APPLICATIONS FOR GENOMIC TECHNOLOGIES IN IMMUNO-ONCOLOGY

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One of the most promising advancements in oncology in recent years is the alignment of new immuno-oncology therapeutic approaches with the tools of precision medicine. Using cell-, tissue- or genomic-based biomarkers, the interaction between an individual's immune system and tumor can be better understood, ultimately enabling a more personalized approach to therapy. Genomic-based biomarkers are powerful tools used to assess tumor mutational burden, production of novel or neo- antigens and hallmarks of genomic instability, which may be useful as measures of response or resistance to immune therapies.

The increased focus on the use of biomarker assays in clinical trials has supported the development of companion diagnostics (CDx) – assays required to identify patients who are suitable for a particular therapy – and complementary diagnostics – assays providing additional information about the benefit versus risks of a particular therapy. Accurate and robust detection of tumor characteristics to stratify patients is already informing clinical decisions. For example, patients with microsatellite instability in colorectal cancer (CRC) and other solid tumors show a better response to immune checkpoint-based therapy when compared to patients with genomically stable tumors. High levels of PD-1/PD-L1 expression also correlate with increased responses to checkpoint inhibitors in a number of cancers.

Despite the benefits of CDx, a variety of factors impact the clinical and commercial use of such assays. For example, having multiple versions of an assay, such as PD-L1 immunohistochemistry, has led to challenges in clinical decision-making as different assay formats and cut-off points complicate efforts to these tools to support treatment decision making. At Covance, we aim to complement anatomic pathology and cell-based biomarkers with genomic assays and technologies as a means to improve decision making for the benefit of the patient.

White paper digest: Applications for Genomic Technologies

- Not all tumors of the same cancer type respond in the same way to a particular immunotherapy, so methods of patient stratification are essential for effective treatment.
- Tumor response to treatment can be affected by microsatellite/genomic instability, tumor heterogeneity, mutational burden and the production of novel or neo-antigens.
- Genomic sequencing using RNA sequencing (RNA-seq) and whole exome sequencing (exome-seq) can detect many types of alterations, and the data can be used to stratify patients based on each tumor characteristic.

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Genomics and transcriptomics-based technologies

Identifying genomic variation is essential for understanding and correlating tumor genotypic changes with cancer phenotype for applications in patient stratification and the further understanding markers of potential therapy response. A number of approaches can be used, including transcriptome and genomic-based sequencing.

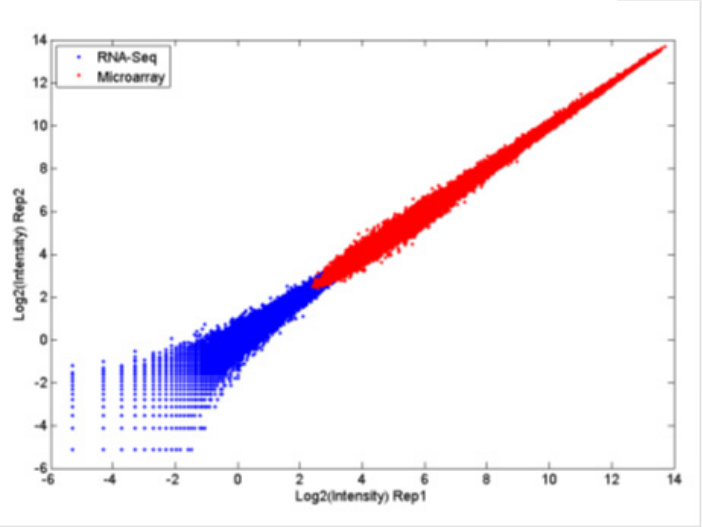

Figure 1. RNA-seq provides increased sensitivity over previous genomics methods

RNA sequencing (RNA-seq) is used to analyze the functional elements of the genome and can quantify specific transcripts and detect alterations such as alternative splicing events and gene fusions. Early efforts to understand transcriptional activity in cancer cells used microarray methods, but next generation sequencing technologies such as RNA-seqcprovide advantages in the form of higher sensitivity and resolution, allowing the analysis of a broad spectrum of expression, including genes that are expressed at a low level (Figure 1).

Whole exome sequencing focuses on the content of all exons, or protein coding regions of genomic DNA, and can define the presence of non-synonymous mutations and single nucleotide variants with great accuracy. This method enables comparison of large scale events such as copy number variations (CNVs) and chromosomal rearrangements, as well as small scale events such as single nucleotide variations across samples.

Methods that potentially combine both RNA-seq and exome-seq datasets can provide more accurate characterization of patient genomic status. However, this combined approach is heavily dependent on advanced computational biology, which limits widespread use of these more robust analyses.

COVANCE HAS DEVELOPED TOOLS TO COMBINE EXOME-SEQ AND RNA-SEQ DATASETS LEADING TO BETTER DEFINITION AND INTERPRETATION OF THE GENOMIC VARIANTS THAT ARE EXPRESSED IN THE TUMOR.

Genome sequencing for patient monitoring in immuno-oncology trials

Current methods of genomic sequencing are most often used prior to treatment in an attempt to understand genetic variations linked to potential response for a given therapy, but a variety of analytical approaches can also monitor therapeutic response.

The sensitivity of genomic methods have reached the level that allow the analysis of tumor DNA circulating free in the plasma, offering the potential to monitor therapeutic response by following specific variants found in the tumor (mutations and CNVs).

The longitudinal monitoring of genomic parameters can provide insights into patient tumor response to treatment and thereby provides valuable information required to make informed treatment decisions.

Genomic sequencing for development of novel immunotherapies

Datasets gained from extensive genomic sequencing can also be used to accurately detect and predict the existence of potential neo-antigens/neo-epitopes in the tumor sample. Studies have indicated that the level of either overall mutation burden or neo-antigens can be predictive of responses to immunotherapies.

In a previous collaboration we evaluated and categorized RAS-activated CRC tumors based on low, medium and high RAS signature scores. In this study, a combination of exome- and RNA-seq datasets identified over 650 expressed mutations, which included approximately 6,000 altered peptides, many of which could be targets for personalized immunotherapy responses.

Future of genomics in immunotherapy diagnostics at Covance

Genomic sequencing is used to understand the number and type of variations found in tumor samples, and when and how disease-related genes are expressed. Using bioinformatics tools, we can combine this information to identify the genes and biomarkers relevant to the patient to guide potential clinical decisions before and during treatment.

The field of immuno-oncology is continuously evolving, and working across the enterprise of Covance and LabCorp enables us to better understand tumor biology by utilizing specialty biomarker services. We have the potential to use this information to identify patients with specific tumor biology from histopathology and biomarker data in the LabCorp Database. Containing relevant health information on over 142 million de-identified patients, this database presents a unique opportunity to help identify patient populations and trial locations faster than other methods.

In the future, analysis of combined RNA- and exome-seq datasets may also provide valuable insights into immune composition in the tumor microenvironment, tumor immunogenicity, tumor mutational burden, and mechanisms behind immune evasion of the tumor, and tumor extrinsic factors such as the composition of the microbiome.

The increasing focus and development of genomic sequencing methods, combined with a greater variety of sample types, results in a wealth of data that can be utilized to increase the efficiency and speed of the assay and drug development process across all cancer types and patient subsets.

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