Cancer Genetics and Implications for Clinical Management

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KEYWORDS

• Genomics • Next-generation sequencing • Pancreatic cancer
• Stratified medicine • Translational medicine

KEY POINTS

- Molecular heterogeneity of cancer leads to disparate molecular phenotypes with variable disease outcomes and responses to therapy in histologically indistinguishable cancers.
- There are opportunities for potential rapid improvements in cancer outcomes by adopting a more selective or stratified approach to therapy.
- Analysis of genomic data is identifying candidate actionable molecular phenotypes with existing therapeutics (repurposing) approved for use in other cancers.
- Successful translation of genomic discoveries necessitates a shift in cancer trial design and clinical service delivery to incorporate low-prevalence actionable phenotypes across multiple cancer types.
- Whole-genome sequencing has revealed that genomic aberrations in addition to point mutations in coding sequences have the potential to provide clinically useful biomarkers.
- Analysis of exceptional responders may inform how current therapeutics decision-making can be improved, and provide a mechanism for development of novel therapies.

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INTRODUCTION

The concept that chromosomal abnormalities may result in cancer was initially proposed a century ago,[1] but only 40 years have passed since Sakurai and Sandberg[2] more definitely published an original report suggesting that certain tumor genomic changes could influence the clinical management of cancer. Their karyotype aberration classification represented the first example of how the genetic information of cancer cells could inform clinical decision making.

It is now well accepted that most cancers are driven by genomic alterations that dysregulate key molecular pathways influencing cell growth, survival, and other hallmarks of cancer. Cancer genomics refers to the study of tumor genomes at multiple levels, including changes in DNA sequence, structure, the epigenome (methylation, histone modification), and the transcriptome (messenger RNA and noncoding RNA). The spectrum of genetic dysregulation promoting tumorigenesis includes gene activation or inactivation, and changes in gene expression.[3] These advances have begun to challenge traditional clinical approaches in oncology, in which patients' treatment is focused exclusively on the tumor tissue of origin. The ability to harness the full clinical potential of tumor genetic information has only recently become manifest and although the primary site of origin matters, so too do its genomic characteristics.

Aberrations playing crucial roles in tumorigenesis and progression, described as driver events, may confer critical tumor dependencies, with addiction of a cancer cell to one or several specific molecular pathways. Identification of biologically important genes and pathways commonly disrupted across different cancer types can generate clinically relevant diagnostic, predictive, prognostic, and therapeutic information.[4]

Technology has redefined the field, with the advent of large-scale genomic surveys systemically capturing cancer genomic information orchestrated by collectives including the International Cancer Genome Consortium (ICGC)[5] and The Cancer Genome Atlas (TCCA),[6] replacing serial investigation of genetic defects. Systematic and scalable methods of genetic analysis, captured by the term genomic sequencing, have facilitated the characterization of thousands of cancer genomes. Translating this systematic knowledge from individuals and their tumors may improve clinical outcomes for patients with cancer; however, rigorous evaluation of this genomics-driven cancer medicine hypothesis will require logistical transformation and innovation guided by conceptual advances in pretherapy and posttherapy tissue acquisition, specimen processing, tumor genomic profiling, data interpretation, clinical trial design, and the ethical return of genetic results to clinicians and their patients.

This article outlines aspects of recent progress in cancer genomics and provides a perspective for potential clinical applications of genomic research to advance personalized medicine and oncologic strategies.

UNDERSTANDING THE CANCER GENOME LANDSCAPE AND TRANSLATING ADVANCES FOR THERAPEUTIC GAIN

As clinicians better understand the molecular pathology of cancer, substantial complexity is being discovered, identifying a composite of multiple diseases, rather than the few that were previously defined morphologically.[7] Emerging data from large sequencing initiatives encompassing various cancers[6,8] unveil an array of molecular aberrations in histologically indistinguishable cancers. As next-generation sequencing (NGS) and other omic technologies further advance, reclassification based on molecular criteria should provide sufficient granularity to define the distinctiveness of individual cancers.