Twenty-First Century Precision Medicine in Oncology: Genomic Profiling in Patients With Cancer

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Abstract

The advent of next-generation sequencing has accelerated the implementation of genomic profiling in the care and management of patients with cancer. Initial efforts have focused on target identification in patients with advanced cancer. Prognostication, resistance detection, disease monitoring, and early detection efforts are also underway. This review highlights some of the challenges in this evolving space. This includes choosing between gene-panel and comprehensive approaches, DNA and transcriptome data integration, reduction of false-positive variants, addressing tumor heterogeneity, establishment of workflows to address unsolicited findings, and data sharing and privacy concerns.

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The announcement of several large initiatives including the US Cancer Moonshot Initiative[1] and the Genomics England Initiative[2] have reinvigorated the precision medicine space. Given the genetic basis for cancer, the application of precision medicine to oncology has proven to be a natural evolution in this area. The initial foray has been in the context of biomarker-guided therapy selection. However, given

TABLE 1. Selected Prospective Tumor-Specific Trials of Molecular Profiling–Directed Therapy

Program	Lead organization	Trial design	Tumor type	Indication	ClinicalTrials.gov identifier
Lung-MAP	SWOG/NCTN	R	Squamous cell lung cancer	Treatment selection	NCT02154490
SAFIR-02 Lung	UNICANCER	R	Lung cancer	Treatment selection	NCT02117167
SAFIR-02 Breast	UNICANCER	R	Non-HER2 advanced breast cancer	Treatment selection	NCT02299999
I-SPY2	UCSF/MD Anderson Cancer Center	AR	Neoadjuvant breast cancer	Treatment selection	NCT01042379
SU2C Melanoma/GEMM	Yale/TGen	R	Non-V600E melanoma	Treatment selection	NCT02094872
FOCUS-4	Cancer Research UK	R	Colon cancer	Treatment selection	NA
SPECTA	EORTC	NR	Colon cancer	Treatment selection	NA

AR = adaptively randomized; EORTC = European Organisation for Research and Treatment of Cancer; GEMM = Genomics-Enabled Medicine for Melanoma; HER2 = human epidermal growth factor receptor 2; I-SPY2 = Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And Molecular Analysis 2; LUNG-MAP = Lung Master Protocol; NA = not applicable; NR = nonrandomized; R = randomized; SPECTA = Screening Patients for Efficient Clinical Trial Access; SU2C = Stand Up to Cancer; SWOG/NCTN = Southwest Oncology Group/National Clinical Trials Network; TGen =Translational Genomics Research Institute; UCSF = University of California San Francisco.

technological improvements in sequencing technologies and more thorough evaluation of genotype-phenotype relationships, applications to prognostication and early detection are growing increasingly common.

BACKGROUND ON MOLECULAR PROFILING IN CANCER

Molecular profiling–directed treatment of cancer traces its origins to paradigms such as the use of estrogen receptor and progesterone receptor[3] and Erb-B2 receptor tyrosine kinase 2 (ERBB2)/human epidermal growth factor receptor 2 (HER2) assessment in breast cancer.[4] A study conducted by Von Hoff et al[5] using oligonucleotide microarrays for gene expression, fluorescent in situ hybridization, and immunohistochemistry for tumor profiling followed by treatment assignment provided a conceptual framework for current efforts. Since the sequencing of an individual human genome in 2007,[6] massively parallel next-generation sequencing (NGS) has revolutionized most facets of scientific discovery and made major inroads into application in human health, particularly in the field of oncology, with potential utility encompassing the spectrum of early detection, diagnosis, prognosis ascertainment, recurrence detection, risk assessment, and treatment selection.

STUDIES OF CLINICAL APPLICATION OF NGS AND AREAS OF CONTROVERSY AND CONTENTION IN CANCER

As genomic profiling has become more ubiquitous in clinical practice, a number of retrospective institutional evaluations provided impetus for ongoing exploration of this approach, albeit with variable levels of success.[7,8] Although these efforts should be lauded for helping lay out an appropriate structural framework for the application of precision medicine to oncology, they carry a number of inherent limitations. These include selection bias present in single-cohort studies lacking a control arm, ascription of success to alterations being identified simply as actionable (instead of more rigorous criteria that would classify alterations as useful or not on the basis of strength as a predictive marker for therapeutic efficacy), or leading to change in therapy (irrespective of such a change producing a favorable outcome), heterogeneity of histologic tumor types, and inflation of value of broad-based NGS profiling in the setting of inclusion of patients with well-characterized alterations (eg, patients with BRAF V600E melanoma) in reported studies.

Pursuant to these initiatives, a number of prospective efforts are ongoing in both tumor-specific and tumor-agnostic settings (Tables 1 and 2). These trials are using an array of designs ranging from nonrandomized single-cohort to randomized/adaptively randomized trials.

The SHIVA trial conducted by the Institut Curie[11] highlighted the challenges of the application of precision medicine. In this randomized controlled trial evaluating genomic profiling–directed therapy vs use of clinically available agents, no difference was noted between the experimental and control arms

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