Clinical Omics - Genomics to Metabolomics and Onwards to the Multi-Omics Frontier

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Omics encompasses system-wide multiplexed technologies that analyze all biological molecules of a specific type in a system. Genomics analyzes all genes to identify protein-coding mutations, such as some single nucleotide polymorphisms (SNPs), or copy-number variants. Epigenomics evaluates genome-wide epigenetic modifications, for instance gene promotor methylation status or histone modifications, which would regulate gene expression. Transcriptomics is the domain of all RNA transcripts (*i.e.*, gene expression), including messenger RNAs, microRNAs, long non-coding RNAs, among others. Proteomics and metabolomics are the sum of all proteins and metabolites, respectively, in a system. Finally, multi-Omics integrates two or more Omics to obtain a more comprehensive and complex patient profile than achieved by any single Omics.

In clinical applications, Omics technologies have several goals, such as identifying biomarker panels that can predict clinical outcomes. Diagnostic biomarkers determine the presence or absence of a specific disease in an individual, whereas prognostic biomarkers are used to anticipate disease course and outcome for a patient, for instance aggressive versus less aggressive tumors. Predictive biomarkers, on the other hand, provide information on a patient's expected treatment outcome, whether or not they will have a favorable response to a particular drug.

Another emerging and important application of Omics technologies, as their costs continue to drop, is for personalized or precision medicine. An Omics profile is created from a patient which can be used to inform several clinically important parameters, for instance, disease stratification, a personalized drug regimen and even drug safety by evaluating pharmacogenomics. In clinical research or practice, Omics can be applied to patient samples, such as biofluids (*e.g.*, blood, urine, cerebrospinal fluid) or tissue (*e.g.*, skin or tumor biopsy).

In this list, we divulge the latest research in clinical Omics, illustrating each technology with specific examples at the stages of clinical research, clinical trial or clinical applications.

Genomics

Perhaps the most widespread application of genomics is using next generation sequencing (NGS) to profile tumor DNA to identify mutations, which can be leveraged for personalized treatment. In this vein, the Food and Drug Administration (FDA) has cleared genomic profiling tests that identify mutations in a large panel

of frequently mutated cancer genes. This genomic approach is completely transforming clinical trial design. Whilst older trials recruited patients by tumor location and histological characteristics, newer umbrella or basket trials recruit patients that are stratified by actionable mutations, assigning them to a targeted treatment arm. This has been successful for several trials, such as the Lung-MAP and BATTLE trials for lung cancer. This new paradigm in genomics-based trial design is also influencing regulatory approvals. Larotrectinib, a tropomyosin kinase receptor inhibitor, was recently the first drug approved by FDA indicated for any cancer harboring a *NTRK* fusion rather than for a specific type of cancer.

Although the vast majority of clinical studies have focused on cancer, genomics is being applied to other diseases, such as identifying genetic predisposition to gestational diabetes or autism spectrum disorders. One study used NGS to profile mutations in one hundred families with 119 children suspected of harboring a monogenic neurodevelopmental disorder. By identifying mutations, genomics NGS altered the direction of clinical care or the underlying cause of disease in 49% of newly diagnosed families. Moreover, NGS at symptom onset rather than at the time of study would have led to a diagnosis six years earlier.

NGS is also being used in a personalized approach to pharmacogenomics, the study of inter-individual variation to drug response. Protein-coding SNPs to metabolizing enzymes can influence the rate of drug conversion in the body, which affects efficacy. Certain SNPs can also render patients susceptible to toxicity from specific drugs. Although there are common SNPs, NGS is capable of detecting all SNPs, including rare SNPs, which account for 20-40% of inter-individual variation. The Ubiquitous Pharmacogenomics (U-PGx) trial consortium is assessing the cost-benefit of NGS for pharmacogenetically guiding personalized treatment.

Epigenomics

Epigenetic changes are heritable modifications that do not alter the DNA sequence, such as DNA and histone methylation and miRNA post transcriptional regulation. The epigenome has a stake in many diseases, including cancer, Alzheimer's disease, obesity, diabetes and others. The FDA has cleared the Epi proColon test, an *in vitro* diagnostic test, that detects the methylation status of Septin 9 DNA, linked to colorectal cancer. However, the test is targeted to the methylation status of just one gene. Now, epigenomics is addressing genome-wide changes in DNA methylation state (methylome), for instance in DNA from gastric cancer patients.

Epigenetic modifications are reversible and can be influenced by the environment, *e.g.*, obesogenic diet, such as in obesity and Type 2 diabetes (T2D). Obesity and T2D leads to several comorbid conditions, such as cardiovascular disease, that increase mortality and lower quality of life. Unfortunately, obesity may be recalcitrant to weight-loss programs, such as bariatric surgery or high-intensity interval training, and may require multiple interventions. The NEWTON study was launched to classify obese patients by epigenetic status, which may help inform the best treatment course. Another study is testing whether exercise can alter the epigenome of obese or T2D individuals to reverse disease epigenetic phenotype. Similarly, the iReAct Study was recently launched to determine epigenetic changes upon exercise.

Transcriptomics

The clinical research field of transcriptomics has been dominated by cancer biomarker studies, such as for lung, breast, and colorectal cancer among others. However, transcriptomics is also frequently used in clinical research of other illnesses, such as cardiovascular disease and dementias. Transcriptomics analysis of breast tumors can be used to classify cancers, which has led to the development of a 50-gene panel used

in an FDA-cleared diagnostic test, the PAM50. The PAM50 characterizes breast tumors as Luminal A, Luminal B, HER2-enriched, or Basal-Like, which has important treatment implications. A patient's breast tumor type informs treatment regimen, for instance Luminal A and B tumors are subject to hormone adjuvant therapies, HER2-enriched tumors subject to anti-HER2 interventions, and Basal-Like, which are mostly frequently triple negative tumors that do not express receptors, to cytotoxic agents.

Proteomics and Metabolomics

These Omics technologies have generally not moved into the clinic yet, in part due to technological barriers. Genomics, epigenomics and transcriptomics rely on nucleic acid technologies, which are well-established and publicized. Proteomics and metabolomics rely on mass spectrometry (MS) techniques, which require specialized technical skills, expensive instrumentation and are subject to inter-lab variability due to variations in instrument choice or software used for data analysis.

Despite these difficulties, advances are being made. In clinical research, tumor proteomics can help diagnose patients and identify those that respond to treatment by EGFR inhibitors. The FDA has cleared MS platforms for identifying microorganisms in infectious diseases as part of clinical practice. The detected species are usually microbial proteins, *e.g.*, abundant ribosomes, and the specific pattern of detected peaks can be used to match up to a database of known microorganisms. The MS method is rapid, sensitive, and specific and has surpassed previous methods of microbial identification. Metabolomics is also being used in clinical research to identify biomarkers. For instance, in cancer metabolomics, lipidomics for early Alzheimer's disease or amyotrophic lateral sclerosis diagnosis.

Multi-Omics: The next frontier

Although each Omics technology can separately contribute significantly to clinical practice or a patient's individualized care, it is limited within a specific domain at the genetic, epigenetic, transcriptomic, *etc* level. To get a fuller picture, several Omics can be integrated into a multi-Omics landscape, which provides more information on the patient's molecular profile and can help meet several challenges. For instance, identifying Mendelian mutations from a genomic profile for recessive disorders is more challenging if the mutation is not archived in a database or the mutation occurs within a non-coding intron, which alters splicing and hence protein sequence. For such cases and other subtler mutations, studies have shown combining genomics with transcriptomics can improve the diagnosis of Mendelian monogenic diseases.

Another multi-Omics application is to reveal the genetic architecture of common diseases, such as diabetes and autism spectrum disorder, which arise from multiple mutations (polygenic) or whose causal etiology are not precisely known. Multi-Omics still faces obstacles before it can be translated to the clinical bedside, for example, deciding which is the optimal tissue for analysis, what identified targets are actionable *etc*. Once surmounted, however, multi-Omics holds great promise for clinical practice.