Expert Opinion

Precision oncology in Low and Middle income countries: a word of caution

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INTRODUCTION

Precision Oncology (PO) is increasingly becoming integral to the modern multidisciplinary care of cancer patients.¹ PO aims to pair a target or biomarker which is the driver or actionable mutation to a drug that is available, affordable, and helps patients live longer with a better quality of life - a big ask! The hype of PO drives oncologists and patients to go for tests that may have far-reaching implications especially in low and middle-income countries (LMICs). The true success story of PO has been the management of patients with non-small cell lung cancer, though this has not been replicated in other cancers.²

The real-time data on knowledge of molecular oncology among oncologists in India was conducted through an online survey recently. Among the 74 respondents, almost 70% did not have provision for molecular tumor boards in the hospital with a quarter unaware of the agencies for accreditation of the molecular reports. The awareness of a treating oncologist towards providing PO care towards each patient seems to have slowly improved.³ However, it is still unmatched with the number needed to benefit in a developing and large demographic country like India. This is reflective of other LMICs and much needs to be done to improve the training of oncologists.

We discuss some of the challenges to the implementation of PO in LMICs:

1. **Universal testing in all patients with advanced cancers** The use of wider panel next-generation sequencing (NGS) in all patients with advanced cancers often reveals multiple genomic alterations. Recent advances in drug treatments have been obtained with drugs that target pathways, but not all DNA alterations detected in NGS lead to clinically significant effects on these pathways. There are no randomized trials that have assessed the effectiveness of NGS in prolonging the life of cancer patients, though the impact depends on the type of cancer. PO has overhauled the concept of “one size fits all” with treatments like chemotherapy, but it is also true that all cancers will not benefit from blanket NGS.⁴
2. **Implementation challenges** Sequencing can identify multiple mutations, some of which may be targetable, but only very few actually determine the cancer biology and are labeled as “driver mutations.” We

still do not know enough to determine the functional relevance of all the mutations detected in a sample. To differentiate between driver versus passenger mutations, clonal versus subclonal mutations, and interpret the equivocal amplifications in various tumor types is the challenge.

3. **Which technique? Which panel?** NGS is the preferred technique for the detection of genetic alteration and there are broad and small NGS panels based on the number of genes under evaluation. DNA-based or RNA-based techniques are used in NGS. Access to whole exome and whole genome NGS both in logistic and financial terms is a challenge faced by the patients and oncologists in LMICs. The pathway from point of collection of a sample, transport, sequencing, analysis, and reporting faces difficulties due to multiple reasons like lack of basic infrastructure, lack of training in collecting the sample, outsourcing to testing laboratories outside the country, etc.
4. **Interpretation challenges** NGS reports not only report the molecular alterations of clinical interest (“pathological variants”) but also many alterations termed aptly as Variations of Unknown Significance (VUS). A majority of the reports have no actionable mutations and no clinical benefit is implied by the NGS report.⁵ Many times, they lead to therapeutic and ethical dilemmas when there are suggestions regarding the use of drugs based on their efficacy in other cancers. For a patient in whom multiple pathogenic variants are identified, which target should be druggable is a dilemma for most of us with no clear answers or evidence. Molecular or genomics review boards are essential to discuss these reports in the presence of germline geneticists as some of the pathogenic variants identified have implications for the patient’s family and germline testing has to be requested after adequate counseling.
5. **Financial Toxicity** A review on the application of NGS for improving cost-effectiveness and clinical effectiveness analyzed 56 articles containing 21,823 patients of which 83% of samples had at least 1 mutation and 37% of patients received treatment based on NGS. However, there was a diverse definition of “actionable mutation” among the 56 studies included. Cost-effectiveness varied from \$59,000 (Rs 4,300,000)

per person-year of life saved for colorectal cancer to nearly \$500,000 (Rs 37,000,000) per person-year of life saved.⁶

Depending upon the number of genes tested for NGS, the cost of the tests can vary from \$530 (Rs 40,000) for a 52 gene panel like Oncotype DX to \$3,500 - \$6,500 (Rs 250,000-500,000) for a 500-700 gene panel like Caris or Foundation. The majority of patients in LMICs self-fund their treatments. The usual dictum most oncologists practice is to not do the test if patients have resource limitations, for example, not doing the IHC for Her 2 if patients cannot afford trastuzumab. There are patient support programs that provide coupons for testing for the genes like EGFR, Her 2, ALK, ROS-1 but these are funded by the pharmaceutical company which also make or provide the drugs raising issues about conflict of interest.

The affordability of patients in LMICs towards targetable drugs is influenced by the availability of generic drugs. In absence of generic drugs, the actual use of even highly clinically effective drugs like trastuzumab has been reported as less than 10%.⁷ The newly approved drugs are expensive and unaffordable for most patients. In this context, finding out if there is a useful molecular alteration after incurring the cost of the test is not clinically meaningful for the patient. Compassionate access programs are an option for the patients in LMICs, but often they have only a short period of implementation.

6. **Patient confusion and guilt** Most of the reports provided have a list of recommended treatment options which includes newer drugs with no concern for local availability, approval, or cost implications. The variety of treatment options available as per the molecular testing and the further guided therapy causes turmoil to the patient and the caregiver. In the process of informed decision-making, patients with more than one mutation type are highly likely to undergo confusion along with the guilt of choosing the alternative therapy due to financial burden and the fear of inferior outcomes. Oncologists face the dilemma of whether or not to discuss some of the treatments which are exorbitantly expensive and out of reach of most patients in LMICs.

Some of the NGS reports detect a somatic mutation which can have germline implications for the family and triggers germline testing. Given the shortage of genetic counselors, this needs to be thought through before requesting the test, but it seldom is.

7. **Outcomes** There needs to be evidence-based validation for the hypothesis that targeted therapy based on tumor genetics is better than conventional therapy. There have been no randomized trials to assess the effectiveness of NGS sequencing in prolonging life. The French academic study SHIVA in heavily pre-treated patients with advanced cancer showed that the use of molecularly targeted therapy outside of their indications of use did not improve outcomes -

the trial assumed that the treatment of physician's choice would be suboptimal versus an algorithm.⁸

The effect of utilizing biomarkers to improve health outcomes was conducted using individual-level data for various cancer types in Norway. The impact of biomarker testing on the probability of survival at 3 years and the decline in premature mortality were analyzed. It was found that the biomarker testing availability correlated with an improvement in survival probability and a decrease in premature mortality. However, with an increase in the number of drugs available based on biomarkers, the effect of testing decreased over the survival outcomes. Also, biomarker-guided treatment was associated with a decrease in premature mortality, whereas non-guided therapy surprisingly was associated with an increase in survival probability.⁹

A prospective study done at Michigan using DNA and RNA sequencing NGS to direct therapy of 1,138 patients was reported to have a potential clinical actionable mutation in 80%. However, only 16% received sequence-directed therapy and 37% of these patients had a clinical benefit at 6 months and around 20% had an exceptional response at 12 months or more. 50% of CUP were reclassified to alternative diagnosis and 23% underwent sequence-directed therapy. Interestingly 1 in 6 patients had pathogenic germline variants which had therapeutic implications for the patient and for offering genetic counseling and testing to the family.¹⁰

WHAT CAN BE DONE TO MITIGATE THE CHALLENGES?

Some of the common scenarios faced in LMICs are 1) non-availability of the drug 2) drug being unaffordable 3) non-availability of compassionate access programs 4) non-availability of clinical trials identified in the report given to the patients.

Science has no boundaries and discrimination based on finances or nations is not right. Patients from LMICs deserve the best chances to get their life prolonged and have a better quality of life too. There needs to be a moral and ethical consideration to discover ways to make newer drugs improve overall survivability in LMICs.

Some suggestions are:

1. PATIENT'S RIGHT TO INFORMATION

To not request NGS without adequate counseling and discussion of downsides of the test itself. Patients must be well informed about the nature of disease, the cost involved in diagnosis, waiting time, and interim treatment options available or applicable while awaiting the results, cost-effective targeted therapy available for the panel testing in their country, and the outcomes.

2. COST-EFFECTIVE TESTING

To develop cost-effective targeted panel testing which will cut down the cost of testing and save for the treatment expenditure must be thought of scientifically and implemented in healthcare. Testing for specific targets can vary from single gene testing with IHC, FISH, or multigene testing using a limited NGS panel whichever is the minimum standard required for diagnosis. 'One size does not fit all' and hence individualized decision making is important for choosing the right test at the right cost for the rightly chosen patient.

3. MOLECULAR TUMOR BOARD

Molecular tumor boards with the genetic platform representatives, clinicians, molecular pathologists, geneticists to simplify the complex NGS reports, to discuss the implications of technical jargon in the reports, and to raise the awareness of judicious use of NGS in patients from LMICs. Individualized decision-making to aid the patient and caretaker must be carried out with the expert panel to provide the best outcomes possible.

4. PATIENT ASSISTANCE PROGRAMS

Accessibility of patient assistance or compassionate use access programs in LMICs as it is being done in High-Income Countries (HIC). This denies a vast majority of patients the standard of care treatment options. The availability of cancer-directed therapy must be made through government or pharmaceutical-driven patient assistance programs.

5. VALUE-BASED PRICING MODEL

Implementation of value-based pricing models in each country or LMIC is a priority that must be adopted. For example, the main drivers of NICE (National Institute for Health and Care Excellence) appraisals are quality-adjusted life years (QALY) and incremental cost-effectiveness ratio thresholds which will indirectly influence the pricing set freely by the pharmaceutical companies.

6. GUIDELINE UPDATES

Health technology assessment and implementation of guidelines that include newer drugs or technologies must be updated periodically. These guidelines, curated by an expert team in the field, will help to provide the optimal standard of care throughout the country. Uniform consensus will help in multiple aspects: from patient care to the making of health policies in the country.

7. GOVERNMENT LEVEL INITIATIVES

The engagement of governments is the key stakeholder in increasing gross domestic product on healthcare spending. The majority of LMIC do not have well-established government insurance programs that cover the healthcare of their citizens. For example, the healthcare system in India is diverse and differs at each state government level to cover

only a predefined cost limit. Beyond the cost limit, the patient has to take on a huge debt to complete or continue his cancer treatment. As per the latest data, India spends only 1.2% of its GDP on the health care system. Tertiary care oncology centers that are well connected to funding organizations or NGOs are a boon to patients classified under "below poverty line" and those with inadequate financial and social support.

INDIA AS AN EXAMPLE - STEPS IN THE RIGHT DIRECTION

DIAMONDS

The Department of Health Research in India has collaborated with the Indian council of medical research (ICMR) and has established guidelines for advanced Molecular Oncology Diagnostic Services (DIAMOnDS project). The main objective is to strengthen the diagnostic research, geographical spread of services and provide free-of-cost diagnostic services and evidence-based health care for cancer patients. The plan is to conduct a two phase, six step pilot model and to scale up later to the entire country.¹¹ The six steps in the pilot project are as follows:

1. PHASE I

- Identifying institutes in four zones of India to set up oncopathology labs
- Providing facilities, infrastructure, and manpower
- Establishing and standardizing the tests

2. PHASE II

- Creating awareness about the available facilities at the zonal labs
- Networking between hospitals and medical colleges for proper guided referrals
- Monitoring and evaluating services for improvements

GENOME INDIA PROJECT

The Genome India Project was started in 2020 with the aim of collecting around 10,000 samples from the general population across the country in its first stage. The second stage would be to collect genetic samples from patients with three broad categories - cardiovascular diseases, mental illness, and cancer. It is aimed to identify the genomic and molecular data to embed the principles of precision medicine in research, clinical practice, and policy levels. Through genomic projects, it is expected that India would be one of the major stakeholders in the genomics industry.¹²

CONCLUSION

Doing NGS or molecular profiling is pointless if our patients cannot afford it or do not have access to the drugs recommended by these tests. Financial toxicity resulting from the tests may lead to catastrophic expenditure which pushes

the patients into poverty. The collation of real-world evidence of the impact of molecular tests and recommendations made or implemented needs to be collected and analyzed so that the patients can make an informed choice.

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