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 expeditiously and at a fraction of the costs associated with traditional sequencing methods. 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, 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 immunoncology agents in a histology agnostic setting, including the approval of the TRK inhibitor, larotrectinib, for patients with TRK fusion–positive solid tumors and more recently the approval of pembrolizumab for patients with tumor mutational burden–high solid tumors. Further, targeted therapies previously approved in a histology-specific setting, such as BRAF inhibitors in melanoma and trastuzumab in human epidermal growth factor receptor 2 (HER2)–positive breast cancer, have demonstrated promise in other tumor types harboring the relevant alterations, leading to regulatory approvals in these settings. 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. 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. 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 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...
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%. 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. However, although using fresh biospecimens to identify actionable alterations is preferred in a precision oncology platform, logistical challenges frequently steer

| 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          | 527b                        | 11b            | 12        |
| MD Anderson                  | Single-center      | DNA: 10-gene NGS panel (hotspot)                                        | 1,144              | 1,144           | 211                         | 18             | 13        |
| Personalized Cancer Therapy Program |         | DNA: 11- to 50-gene NGS panel (hotspot)                                 | 2,000              | 2,000           | 83                          | 4              | 14        |
| MD Anderson                  | Single-center      | DNA: 236 genes                                                           | 339                | 339             | 122                         | 36             | 15        |
| Personalized Cancer Therapy Program |         |                                                                         |                    |                 |                             |                |           |
| 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              | 20        |
| 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             | Single-center      | DNA: 215-gene NGS panel (all exons and selected introns)                | 73                 | 73              | 9                           | 12             | 23        |
| Hospital Study               |                    |                                                                         |                    |                 |                             |                |           |

Abbreviations: CGH, comparative genomic hybridization; HER, human epidermal growth factor receptor 2; NGS, next-generation sequencing; WES, whole exome sequencing.
aMatch rate = number of patients matched/number of patients with genomic profiling results.
bAmong the first 5,009 patients.
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.30 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.

AFFILIATIONS

1Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX
2Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX
3Department of Clinical Oncology, Phase I Clinical Trial Center, Kingboard Precision Oncology Program, The Chinese University of Hong Kong, Hong Kong, China
4Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), The University of Texas MD Anderson Cancer Center, Houston, TX
5Khalifa Institute of Personalized Cancer Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX
6Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX
7The Institute for Applied Cancer Science, The University of Texas MD Anderson Cancer Center, Houston, TX

See accompanying article https://doi.org/10.1200/PO.20.00261

CORRESPONDING AUTHOR

Timothy A. Yap, MBBS, PhD, The University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd., Unit 455, Houston, TX 77030; e-mail: tyap@mdanderson.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: Clinton Yam, Timothy A. Yap
Provision of study materials or patients: Timothy A. Yap
Collection and assembly of data: Clinton Yam, Timothy A. Yap
Data analysis and interpretation: Clinton Yam, Timothy A. Yap
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).
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, Kummer M, et al: Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 378:731-739, 2018

4. 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

5. Wheler JJ, Janku F, Naing A, et al: Cancer therapy directed by comprehensive genomic profiling: A single center study. Cancer Res 76:3703-3713, 2016

6. 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

7. 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

8. Massard C, Micheli 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 7:865-880, 2017

9. Heoong 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

10. 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

11. 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

12. De Paoli-Iseppi R, Johansson PA, Menzies AM, et al: Comparison of whole-exome sequencing of matched fresh and formalin fixed paraffin embedded melanoma tumors: Implications for clinical decision making. Pathology 48:261-266, 2016

13. 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

ACKNOWLEDGMENT

T.A.Y. acknowledges the MD Anderson Cancer Center support grant (P30 CA016672) and is a V Foundation V Clinical Scholar (VC2020-001), which supports a Program of Clinical Trials targeting the DNA damage response (DDR).

Any opinions, findings, and conclusions expressed in this material are those of the authors and do not necessarily reflect those of the sponsors.
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