Short Communication

iMedPub Journals
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Journal of Clinical & Experimental Orthopaedics
ISSN 2471-8416

2021
Vol. 7 No. 7: 78

The new paradigm of precision medicine: Evidence-based clinical oncology

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Citation: Marilyn M. The new paradigm of precision medicine: Evidence-based clinical oncology. J Clin Exp Orthop Vol. 7 No. 7: 70.

Abstract

Precision medicine is an emerging approach for disease treatment and prevention that takes into consideration the variations in genomic makeup, environmental exposure, and social economic status of each individual. Evidence-based oncology integrates the clinical expertise, patient values and the best available evidence, especially the cancer genomic information of a patient in clinical decision making. Next-generation sequencing (NGS) technologies have revolutionized genomic research by decreasing the cost of sequencing while increasing the throughput. Clinical application of NGS in cancer can detect clinically actionable genetic/genomic alterations that are critical for cancer care. In certain cancers, patient risk and prognosis can be predicted based on the mutation profile identified by NGS. Many targeted therapies have been developed for cancer patients who bear specific genomic alterations. However, choosing right NGS techniques for appropriate clinical applications can be challenging, especially in clinical oncology, where the material for testing is often limited and the turn-around time of testing is frequently constrained to just a few days. Currently, targeted NGS approaches have emerged as the best fit for clinical oncology.

Keywords: Precision medicine; NGS; oncology

Received: Nov 08, 2021, **Accepted:** Nov 18, 2021, **Published:** Nov 28, 2021

Introduction

We have developed and validated multiple large NGS panels that allow the detection of single nucleotide variations (SNVs), small indels, copy number variations (CNVs), and novel fusion genes in different cancers, as well as pathogenic variants associated with cancer predispositions. These panels have been applied to thousands of clinical cases and have provided critic genomic information to aid in patient management decision making. Currently, whole exome and whole genome sequencing are mostly used in cancer research. As the cost of running NGS-based test continues to decrease and software for NGS data analysis continues to improve, clinical application of whole exome, whole genome, and whole transcriptome sequencing in precision cancer care is just a matter of time. The goal of precision medicine is simply to deliver the right cancer treatment to the right patient at the right dose and the right time. Several lines of investigation came together nearly simultaneously to usher in the beginning of the precision oncology era. In 1998, the BCR-ABL rearrangement in chronic myeloid leukemia was successfully targeted by the small molecule imatinib, leading to dramatic clinical remissions and U.S. Food and Drug Administration approval in 2001.

The first draft sequence of the human genome was accomplished the same year, followed by the first cancer genome. Rapid discovery of multiple, nonoverlapping driver mutations and tyrosine kinase inhibitors with clinically effective inhibitory properties in non–small cell lung cancer and melanoma led to assays of alterations performed by polymerase chain reaction (PCR) quickly and inexpensively. Use of these biomarkers to drive treatment decisions in solid tumors raised expectations and interest in molecular profiling. Sequencing technology and costs improved rapidly during the early 2000s, particularly with the advent of NGS on formalin-fixed, paraffin-embedded tissue whereby massive parallel sequencing allows determination of alterations in a large number of genes through a timely, cost-effective process. Underpinning precision oncology is the concept of somatic mutations as the foundation of cancer development.Mutations in oncogenes rendering them constitutively active are considered driver mutations and are central control points for progression of malignancies. Conversely, tumor suppressor genes, involved naturally in controlling tumor pathogenesis, can cause cancer progression when inactivated through mutation or allele loss. Multiple processes result in dysregulation of the genetic machinery in DNA RNA or protein, leading to altered expression of the protein coded for by the gene. To capture the entire spectrum of potential alterations, multiple technologies, termed a multi- or pan-omic approach, are best considered.

The vast number of choices of technologies, commercial entities offering testing, and sometimes conflicting results have overwhelmed clinicians looking to obtain molecular information that will result in clinical utility for their patients. Even in academic centers, oncologists report varying confidence in their ability to use the genomic findings appropriately. At its most fundamental level, a genomic test with clinical utility should be predictive of a treatment response from a targeted agent. An early example in solid tumor oncology was the ability to test for HER2 positivity as defined as fluorescent in situ hybridization–based gene amplification or immunohistochemistry to demonstrate overexpression of the protein. Positive results predicted response to trastuzumab-based therapies, whereas HER2-negative tumors did not derive benefit from this approach. As we have moved into multiplex testing of many genes or other biologic species, including messenger RNA and proteins, the same criteria should apply—is the variant alteration sufficiently predictive of response to a paired agent? To date, success in using precision approaches to treatment have been mixed. A prospective phase II study of molecular profiling to assign matched therapy did not show superior outcomes for the matched group but suffered from serious methodologic design issues. Large retrospective series have documented that 80%–90% of patients tested will have potentially actionable genomic alterations, although the definition of actionable can vary substantially. However, only a minority of patients to date actually receive genomically directed therapy, usually on a clinical trial.

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