Precision Medicine Technology - Clinical *Evidence*

Next Generation Sequencing in the Treatment of Cancer

Next Generation Sequencing (NGS) technology, a revolutionary form of DNA analysis, enables the reading of the entire human genome to determine its unique genetic code whereas older forms of sequencing can only analyze one section of DNA at once. It identifies hundreds of biomarkers and mutation drivers; permits the interrogation of normal and abnormal genes; and provides the foundation upon which a genomic profile for a person or a malignant tumor can be developed. Liquid biopsy is a non-invasive technique of obtaining bodily fluids, such as blood, urine, saliva, etc. to analyze different types of biomolecules including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs) and exosomes from which NGS may be performed. NGS has changed the testing and treatment paradigm to become the new standard of care for cancer diagnostics and treatment (as more cancer drugs require genomic data to be prescribed).

Several peer-reviewed studies, published in leading scientific journals, demonstrate the clinical efficacy / efficiency of clinical NGS testing.

NCCN

National Comprehensive Cancer Network clinical practice guidelines for cancer of an unknown primary site state that NGS may be considered after initial determination of histology has been made to identify potentially actionable mutations that could guide therapy decisions.

Gut

Preoperative next generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia. Singhi AD et al. Gut. 2018 Dec; 67(12):2131-2141. doi: 10.1136/gutjnl-2016-313586. Epub 2017 Sep 28. PMID: 28970292; PMC6241612.

Journal of Thoracic Oncology

Liquid biopsy for advanced NSCLC: A consensus statement from the International Association for the Study of Lung Cancer Rolfo C, Mack P, Scagliotti GV, et al. J Thorac Oncol. 2021 Oct;16(10):1647-1662.

JAMA Oncology

Clinical Implications of Plasma-Based Genotyping with the Delivery of Personalized Therapy in Metastatic Non–Small Cell Lung Cancer. Aggarwal C, Thompson JC, Black TA, et al. JAMA Oncol. 2019;5(2):173–180. doi:10.1001/jamaoncol.2018.4305

Clinical Cancer Research

Clinical utility of comprehensive cell-free DNA analysis to identify genomic bio-markers in patients with newly diagnosed metastatic non-small cell lung cancer. Leighl NB, Page RD, Raymond VM, et al. Clin Cancer Res. 2019 Aug 1;25(15):4691-4700.

The Oncologist

Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. Johnson DB et al. Oncologist. 2014 Jun;19(6):616-22. doi: 10.1634/theoncologist.2014-0011. Epub 2014 May 5. PMID: 24797823; PMCID: PMC4041676.

International Journal of *Molecular Sciences*

Next-generation sequencing in oncology Genetic diagnosis, risk prediction and cancer classification. Kamps R, Brandao RD, van den Bosch BJ, et al. Cho WC, ed. International Journal of Molecular Sciences. 2017;18(2):308.

Healthcare - AI Technology that Supports Cancer Therapy Selection

Combination therapy is a treatment modality whereby two or more therapeutic agents are used to enhance efficacy (vs. the monotherapy approach) by targeting key pathways in a synergistic or additive way. Proven to be so successful for cancer that drug makers now research, and market, pre-packaged multi-drug therapies. The safety, efficacy and cost-effectiveness of combination therapy is well documented.

Drug repositioning (off-label drug use) is a therapeutic approach whereby current therapeutic agents primarily used to treat one indication are used to treat a different one (e.g., cancer). Apart from "pre-packaged" FDA-approved combination therapies intended to address known gene mutations (e.g., those targeted by OPDIVO + YERVOY), drug repositioning is most commonly associated with the use of FDA-approved drugs in combinations that are intended to address gene mutations in novel ways; the premise being that there is a greater likelihood that a novel combination therapy will yield a better outcome the first time vs. repeated attempts using ordinary treatments (often at a lower overall long-term cost). Typically (but not always), at least one drug is used as intended and, in all cases, approved drug safety protocols and known pharmacokinetic profiles are evaluated and expertly addressed.

Numerous peer-reviewed studies, published in leading scientific journals, demonstrate that physicians who are equipped with the latest precision medicine technologies are more likely to identify and select a genomically justified therapy option, the first time … and that identifying novel combinations of FDA-approved drug therapies — supported by these technologies — is now a reality. Indeed, one such AI-supported tumor-specific, biomarker-based tool that ranks and scores possible cancer therapies (*CureMatch*) is such a new technology that the AMA just recently (January 1, 2023) issued a new Category III CPT Code (0794T) to track the use of this groundbreaking innovation.

Genome Medicine

Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naïve study
Sicklick….Kurzrock, Genome Medicine 2021

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Significance of scores generated by a cancer therapy matching engine for patient outcomes.
Perlina, ASCO, 2021

nature medicine

Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study
Sicklick, Nature Medicine 2019

nature COMMUNICATIONS

Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy patients
Kato, Nature, 2020

cancers

The Crossroads of Precision Medicine and Therapeutic Decision Making
Boichard…..Kurzrock, Cancers, 2020

ESMO Open Cancer Horizons

Comparison of Three Commercial Decision Support Platforms for Matching of Next-Generation Sequencing Results with Therapies in Patients with Cancer
Perakis, ESMO Open, 2020

Molecular Cancer Therapeutics

Precision Oncology: The UC San Diego Moores Cancer Center PREDICT Experience
Schwaerderle…Kurzrock, Molecular Cancer Therapeutics, 2016

Pharmacogenomics and Cancer Medication Dosing

Drug company dosage guidelines are typically based on the general population's ability to absorb, distribute, metabolize and excrete the medication. Complication arise as many people fall outside the manufacturers' intended therapeutic index for safe and efficacious dosage and these patients are subject to a far greater risk for an adverse drug reaction (ADR) *when dosage guidelines are followed*. This is exacerbated when the therapeutic index is narrow. Because ADRs represent a major cause of morbidity and mortality, the FDA has identified more than two hundred drugs that may not work as commonly prescribed for those with specific gene variants.

Most drugs are metabolized by various enzymes, and some are made more active, less active or even inactive through the patient's unique metabolism. The challenge in establishing an optimal medication regimen is to make sure that the active form of a drug stays in the system long enough to perform as intended. Pharmacogenomics (PGx) looks to predict how individual genetic variability impacts medication absorption, metabolism and activity by looking for variants in a person's genes to determine how the patient will react to various drugs.

Peer-reviewed studies, published in leading scientific journals, demonstrate that providing oncologists with preemptive PGx information along with clinical decision support enables individualized dosing decisions that can result in improved patient outcomes and fewer ADRs.

JCMT Journal of Cancer Metastasis and Treatment

Pharmacogenomics in colorectal cancer: current role in clinical practice and future perspectives Battaglin, F.; Puccini A.; Naseem M.; Schirripa M.; Berger MD.; Tokunaga R. et al J. Cancer Metastasis. Treat. 2018, 4, 12. http://dx.doi.org/10.20517/2394-4722.2018.04

BMC Biomarker Research

Application of pharmacogenetics in oncology Miteva - Marcheva, N. N., Ivanov, H. Y., Dimitrov, D. K. et al. BMC Biomarker Research 8, 32 (2020). https://doi.org/10.1186/s40364-020-00213-4

Science Translational Medicine

Genomic medicine: a decade of successes, challenges, and opportunities McCarthy JJ, McLeod HL, Ginsburg GS. Sci Transl Med. 2013 Jun 12;5(189):189sr4. doi: 10.1126/scitranslmed.3005785. PMID: 23761042.

IntechOpen

Pharmacogenetics and Cancer Treatment: Progress and Prospects Ruwali M (January 29, 2019) IntechOpen Molecular Medicine. DOI: 10.5772/intechopen.83424.

Future Medicine

Pharmacogenomics at the center of precision medicine: challenges and perspective in an era of Big Data Primorac, Bach-Rojecky et al Future Medicine Ltd, Pharmacogenomics Vol 21, Issue 2, January 2020, Pgs 141-156, https://doi.org/10.2217/pgs-2019-0134

frontiers in Genetics

Pharmacogenomics in oncology care Filipski KK, Mechanic LE, Long R and Freedman AN (April, 2014) Frontier Genetics. 5:73. DOI: 10.3389/fgene.2014.00073

BJCP British Journal of Clinical Pharmacology

Pharmacogenomics of anticancer drugs: Personalising the choice and dose to manage drug response Carr DF, Turner R, and Pirmohamed M, Vol 87, Issue 2; 05 June 2020 https://doi.org/10.1111/bcp.14407