

Precision Oncology: An Overview

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In this Special Series issue, *Journal of Clinical Oncology* presents a systematic assessment of cancer genomic information and its accelerating clinical impact. In the scientific literature and lay press, the relevant discipline is often called personalized, or precision, cancer medicine. The word personalized conveys the sense that cancer genomic data may facilitate rational treatment choices that are tailored to individual patients. The term precision refers to prospects for enhanced molecular resolution, mechanistic clarity, and therapeutic co-gency that may accompany clinical implementation of genomics technologies. We have chosen the term genomics-driven cancer medicine in recognition of the fact that knowledge that emanates specifically from the cancer genome will likely continue to direct the opening act of precision oncology as it plays out in clinical and translational studies over the next several years.

Although precision medicine will inevitably permeate many diseases (both cancer and noncancer), oncology arguably sits at its vanguard. One obvious reason is the fact that cancer is a genomic disease: most cancers harbor a cocktail of mutated (or otherwise altered) oncogenes and tumor suppressors that work in concert to specify the molecular pathways that lead to their genesis, maintenance, and progression. Toward this end, oncology research has benefitted immensely from the proliferation of worldwide efforts to characterize the genomes of thousands of cases spanning nearly all major cancer types.¹ As described in the opening article of this Special Series issue,² the same technologic and analytic advances that have enabled a comprehensive catalogue of cancer genes are

becoming increasingly malleable for advanced clinical diagnostics. Together with the expanding compendium of targeted anticancer agents in clinical development or active use, oncology has served as a proving ground for the genomics-driven framework that is unique among medical specialties.

Conceptually, the implementation of genomics-driven cancer medicine might seem straightforward (Fig 1): first, characterize the genomes of patients' tumors using state-of-the-art technologies; second, filter the genomic data through a knowledge base of existing and emerging anticancer drugs; and third, present an annotated list to the treating oncologist that can be incorporated into clinical decision making. However, multiple challenges must be addressed to bring this ambitious goal to fruition. To begin with, high-quality genomic information must be obtained consistently in the diagnostic setting—often from sparse amounts of archival tumor tissue. The article by MacConaill³ reviews the remarkable technologic advances that make large-scale genomic data generation feasible in a clinical setting. Although questions persist regarding the extent of genomic data needed, the cost-effectiveness of various platforms, and how rapidly clinical genomic data can be delivered, it seems clear that available technologies for genome characterization are fast becoming equipped to meet the demands of precision oncology.

The analytic challenges that accompany comprehensive genomic data have proven more problematic. The somatic and germline alterations that are relevant to each cancer must be identified with high

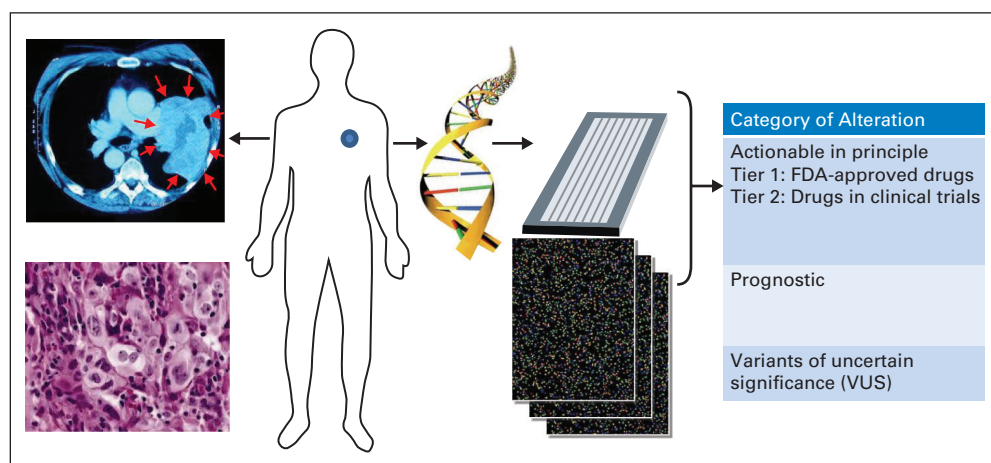


Fig 1. A schematic for genomics-driven cancer medicine.

accuracy, and clinically actionable, so-called driver events must be distinguished from the much larger set of passenger alterations that are present in tumor DNA. As pointed out by Van Allen et al,⁴ rigorous analysis and astute clinical interpretation of comprehensive genomic data is impossible without the assistance of computational algorithms to support clinical-grade data interpretation. Although numerous aspects of clinical computational biology remain in their infancy, a variety of resources and approaches have already emerged that may assist clinicians as they prepare for the unprecedented flow of tumor and germline genomic information.

The genome era also poses clinical development challenges. Oncology investigators must forge a cohesive framework whereby genomic information propels a new generation of evidence-based clinical trials. The article by Sleijfer et al⁵ outlines several possible templates for clinical trial designs that may accommodate smaller numbers of patients with discrete genetic alterations in the face of an ever-expanding repertoire of experimental anticancer agents. Moreover, patients, their families, and oncologists alike must come to grips with several psychosocial and ethical challenges that are brought forth by clinical cancer genomic information. Lolkema et al⁶ evaluate a series of issues that pertain to the possible ethical duty to return actionable genetic results, difficulties surrounding incidental somatic and germline findings, and informed consent for genetic studies and data sharing.

Having considered these challenges and their possible solutions, the narrative shifts toward the implementation of genomics-driven medicine within the oncology enterprise and examples of its impact. The task of incorporating a precision medicine infrastructure into a large academic cancer center is reviewed by Meric-Bernstam et al.⁷ Key aspects include the development of Clinical Laboratory Improvement Amendments–based genomic testing for clinical trial enrollment, platforms that support repeat biopsies and tissue banking, and decision support program development, among others.

Considerable attention is given to specific examples and lessons learned from the ongoing integration of cancer genomic data into clinical oncology disease management. Lung cancer has provided a solid tumor exemplar for genomics-driven cancer medicine ever since the emergence of epidermal growth factor receptor–directed therapy in 2004. The article by Buettner et al⁸ chronicles the evolution of multifaceted gene-directed therapies in this malignancy and the growing importance of a genetic taxonomy for treatment and rational clinical trial design. Roychowdhury and Chinnaiyan⁹ survey the impact of genomics in prostate cancer—from screening to treatment of advanced disease. Dienstmann et al¹⁰ extend these assessments across a spectrum of solid tumors, while also addressing the challenges of tumor heterogeneity and various conceptual approaches to clinical trials.

Although several well-known examples of genomics-driven medicine derive from solid tumors (eg, trastuzumab in breast cancer, imatinib in GI stromal tumors, and erlotinib in lung cancer), key elements of this paradigm originated in hematologic malignancies. Accordingly, Rampal and Levine¹¹ provide an update on the major genetic discoveries that have affected the prognosis and treatment of leukemia, lymphoma, and multiple myeloma. Finally, Janeway et al¹² describe the spectrum of genetic alterations that are currently influencing biologic and prognostic knowledge of pediatric cancers. Genetics-driven clinical trials pose special challenges in the pediatric population; however, examples are emerging of subsets in which such studies may prove meritorious.

The issue concludes with a perspective by Mendelsohn,¹³ who chronicles the transformation in cancer care over the last 40 years through the lens of genetics and molecularly targeted therapies. Its overarching theme, borrowed from a Tahitian painting by Gauguin, surveys the past, present, and future of the genomics-driven paradigm. Together with the other articles in this Special Series issue, this perspective blends the promise of precision cancer medicine with a sobering reminder of the many obstacles that must be circumvented even to render a thorough test of its inherent hypotheses. Despite the hype, one presently cannot assert with confidence that genomics-driven medicine will win the day across all cancers. Nonetheless, the confluence of science, technology, and drug discovery has produced a tractable investigative path with a reasonable chance to improve the outcomes of many patients with cancer. From the perspective of patients and their oncologists who struggle daily with advanced cancer, the genomics-driven framework seems to echo the César Vallejo poem,¹⁴ the content of which speaks of suffering, but the title of which reads: “I am going to speak of hope.”

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