Partnering to Deliver Next-Generation Cancer Diagnostics

In the future, a universal oncology test system can drive the transition from companion diagnostics to companion therapeutics.

Introduction

The application of genomics in cancer has led to an improved understanding of the disease. To date, 138 known driver genes have been discovered—74 tumor suppressors and 64 oncogenes—that drive tumor growth through 12 cellular signaling pathways.[1] These pathways have become the focus of small-molecule inhibitor drugs, primarily targeting kinases. While the number of available targeted therapies is limited, an estimated 800 oncology drugs are in development, many of which are designed to target specific mutations.[2]

Yet, the tumor genomic landscape is heterogeneous and researchers are finding that it evolves as cancer progresses. Targeted therapies can be used to affect the pathways during tumor growth. Single-analyte companion diagnostics exist for many of these drugs. However, the need to assay each variant sequentially does not support an effective treatment paradigm.

Illumina next-generation sequencing (NGS) systems are the gold-standard in cancer research throughout the world. Rather than detecting single analytes, NGS-based panels can simultaneously detect the presence of multiple analytes in human samples.

With a focus on bringing the power of NGS to clinical diagnostics, Illumina is forming partnerships with pharmaceutical companies and the clinical community to create a universal oncology test system (under development). This NGS-based oncology test will consist of multiple biomarkers identified through the partnership. In addition, Illumina is working with world-renowned cancer centers to develop and recommend standards around the use of NGS to guide decision making in clinical oncology. The goal will be the development of regulatory agency–approved universal oncology–based tests to support therapeutic selection.

Illumina has a proven success record of working with the FDA to clear NGS tests for clinical use. In November 2013, Illumina was the first company to market a CE-marked, FDA-cleared high-throughput DNA sequencing system, the MiSeqDx® System.

Impact of Tumor Heterogeneity on Treatment Decisions

The molecular heterogeneity of tumors is well-known. Multiple driver mutations (targets) can be present within individual patients and tumors between patients with the same form of cancer. The genomic landscape changes with response or resistance to different therapeutic regimens. More effective multidrug treatment regimens have replaced single-drug approaches. With each cancer patient representing a novel confluence of cancer variants, clinicians, and pharmaceutical companies are faced with several challenges:

- Is there a baseline combination of molecularly targeted drugs for certain cancers?
- How do we optimize the drug combination for each patient?
- Do the drug combinations need to affect multiple pathways?
- Are there instances where the drug combinations affect multiple nodes in the same pathway?

Within this therapeutic environment, single-analyte companion diagnostics are costly and time-consuming to develop. They must be performed sequentially to obtain the necessary data if multiple single-target cancer drugs are being considered for therapy. Limited tissue sample availability prohibits repeat testing.

The genetic complexity of tumors requires assessment tools that capture a complete view of the tumor landscape, making measurements easier and more economical. Researchers have used NGS for years to scan the genome in search of cancer variants. By offering a broader view of a patient's genomic landscape, an NGS-based assay panel enables the simultaneous assessment of multiple markers.

A New Genomic Ecosystem for Precision Oncology

Recognizing the clinical value of a multiplexed NGS approach, Illumina is partnering with the pharmaceutical and oncology community to develop a universal oncology test system. The benefits of this NGS-based tumor assessment assay will be numerous. For pharmaceutical companies, it will streamline the validation of clinically relevant variants, the development of new cancer drugs, and the implementation of these new therapies into clinical treatment regimens (Table 1).

Table 1: Universal Oncology Test System Objectives for Supporting Pharmaceutical Development Programs

Standardize: To enable standardization of a multiplexed platform for evaluating relevant genes.
Streamline: To optimize the introduction of new biomarkers by using a standardized system.
Decentralize: To deliver a universal platform for decentralized routine testing, enabling rapid commercial access.
Collaborate: To facilitate combination trials within and across pharmaceutical companies.

In development.

The planned universal oncology test system will inform critical treatment decisions by offering genetic insights into a patient's tumor. The goal of this multiplexed molecular analysis tool is to enable clinicians to pair appropriate targeted cancer therapies with patients diagnosed with certain molecular disease profiles.

The Vision for a Universal Oncology Test System

Through individual partnerships with leading pharmaceutical companies, Illumina will identify the emerging set of solid tumor biomarkers relevant to cancer drug development in each company (Table 2). After the list of tumor biomarkers is defined, reviewed, and approved by all pharmaceutical partners, Illumina will begin development of a universal oncology test system.

In delivering a solution that meets FDA approval standards, Illumina will apply its innovative capabilities of sample extraction, library preparation, sequencing, and informatics products. Illumina will conduct studies to satisfy the approval requirements of a universal oncology test system. It will also support pharma partners in their use of a universal oncology test system to develop and validate clinical claims to support their therapeutic pipelines.

Table 2: Planned Features of a Universal Oncology Test System

Feature	Description
Variant Selection	Coverage of the relevant genes defined by pharmaceutical company pipelines and currently available therapeutics
Variants Covered	Single nucleotide variants, insertions and deletions, copy number variation, gene rearrangements/ translocations, and other structural variants
Variant Reporting	Variant reporting software, with appropriate annotation, provided by Illumina
Sample Source	Limited nucleic acid inputs extracted from FFPE

Driving NGS Standards for Oncology

As NGS shifts toward clinical use in cancer, Illumina recognizes the importance of having established standards for adoption of NGS-based tests. To this end, Illumina has joined world-renowned cancer centers, key opinion leaders, and pharmaceutical companies to support the use of NGS in oncology. The priority is to define the principles and content of the "cancer actionable genome"—a comprehensive description of genomic alterations that define individual patients' tumors.

Recommendations will include best practices for biopsy, sample storage and transport, and extraction; technical performance standards for DNA sequencing; standards for variant calling, annotation, and interpretation; and, guidelines for the format and content of clinical reports. After it is defined, Illumina will help oncologists and pathologists determine optimal therapeutic and testing strategies to improve patient outcomes. Ultimately, these standards will facilitate the development, regulation, commercialization, and reimbursement of NGS-based tests that deliver more informative, reliable, reproducible, and actionable data to physicians and their patients.

Clinical Sequencing and Data Management in the Future

Illumina sees a future in which data delivery occurs in real time and includes annotations reflecting the most current understanding of biology and clinical application. The company is investing in building a future where informatics, integration with public and proprietary annotation databases, and delivery through electronic medical records and laboratory information management systems all function in harmony. Regulatory, privacy, security, and other questions must be resolved before this vision comes to fruition in the cloud. When it does, future diagnostic information will be a critical component to manage patient care.

Partnering with Illumina

At Illumina, our goal is to apply innovative sequencing technology to the analysis of genetic variation and function, making studies possible that were not even imaginable just a few years ago. These studies will help make the realization of precision medicine possible.

Currently, Illumina is the leading manufacturer of NGS instruments, supporting systems worldwide with an industry-leading 80% market share.[3] In addition to its research and development prowess, Illumina has assembled a diagnostics leadership team with outstanding clinical experience to support the development, regulatory submissions, approval, and launch of a universal oncology test system.

Summary

Illumina is partnering with pharmaceutical companies and the clinical community to develop a universal oncology test system and standards for applying NGS in a clinical oncology setting. This NGS-based oncology test will include validated biomarkers and is intended to enable researchers and clinicians to gain insights into the genetics of a tumor. A universal oncology test system aims to streamline the validation of clinically relevant variants and the development of new molecular-based cancer therapeutics. The goal of this multiplexed molecular analysis tool is to enable clinicians to match patients with certain molecular disease profiles with approved targeted therapies.

References

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3. Herper M. Flatley's law: The company speeding a genetic revolution. *Forbes.* 2014. www.forbes.com/sites/matthewherper/2014/08/20/flatleys-law-how-one-company-became-the-force-behind-medicines-genetic-revolution/ Published September 8, 2014. Accessed November 30, 2015.

In development.

Table 3: Illumina Certified Sequencing Service Providers

North America	Europe	Asia Pacific
Ambry Genetics	Alacris	Australian Genome Research Facility (AGRF)
Beckman Coulter Genomics	AROS Applied Biotechnology	Berry Genomics
British Columbia's Genome Sciences Centre (BCGSC)	BaseClear	BGI Hong Kong
Broad Institute	Centro Nacional de Análisis Genomico (CNAG)	BGI Shenzhen
Cold Spring Harbor Labs	CNRS France - Lille	ChunLab, Inc.
Columbia Genome Center	Cologne Center for Genomics	DNA Link, Inc.
Epigenomics Shared Facility (ESF)	Estonian Genome Center	Genergy Biotechnology
Expression Analysis	FASTERIS SA	GENEWIZ, Inc.
GeneDX	GATC Biotech	Genomic Medicine Institute
GENEWIZ, Inc.	GENEWIZ, Inc.	GCA Corp.
Genome Technology Access Center	Genomix4Life S.r.l.	Hawkesbury Institute for the Environment
Georgia Genomics Facility	IGA Technology Services Srl	Hokkaido System Science Co., Ltd
LabCorp Clinical Trials	IMGM Laboratories GmbH	Macrogen Inc.
Lucigen Corporation	Laboratory of Molecular Medicine and Genomics, University of Salerno	Micromon
McDonnell Genome Institute at Washington University	Laboratory of Molecular Medicine and Genomics, University of Salerno	National Taiwan University
McGill University and Génome Québéc Innovation Centre	LGC Genomics	Novogene
MOgene, LC	LIFESEQUENCING SL	Polaris
Mount Sinai, Genomics Core Facility	NEO New Oncology AG	The Ramaciotti Centre
National Center for Genome Resources (NCGR)	NIMR Genomics Facility (National Institute for Medical Research)	Samsung Genome Institute (SGI)
New York Genome Center	Norwegian Radium Hospital and University of Oslo	Shanghai Biotechnology Corporation
PerkinElmer, Inc.	NTNU Genomics Core Facility	Takara Bio, Inc.
Personalis	Oxford Genomics Centre	TheragenEtex Bio Institute
Sequensys	Parco Technologico Padano	Yourgene Bioscience
SeqWright	Science for Life	
University of Illinois	ServiceXS B.V.	
University of Toronto	Source BioScience LifeSciences	
Vaccine and Gene Therapy Institute of Florida	University of Oxford Wellcome Trust Centre for Human Genetics	
Zymo Research Corporation	Uppsala University	

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