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A Survey on Unmet Need for Uniform Next-Generation Sequencing Reporting in India

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Abstract

Introduction: Next-generation sequencing (NGS) has paved the way for precision oncology in oncology clinics today. With rapidly advancing therapeutics, it is becoming increasingly important to obtain information about the molecular milieu of a patient's tumor. However, reporting and interpreting of NGS is fraught with complexity and variability. To understand the questions surrounding NGS reporting in India, we conducted a survey.

Objectives: The aim of this study was to assess the gaps in NGS reporting and interpretation in Indian medical oncology clinics.

Materials and Methods: An anonymized 10-question survey-based study among Indian medical oncologists through Google forms was conducted between October 4 and 8, 2022.

Results: The sample size was $n = 58$. Seventy-one percent felt there was heterogeneity in NGS reporting, 72% were unaware of NGS reporting guidelines, and 62% did not feel the need for a molecular scientist assist in NGS interpretation. Almost all (98%) felt there was a need for uniform NGS reporting as well as an Indian NGS repository and data-sharing system (93%).

Conclusion: Our survey highlights the need for a uniform national guideline concerning NGS reporting.

Keywords
- next-generation sequencing
- uniform reporting
- guidelines

Introduction

Precision medicine or personalized medicine uses molecular diagnostics to guide diagnosis and prognosis and to offer individualized therapy based on the presence of somatic and/or germline genetic alterations.[1] Next-generation sequencing (NGS) allows for multiple parallel sequencing of the whole genome, exome, or a targeted gene panel in a short time span. This has propelled the use of precision medicine in oncology clinics today with an unprecedented speed.[2] The relevance of NGS in the management of malignancy continues to grow with the advent of tissue-agnostic therapy.[3] However, there are multiple limitations to the purported benefits of utilizing NGS in clinical practice—difficulty in the interpretation of complex reports, lack of validation, sensitivity and specificity of reported results, relevance to variants detected, continuously evolving data, identifying fusions and indels, and the high cost of NGS. Tumor heterogeneity and adequate tissue material remain an added challenge. Once a proven targetable mutation is detected, access to costly drug

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and lack of clinical trials in India create an unnecessary, uncomfortable situation for the patients and their doctors.[4,5]

To counteract these limitations, organizations have developed guidelines, from correct processing of the tissue samples to methods of validation and establishing controls to proper ways to compile an NGS report so that it is easier to apply in clinical settings.[6–9] To understand the real-world challenges medical oncologists face in the country, we planned a short survey.

Materials and Methods

We conducted an anonymized survey-based study among Indian medical oncologists. Practicing medical oncologists were questioned regarding their views on NGS reporting and its applicability in day-to-day practice. The survey consisted of 10 questions, with yes/no ± maybe as options for 7 questions; 1 was on a Likert format of graded responses, and 2 were open-ended. Details of the survey are depicted in ►**Table 1**.

This survey was conducted from October 4 to 8, 2022. The survey was circulated through social media apps and email. Google forms platform was used. All data were anonymized and the study was performed in accordance with the ethical standards of the Helsinki Declaration of 1964 and its later amendments.

Outcome of the study: to identify the pitfalls in NGS reporting and interpretation in routine practice of medical oncology in India through open- and close-ended questions.

Inclusion criteria and exclusion criteria: any medical oncologist practicing in India who was willing to fill the questionnaire was included in the study, irrespective of gender, locality, and type of practice or years of experience.

Statistical analysis data were collected and analyzed using Microsoft Excel for Mac, version 16.43 (Redmond, WA, United States) and Google forms platform. Descriptive statistics were used to assimilate and represent data, and frequencies, percentages, means, and standard deviations were used where appropriate.

Table 1 Survey questionnaire

No.	Questions	Answers
Q1	Are you a medical oncologist?	Yes No
Q2	How often do you feel that there is heterogeneity in NGS reporting in India or elsewhere?	Often Rarely Not relevant to me
Q3	Do you feel that for every NGS report, you need help from a molecular scientist?	Yes No
Q4	Have you ever come across NGS reporting guidelines?	Yes No
Q5	If yes, please mention the guidelines and how many molecular laboratories follow the guidelines?	Long answer
Q6	Do you feel there is a need for uniform NGS reporting?	Yes No
Q7	In how many cases, do you feel helpless when NGS reports give options of unavailable therapy in India?	100% 75–100% 25–75% <25%
Q8	Do you feel that there is a need for uniformity, accountability, and quality assurance of NGS procedure and reporting in India?	Yes No
Q9	Do you feel that India should have a NGS repository and data-sharing system?	Yes No Maybe
Q10	What parameters do you want in NGS reporting?	Open question

Abbreviation: NGS, next-generation sequencing.

Result

Fifty-eight medical oncologists responded to the survey. The responders felt that there was heterogeneity in NGS reporting 71% of the time (►**Fig. 1**). Seventy-two percent of medical oncologists were unaware of any NGS reporting guidelines; the remaining were aware of some guidelines, such as European Society of Medical Oncology (ESMO)-ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) guidelines, College of American Pathologists-Clinical Laboratory Improvements Advisory Committee (CAP-CLIAC) guidelines, American College of Medical Genetics and Genomics and the Association for Molecular Pathology(-ACMG/AMP), and AMP-American Society of Clinical Oncology (ASCO)-CAP. Barring one person, most of them were unaware of whether the labs in India were adhering to any guidelines.

While the majority (62%) did not feel the need for a molecular scientist to interpret an NGS report, overwhelmingly, 98% felt an unfulfilled need for uniform NGS reporting. When asked if there was a "need for uniformity, accountability and quality assurance of NGS procedure and reporting in India," 97% responded in the affirmative. Similarly, almost all (93%) agreed that India should have an NGS repository and data-sharing system (►**Fig. 2**).

About 40% felt helpless when NGS reports suggest a therapy inaccessible to their patients (►**Fig. 1**).

The final question asked the participants what parameters they would like to include in NGS reporting. The responses included suggestions such as a quality check, an explicit depiction of the method used, depth of reading, the number of reads, number of genes covered, tumor content, variant allele frequency and variants of unknown significance, allele frequency, actionable mutations and available drugs as well as incidence and available data of uncommon mutations, the tier of the mutations, fusions and whether RNA is used for checking them, tumor mutational burden with microsatellite instability, both RNA and DNA sequencing, mutations with prognostic implications, lab accreditation details, the platform used, haplotype map utilization for limits of detection, whether it is validated and compared to standard, and reporting in the context of the primary tumor diagnosis.

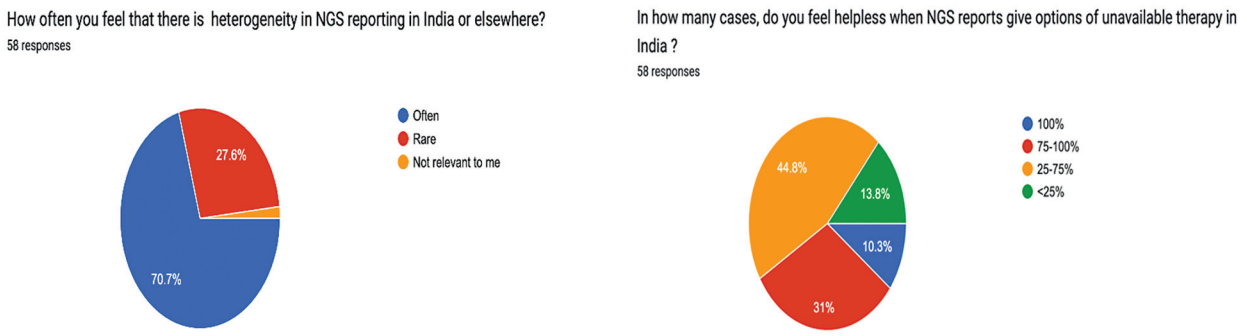

Fig. 1 Pie chart showing the distributions of answers to Questions 2 and 7.

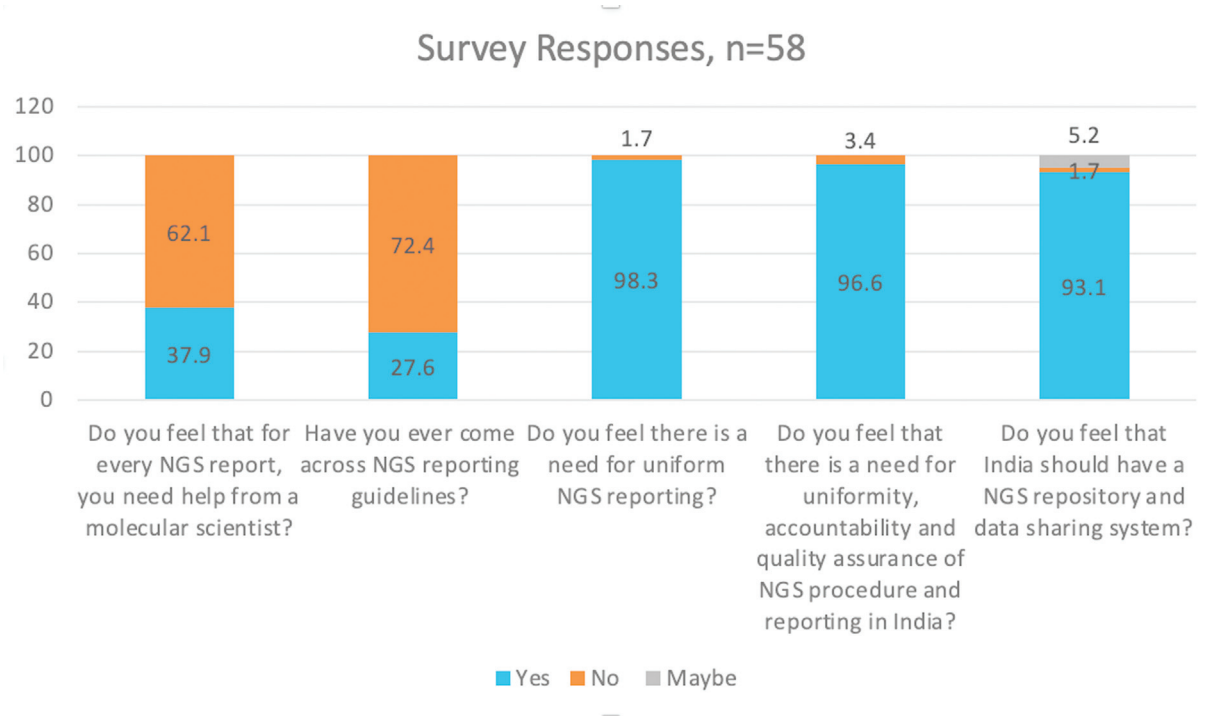

Fig. 2 Bar diagram depicting answers to survey questions 3, 4, 6, 8, and 9.

Incorporation of the option of a certified genetic counsellor for both pre- and posttest counselling was also suggested.

Discussion

There is a pressing requirement for standardization of NGS reporting, validation of existing tests against a gold standard, and formalizing a set of recommendations per tumor site. Furthermore, the interpretation of a positive result, its applicability to a particular patient, and the ramifications of cost are essential concerns.

The promise of precision medicine comes from specific therapies tailored to the genomic landscape of a patient's tumor, the growing successful avenues of tumor-agnostic therapy,[3,10] the favorable toxicity and better outcome profile of targeted therapy that act on oncogenic drivers,[11] and the indubitable success of immunotherapy.[12] However, this arena is clouded with uncertainty and limitations.[13] Even among oncologists using NGS routinely, the confidence to correctly interpret reports is low to moderate.[14] This partly stems from the continuously evolving body of literature surrounding genetic alterations—what is a "variant of unknown significance" today may be a targetable mutation tomorrow. In addition, many abnormalities identified in tumor DNA are often also seen in normal cells, which do not progress to a malignant state.[15] Furthermore, the detection of fusions and genetic aberrations affecting introns are complex and, many times, require additional RNA-based NGS.

A sizeable self-reported survey in 2018 by Freedman et al revealed that 75% of oncologists use NGS in routine clinical practice, with younger age of the physician, setting of an academic center, access to genomic training, and molecular-based tumor boards predicting greater usage. Compared with our study, in which 62% did not feel the need for a molecular scientist to interpret the NGS report, 49% in the study by Freedman et al had no difficulty in comprehending NGS reports.[13]

An important aspect of the applicability of NGS reporting is the financial burden of testing and the action that can be taken if a positive result is obtained. The ESMO/ESCAT guidelines address this issue. They have recommended NGS testing in only certain malignancies, such as lung adenocarcinoma, cholangiocarcinoma, and prostate cancer, where testing by NGS is more financially sound than other methods of molecular testing. On the other hand, for colon cancer, NGS is suggested as an alternative to polymerase chain reaction testing. The ESMO guidelines further have divided the possible genetic alterations into priority levels, labelled as tiers, which help guide management.[9,16]

In contrast to most developing countries, India is one of the few nations contributing to genomic research and development significantly.[17] The unique health care model of India with the availability of approved generic drugs,[18] both government and privatized health care, emerging indigenous techniques of NGS, and the rapidly developing science of precision medicine all culminate in a strong message for the need for standardized NGS reporting guidelines, a sentiment shared by 98% of our responders. Most of our participants felt the need for an Indian repository (93%). There is a need for a repository consisting of Indian variants of known and unknown targets to identify and address ethnic differences, as large international databases such as The Cancer Genome Atlas (TCGA) have largely underrepresented the Asian and African populations.[19,20]

Our study has certain limitations of small sample size and lack of demographic data and predictive factors impacting results, being an anonymized questionnaire. However, it is the first survey of its kind to be conducted in our country that have taken the questions of importance to the community and academic oncologist alike.

Conclusion

To conclude, our study has highlighted the imminent need of a national-level protocol to be established for the clinical application of genomic data to optimize patient care.

Author Contribution:

Neha Pathak: intellectual content, literature search, manuscript preparation, manuscript writing, and manuscript review.

Anu R. I.: concept, design, intellectual content, data acquisition, data analysis, and statistical analysis.

Padmaj Kulkarni: design, manuscript editing, and manuscript review.

Amol Patel: concept, design, intellectual content, data acquisition, data analysis, statistical analysis, literature search, and manuscript review.

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The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Conflict of Interest

None declared.

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