Global Implementation of Precision Oncology

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Advances in sequencing technologies have provided unprecedented insights into the molecular landscape of tumors. With next-generation sequencing (NGS), comprehensive molecular profiling of tumors can be generated expediently and at a fraction of the costs associated with traditional sequencing methods.[1] On the shoulders of these scientific advances in sequencing technology, genome-driven therapy has been pushed to the forefront of cancer medicine (precision oncology). Since cancer is a disease driven primarily by alterations in the genetic code,[2] it follows that identifying specific alterations driving the malignant process should fuel the development of novel therapeutic strategies. Therein lies the concept of precision oncology—an opportunity to personalize care, with the promise of greater efficacy with less toxicity for the individual patient. Indeed, for a number of patients, this dream has been fulfilled with the recent regulatory approvals of targeted and immuno-oncology agents in a histology agnostic setting, including the approval of the TRK inhibitor, larotrectinib, for patients with TRK fusion–positive solid tumors[3] and more recently the approval of pembrolizumab for patients with tumor mutational burden–high solid tumors.[4] Further, targeted therapies previously approved in a histology-specific setting, such as BRAF inhibitors in melanoma[5] and trastuzumab in human epidermal growth factor receptor 2 (HER2)–positive breast cancer,[6] have demonstrated promise in other tumor types harboring the relevant alterations, leading to regulatory approvals in these settings.[7,8] However, critics of precision oncology have questioned the cost-effectiveness of large-scale implementation of NGS as a means to improve outcomes for patients with cancer.[9-11] Indeed, rising healthcare costs are a significant concern, especially in countries with a universal health insurance system where budgetary limitations are an important consideration in care delivery.

In this study, Seet et al enrolled 1,015 patients treated over a period of 6 years at the National Cancer Center Singapore on a prospective protocol for genomic profiling—the Individualized Molecular Profiling for Allocation to Clinical Trials (IMPACT) study (NCT02806388). A total of 1,064 NGS analyses were performed on the 1,015 enrolled patients, of which 38% (405/1,064) identified potentially actionable alterations. Of the 405 NGS analyses that identified potentially actionable alterations, 189 were formally discussed at a molecular tumor board (MTB), with 111 patients allocated to a clinical trial following the MTB. Among these 111 patients, 20 were eventually enrolled on a genomically matched clinical trial. Notably, an additional 33 patients were directly enrolled on genomically matched clinical trials without formal discussion at an MTB, for a total of 53 patients. As the authors acknowledge, key limitations of this study include the heterogeneity of NGS assays used and the single-center nature of this experience. The different NGS assays used in this study is an understandable consequence of the evolving molecular testing technologies taking place during the duration of the trial over which patients were enrolled. Although this study was conducted at a single center, the National Cancer Center Singapore is the largest cancer center in Singapore, an island city-state with a total population of 5.9 million.

Most of Singapore's health care is delivered through a government-run, publicly funded system where patients have a shared financial responsibility. Thus, a spike in healthcare costs will have a direct economic impact on patients and be closely scrutinized. Therefore, this study is timely and provides key data for relevant stakeholders to evaluate the feasibility of widespread implementation of precision oncology efforts in the local context. Table 1 summarizes the findings of similar efforts across the globe.[12-23] Briefly, all these studies primarily used DNA-based assays to identify actionable alterations in tumors from patients with advanced cancers who would then be matched to receive genomically matched therapies, mostly in the setting of a clinical trial. There is considerable variation in genomic matching rates across studies, with some studies reporting matching rates as low as 4% and others as high as 36% (Table 1). We believe that the observed variation in matching rates across studies is multifactorial, including differing definitions of what constitutes a match, timely availability of genomically matched studies, clinical fitness of the patient population for clinical trial enrollment, availability of bioinformatic support for variant annotation, and determination of clinical significance. In this study, the authors report a genomic matching rate of 5% (53/1,064), which is similar to a study performed at another academic institution in Singapore[20] but is lower when compared with similar studies across the globe (Table 1). Factors such as geographic variation in the prevalence of actionable alterations, technical differences in the assays used, and availability of genomically matched clinical trials are potential explanations

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TABLE 1. Precision Oncology Efforts Across the Globe

Study	Setting	Assay(s)	Number of Patients	Number of Assays	Number of Patients Matched	Match Rate, %[a]	Reference
North America							
MSK-IMPACT	Single-center	DNA: 341- to 410-gene NGS panel (all exons and selected introns)	10,336	10,945	527[b]	11[b]	12
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 10-gene NGS panel (hotspot)	1,144	1,144	211	18	13
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 11- to 50-gene NGS panel (hotspot)	2,000	2,000	83	4	14
MD Anderson Personalized Cancer Therapy Program	Single-center	DNA: 236 genes	339	339	122	36	15
PREDICT	Single-center	DNA: 182- to 236-gene NGS panel (Foundation Medicine)	347	347	87	25	16
IMPACT/COMPACT	Single-center	DNA: 23- to 50-gene NGS panel (hotspot); Protein: PTEN IHC	1,640	1,640	89	5	17
NCI-MATCH	Multicenter	DNA: 143-gene NGS panel (hotspot); Protein: PTEN, MLH1, MSH2, and Rb IHC	5,540	5,540	686	12	18
Europe							
MOSCATO	Single-center	DNA: 40- to 75-gene NGS panel (hotspot), CGH, WES in limited number of cases; RNA: RNAseq; Protein: MET and phospho-MET IHC	843	843	199	24	19
Asia							
IMPACT-SG	Single-center	DNA: NGS panel (variable number of genes, hotspot); Protein: ALK, cMET, cMYC, FGFR2, HER2, HGF, MMR, NTRK, PTEN, ROS1, and PD-L1 IHC	1,015	1,064	53	5	
IMAC	Single-center	DNA: 50-gene NGS panel (hotspot)	365	365	23	6	20
NEXT 1	Single-center	DNA: 83- to 381-gene NGS panel (hotspot); Protein: PTEN, MET, and HER2 IHC	588	588	60	10	21
TOP-GEAR	Single-center	DNA: 114-gene NGS panel (all exons and selected introns)	187	187	25	13	22
Kyoto University Hospital Study	Single-center	DNA: 215-gene NGS panel (all exons and selected introns)	73	73	9	12	23

Abbreviations: CGH, comparative genomic hybridization; HER, human epidermal growth factor receptor 2; NGS, next-generation sequencing; WES, whole exome sequencing.

[a]Match rate = number of patients matched/number of patients with genomic profiling results.

[b]Among the first 5,009 patients.

for this disparity, and further studies are needed to elucidate this underlying variation.

As significant efforts in distinct geographical areas are underway to enhance the clinical impact of precision oncology, several challenges remain. First, the type of tumor sample used can affect the results of genomic assays and have downstream effects on therapeutic decisions. In a study comparing mutation calls from whole-exome sequencing in matched fresh and archival melanoma tumor biospecimens, the concordance rate was only 43%.[24] The observed lack of concordance between archival and fresh biospecimens is likely to be because of a combination of poor quality DNA from archival specimens and temporal evolution of the molecular landscape of the tumor, due in part to selection pressure from intervening therapeutic efforts.[25] However, although using fresh biospecimens to identify actionable alterations is preferred in a precision oncology platform, logistical challenges frequently steer

care providers and patients toward the use of archival tissue for molecular profiling. The recent emergence of plasma genotyping as a tool to obtain molecular information about the tumor provides an opportunity to obtain real-time genomic information about the tumor while avoiding the need for repeated invasive tumor biopsies. Indeed, the concordance between plasma and tissue genotyping has been reported to be 81% in patients with metastatic non–small-cell lung cancer.[26] Although plasma genotyping can overcome some challenges associated with tumor biopsies, detection of actionable alterations by plasma genotyping is dependent on tumor shedding, which is influenced by several factors including disease burden, tumor location, vascularity, and cellular turnover.[27-29] Indeed, such variations can lead to false-negative results and affect clinical decision making.[30-32] Thus, although we anticipate that plasma genotyping will develop an increasing footprint in longitudinal molecular profiling and change clinical practice, tissue genotyping will continue to be an integral part of precision oncology platforms until efforts to validate and overcome diagnostic limitations associated with plasma genotyping mature.

Second, as evidenced by this and other studies in precision oncology (Table 1), emerging molecular assays are increasingly multiplexed, with more genes being sequenced at greater depth. Although this provides significantly greater information about the molecular profile of the tumor, clinical actionability is heavily dependent on having a robust and multidisciplinary precision oncology decision support system involving clinicians, bioinformaticians, pathologists, cancer biologists, and clinical trial support staff.

Third, the cost-effectiveness of large-scale implementation of precision oncology platforms has yet to be established. In countries such as Singapore where patients bear a significant portion of healthcare costs, a thoughtful patient selection process for a precision oncology strategy will likely reduce the economic burden on patients and governmental funding agencies. For instance, extensive molecular profiling could be reserved for patients with adequate performance status and organ function for clinical trial enrollment. Although the costs of performing molecular assays will continue to fall in the coming years, personnel costs associated with analyzing the data may rise owing to increasing complexity. Thus, a measured approach to precision oncology is key to maintaining cost-effectiveness while maximizing clinical benefit for the individual patient.

In conclusion, this study, along with others conducted in Asia and elsewhere, demonstrates the feasibility of implementing precision oncology efforts across diverse geographical settings. However, having adequate infrastructure and technology to support such an effort is only the first step. Furthermore, such efforts need to be supported by specialized centers with established phase I clinical trial programs equipped with the necessary critical mass of trials evaluating novel agents. Indeed, the promise of precision oncology is delivered only when patient outcomes are improved through the delivery of molecularly matched agents. Thus, a robust precision oncology decision support system needs to be developed in parallel with laboratory infrastructure to ensure accurate and timely analysis of increasingly complex molecular data derived from highly sophisticated assays in a patient-centered context. Finally, such initiatives need to be coupled with joint international collaborative efforts to drive the development of novel molecularly targeted and other agents in the setting of biomarker-driven trials, which is critical to fulfilling the ultimate goal of precision oncology for all patients across the globe.

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REFERENCES

1. Masters GA, Krilov L, Bailey HH, et al: Clinical cancer advances 2015: Annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol 33:786-809, 2015
2. Stratton MR, Campbell PJ, Futreal PA: The cancer genome. Nature 458:719-724, 2009
3. Drilon A, Laetsch TW, Kummar S, et al: Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 378:731-739, 2018
4. Marabelle A, Fakih M, Lopez J, et al: Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: Prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 21:1353-1365, 2020
5. Chapman PB, Hauschild A, Robert C, et al: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364:2507-2516, 2011
6. Baselga J, Tripathy D, Mendelsohn J, et al: Phase II study of weekly intravenous trastuzumab (Herceptin) in patients with HER2/neu-overexpressing metastatic breast cancer. Semin Oncol 26:78-83, 1999
7. Hyman DM, Puzanov I, Subbiah V, et al: Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med 373:726-736, 2015
8. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 376:687-697, 2010
9. Prasad V: Perspective: The precision-oncology illusion. Nature 537:S63, 2016
10. Prasad V, Fojo T, Brada M: Precision oncology: Origins, optimism, and potential. Lancet Oncol 17:e81-e86, 2016
11. Tao DL, Kartika T, Tran A, et al: Phase I trials and therapeutic intent in the age of precision oncology: What is a patient's chance of response? Eur J Cancer 139:20-26, 2020
12. Zehir A, Benayed R, Shah RH, et al: Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 23:703-713, 2017
13. Tsimberidou AM, Iskander NG, Hong DS, et al: Personalized medicine in a phase I clinical trials program: The MD Anderson Cancer Center Initiative. Clin Cancer Res 18:6373-6383, 2012
14. Meric-Bernstam F, Brusco L, Shaw K, et al: Feasibility of large-scale genomic testing to facilitate enrollment onto genomically matched clinical trials. J Clin Oncol 33:2753-2762, 2015
15. Wheler JJ, Janku F, Naing A, et al: Cancer therapy directed by comprehensive genomic profiling: A single center study. Cancer Res 76:3690-3701, 2016
16. Schwaederle M, Parker BA, Schwab RB, et al: Precision oncology: The UC San Diego Moores Cancer Center PREDICT experience. Mol Cancer Ther 15:743-752, 2016
17. Stockley TL, Oza AM, Berman HK, et al: Molecular profiling of advanced solid tumors and patient outcomes with genotype-matched clinical trials: The Princess Margaret IMPACT/COMPACT trial. Genome Med 8:109, 2016
18. Flaherty KT, Gray RJ, Chen AP, et al: Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). J Clin Oncol 38:3883-3894, 2020
19. Massard C, Michiels S, Ferte C, et al: High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: Results of the MOSCATO 01 trial. Cancer Discov 7:586-595, 2017
20. Heong V, Syn NL, Lee XW, et al: Value of a molecular screening program to support clinical trial enrollment in Asian cancer patients: The Integrated Molecular Analysis of Cancer (IMAC) Study. Int J Cancer 142:1890-1900, 2018
21. Kim ST, Kim KM, Kim NKD, et al: Clinical application of targeted deep sequencing in solid-cancer patients and utility for biomarker-selected clinical trials. Oncologist 22:1169-1177, 2017
22. Sunami K, Ichikawa H, Kubo T, et al: Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting: A hospital-based study. Cancer Sci 110:1480-1490, 2019
23. Kou T, Kanai M, Yamamoto Y, et al: Clinical sequencing using a next-generation sequencing-based multiplex gene assay in patients with advanced solid tumors. Cancer Sci 108:1440-1446, 2017
24. De Paoli-Iseppi R, Johansson PA, Menzies AM, et al: Comparison of whole-exome sequencing of matched fresh and formalin fixed paraffin embedded melanoma tumours: Implications for clinical decision making. Pathology 48:261-266, 2016
25. El-Deiry WS, Taylor B, Neal JW: Tumor evolution, heterogeneity, and therapy for our patients with advanced cancer: How far have we come? Am Soc Clin Oncol Ed Book 37:e8-e15, 2017

26. Aggarwal C, Thompson JC, Black TA, et al: Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. JAMA Oncol 5:173-180, 2019
27. Bettegowda C, Sausen M, Leary RJ, et al: Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Transl Med 6:224ra24, 2014
28. Jahr S, Hentze H, Englisch S, et al: DNA fragments in the blood plasma of cancer patients: Quantitations and evidence for their origin from apoptotic and necrotic cells. Cancer Res 61:1659-1665, 2001
29. Diehl F, Schmidt K, Choti MA, et al: Circulating mutant DNA to assess tumor dynamics. Nat Med 14:985-990, 2008
30. Kowalik A, Kowalewska M, Gozdz S: Current approaches for avoiding the limitations of circulating tumor cells detection methods—Implications for diagnosis and treatment of patients with solid tumors. Transl Res 185:58-84.e15, 2017
31. Marchetti A, Del Grammastro M, Felicioni L, et al: Assessment of EGFR mutations in circulating tumor cell preparations from NSCLC patients by next generation sequencing: Toward a real-time liquid biopsy for treatment. PLoS One 9:e103883, 2014
32. Saarenheimo J, Eigeliene N, Andersen H, et al: The value of liquid biopsies for guiding therapy decisions in non-small cell lung cancer. Front Oncol 9:129, 2019

