GDT Received	Response Duration (CR/PR/SD; months)
1	68	Lung cancer	Tissue biopsy	MedGenome	2	5	HER2 exon 20 insertion	T-DM1	7.0
2	63	Lung cancer	Tissue biopsy	Strand	3	1	HER2 exon 20 insertion	Poziotinib	2.0
3	65	Gall bladder cancer	Tissue biopsy	FoundationOne	1	7	HER2 amplification	Trastuzumab and lapatinib	3.0
4	77	Lung cancer	Liquid biopsy	Guardant	0	2	EGFR exon 20 insertion	Osimertinib	6.0[a]
5	58	Pancreatic cancer	Liquid biopsy	Guardant	1	1	BRCA1	Olaparib	1.0
6	42	Cholangiocarcinoma	Tissue biopsy	FoundationOne	1	5	BRIPI	Olaparib	1.0
7	40	Gallbladder cancer	Tissue biopsy	FoundationOne	2	2	HER2 amplification	Trastuzumab	1.0
8	58	Lung cancer	Tissue biopsy	Supratech	2	1	HER2 exon 20 insertion	Poziotinib	6.0[a]
9	59	Ameloblastic carcinoma	Tissue biopsy	Supratech	0	3	PIK3CA, HRAS, FGFR2 mutations	Trametinib and lenvatinib	8.0[a]
10	50	Cholangiocarcinoma	Tissue biopsy	Supratech	1	1	HER2 amplification	Capecitabine and lapatinib	3.0
11	60	Pancreatic cancer	Tissue biopsy	Oncomine focus assay	2	1	HER2—copy-number variation	Trastuzumab	4.0
12	44	Ureteric cancer	Tissue biopsy	FoundationOne	3	7	BRAF mutation	Dabrafenib and trametinib	3.0
13	25	Cholangiocarcinoma	Tissue biopsy	FoundationOne	2	2	HER2 amplification	Trastuzumab and T-DM1 (sequentially)	36.0
14	72	Esophageal cancer	Tissue biopsy	Supratech	0	1	EGFR amplification	Gefitinib	12.0
15	68	Uterine cancer	Tissue biopsy	FoundationOne	2	9	PIK3CA mutation	Alpelisib	2.0
16	76	Uterine cancer	Tissue biopsy	FoundationOne	3	9	HER2 amplification	Trastuzumab and pertuzumab	9.0
17	64	Lung cancer	Tissue biopsy	FoundationOne	0	5	HER2 amplification	Afatinib	2.0
18	58	Unknown primary carcinoma (NOS)	Tissue biopsy	FoundationOne	1	8	EGFR L858R mutation	Afatinib	6.0
19	55	Sarcoma	Tissue biopsy	Datar	3	1	TSC1 mutation	Everolimus	4.0
20	38	Adrenocortical cancer	Tissue biopsy	Oncquest	2	2	KIT R956Q	Imatinib	9.0[a]
21	57	Lung cancer	Liquid biopsy	Datar	3	1	KRAS G12C mutation	Trametinib	1.5

Abbreviations: CGP, comprehensive genomic profiling; CR, complete response; EGFR, epidermal growth factor receptor; GDT, genome-directed therapy; HER2, human epidermal growth factor receptor 2; NOS, not otherwise specified; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine.
[a]Patients are on therapy at the time of last follow-up.

targeted therapy. In this study, we aimed to assess the benefits of CGP in routine clinical practice in India. Patients with solid organ malignancies who underwent CGP were included in our study. Patients found to have genetic alterations, which otherwise would have been detected with a targeted genetic testing, were not included in the study population—for example, patients with HER2 amplification that would have been detected with a HER2 fluorescence in situ hybridization test, or patients with EGFR sensitizing mutation in exon 19 that would have been detected with a targeted EGFR mutation testing.

Of the 221 who were enrolled in our study, actionable mutations were found only in 96 (43%). No mutations or nonactionable mutations were detected in the remaining patients. This is much less compared with studies conducted elsewhere where the proportion of clinically relevant genomic alteration was more than 80%.[1,16,17] However, the proportion of patients who eventually received sequencing-directed therapies on the basis of an actionable genetic alteration identified by CGP assay was 10%. This is comparable to similar studies from other parts of the world.[1,16-18] Clinical benefit, as defined as being on the drug for ≥ 6 months, was noted in only 4% of patients. Although the scope of precision therapies continues to be immense, the patient needs to be made aware of the clinical reality that only a small fraction of patients who undergo CGP receive sequencing-directed therapies and a still smaller fraction actually gain benefit from it.[1] Awareness of these data would help in patient counseling so that the expectations match the real-world scenario. Effective

TABLE 4. Common Targets That Were Used

Genetic Alteration	Frequency, No.	Genome Directed Therapy
HER2 amplification	7	Trastuzumab T-DM1 Trastuzumab and pertuzumab Trastuzumab and lapatinib Lapatinib Afatinib
HER2 or EGFR exon 20 insertion	4	T-DM1 Poziotinib Osimertinib
EGFR mutation	2	Gefitinib Afatinib

Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

communication between the patient and their oncologist would help in the curbing of exaggerated expectations associated with precision therapy.

Clinically relevant genomic alteration reported by CGP platforms can either be a mutation with well-validated targeted treatment or a clinically unproven hypothetical target against which a potential therapy may be successful.[19] Many of the CGP platforms do not prioritize the various targetable mutation discovered and it is often up to the oncologist to select the clinically efficient evidence-based targeted therapy.[19] The use of clinical value-based ranking of actionable mutation similar to European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets would enable the oncologist in selecting actionable mutations with proven clinical benefits.[19] Some highly recommended targets in the European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets include HER2 in breast cancer and ROS1 rearrangements.[19]

CGP in clinical practice should be used with utmost care. We are of the view that the nonjudicious and indiscriminate use of CGP would be of limited clinical value.

Beyond the standard indications, NGS must be restricted to patient populations in specific clinical situations. It may be prescribed in patients with limited therapeutic options where the sequencing-directed therapies may help in enrolling in a clinical trial or receiving an off-label therapy.[20] The clinical utility of genomic profiling is not uniform across all cancers. It is especially helpful in non–small-cell lung cancer, which often presents with several genomic alterations that can be targeted in the initial therapy.[20] Rare cancers without well-defined treatment guidelines or standard drug regimens are another accepted indication for NGS.[20] However, it should be avoided in terminally ill patients with aggressive cancer, and those with poor functional status.[1,20] It should also not be ordered in cancers against which standard conventional therapies with proven clinical value are already available or in those cases where genomic sequencing is unlikely to detect a new targetable genomic mutation or have any substantial influence on therapeutic management.[1,20]

The financial aspect of NGS should also be taken into perspective. Although it is considered as a cheaper alternative to single-gene testing, it continues to remain unaffordable to a large number of patients with cancer in India.[21] Apart from the cost of sequencing, the economic burden resulting from the targeted therapy that ensues must also be taken into account while determining the cost-effectiveness of NGS. The economic impact of precision therapy has added importance in a country like India with limited resources, poor insurance coverage, and high out-of-pocket expenditure. There can also be physical toxicities especially when combination therapies with no previous data are used.

Precision medicine has the potential to revolutionize oncology in the coming years. Genomic profiling was instrumental in improving our understanding of many of the advanced cancers. It has provided us with a wide variety of therapeutic options for cancers that were considered largely untreatable.

TABLE 5. Reasons for Not Getting Genotype-Directed Therapy (N = 75/221; 34%)

Reason	Frequency, No. (%)
Patient still receiving standard of care/off-label option or clinical trial not suggested by CGP report	16 (21.3)
Patient is no longer a candidate for therapy because of poor performance or deteriorating status	14 (18.6)
Treatment not available in India	11 (14.6)
On-/off-label GDT recommended or clinical trial available locally but patient declined	8 (10.6)
Patient offered clinical trial but unable to travel/insurance decline	6 (8)
Lost to follow-up	6 (8)
Oncologist did not consider it worth an attempt	4 (5.3)
Financial constraints	4 (5.3)
Physician preference for no GDT specifically because of rapid disease	4 (5.3)
Disease in remission/no indication for therapy	2 (2.6)

Abbreviations: CGP, comprehensive genomic profiling; GDT, genome-directed therapy.

We must now focus on rational implementation of precision medicine in routine clinical practice. We encourage the integration of CGP into routine clinical practice, especially when it is affordable. However, we must be able to estimate the real-world worth of the assay. To the best of our knowledge, this is the first study from an LMIC context that contextualizes the utility of the assay in a clinical practice setting. Setting up of molecular tumor boards is another implementation measure that can enhance the science of precision medicine from the laboratory to the clinic. It would help oncologists choose therapeutic options with the meaningful clinical benefit. Greater access to clinical trials would enhance our ability to translate the results of genomic profiling to clinical practice.

Our study has some limitations. First, it is a retrospective cohort study and may be subject to recall bias. However, being a multicenter study, our results can be considered more generalizable and valid. Decision to perform CGP was made at the discretion of the primary oncologist and not by institutional tumor boards. Therefore, the decision-making process may be subject to individual physician bias. Comparing the outcomes from our study with the results from molecular tumor board–based decision making will be an important step in testing the impact of such collaborative endeavors. There was also heterogeneity pertaining to the timing of CGP testing. The number of lines of systemic therapy received before CGP varied between 0 to 5. Small sample size and diversity in tumor types are other key limitations.

In conclusion, in our study, we aimed to analyze the clinical value of CGP testing via NGS in routine clinical practice in India. Of the 221 patients sequenced, only 21 patients (10%) received sequencing-directed therapies. Only 4% gained some clinical benefit from the CGP testing. Evidence synthesized in this study could help in the development of clinical interventions aimed at improving the practice of precision medicine in India.

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DATA SHARING STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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