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Turning omics data into therapeutic insights

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Omics technologies have made it easier and cheaper to evaluate thousands of biological molecules at once. These advances have led to novel therapies approved for use in the clinic, elucidated the mechanisms behind disease-associated mutations, led to increased accuracy in disease subtyping and personalized medicine, and revealed novel uses and treatment regimes for existing drugs through drug repurposing and pharmacology studies. In this review, we summarize some of these milestones and discuss the potential of integrative analyses that combine multiple data types for further advances.

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Introduction

The "omics revolution" that has been sweeping biological research since the advent of genomic sequencing has generated an incredible amount of data, and given birth to technologies that make it ever easier and cheaper to measure biological molecules *en masse*. The task of translating those data into actionable therapeutic knowledge, however, remains an area of active research. We briefly review omics data and technologies, discuss the types of questions translational researchers might ask using omics datasets, and highlight important translational advances and accomplishments from the last few years (Figure 1).

The vast promise of omics technologies

"Omics" assays are those that attempt to interrogate an entire layer of molecular activity in a cell or sample. The omics revolution was set off by genomic arrays, which contained hundreds of probes for selected variants in predetermined regions of the genome. Now, omics technologies have expanded to include more unrestricted approaches, such as assays based on next-generation sequencing and mass spectrometry. There are customized assays for each layer of molecular activity, from genomes to metabolomes. A scientist can choose to measure genomics (e.g. whole genome or whole exome sequencing), transcriptomics (e.g. RNA-seq), epigenomics (e.g. bisulfide sequencing, ChIP-seq for histone modifications, ATAC-Seq for open chromatin), the three-dimensional arrangement of the genome (e.g. Hi-C or ChIA-PET), proteomics or phosphoproteomics, and metabolomics (most commonly by mass spectrometry). Each layer's assay comes with its own technical requirements and caveats, but each can give rich, detailed information about the choreography of molecules in a sample.

Increasingly, researchers are recognizing the value of skillful integration of multiple layers of omics data, termed multi-omic studies. Modeling and discovering the interplay between different omic layers can lead to important functional and clinical discoveries [1,2]. A recent example of multi-omic studies successfully leading to translational impact comes from the study of *IDH* mutations in cancer. A 2008 genomics study found common mutations in the *IDH1* gene in glioblastoma that were associated with increased survival [3], and subsequent studies found this mutation in other cancers as well [4]. However, it wasn't until combined genomic and epigenomic studies that the full implications of this mutation were discovered. The mutation in IDH1 and a similar mutation in the IDH2 gene produce altered forms of the encoded enzymes with a gain of function that leads to metabolic, epigenetic, and transcriptomic changes that block differentiation of cancerous cells [5•,6]. Last year, less than 10 years after the studies that identified the mutations, a drug that targets mutated IDH2 was approved for the treatment of acute myeloid leukemia [7,8], and new drugs targeting these enzymes are being developed for other indications.

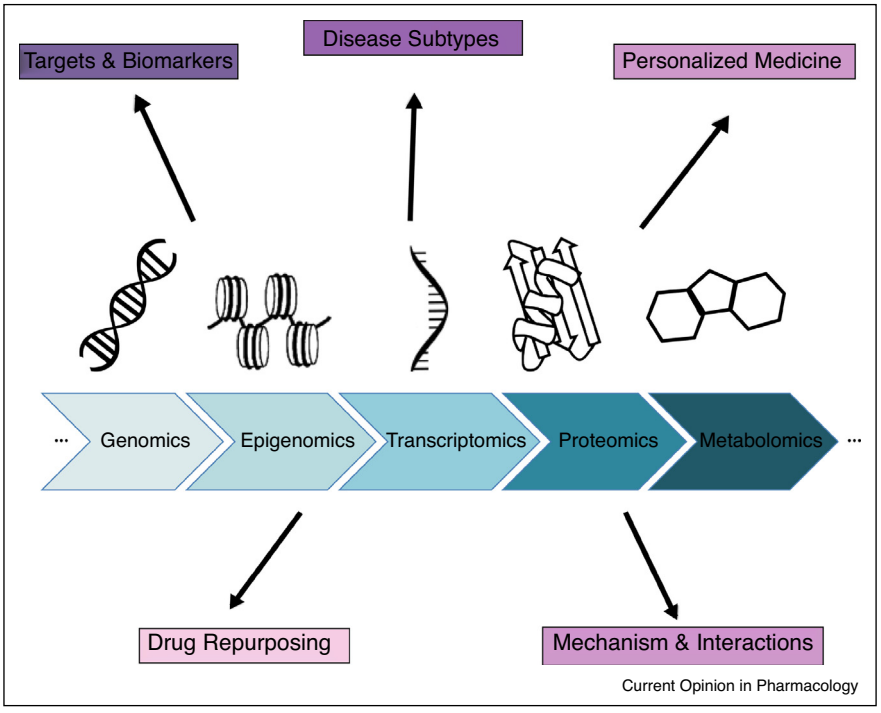
What types of clinical insights can omics data provide?

There are several distinct types of questions one could ask with omics data that would be useful for translational research. Here, we split them into five categories and give recent examples of each.

Disease-altered molecules, therapeutic targets, and biomarkers

A straightforward result of omics studies is a list of molecules that are altered in a disease, or correlated with disease severity. While omics approaches are sometimes derided as 'hypothesis free science,' in reality these lists

Figure 1



Omics data measure entire layers of molecular activity. A few of the technologies are shown in the center. Integrating and analyzing these data can serve several important purposes for translational research.

of molecules are the necessary step of observation from which hypotheses can be generated systematically. The lists of molecules point to pathways that could contain new therapeutic targets, biomarkers, or lead to functional insights into the disease.

Prioritizing these often very long lists of altered molecules is critical. It may seem natural to focus on molecules that are supported by interesting functions known in the literature. However, such an approach ends up reinforcing prior beliefs at the expense of novel discovery. Alternative approaches include focusing on the network or pathways that are enriched in the observed molecules [9].

Functional insights

Omics data can also help researchers come to a better understanding of the mechanism of disease. In the case of genome-wide association studies (GWAS), for example, mechanistic insights are often vital once genomic variants have been statistically associated with a disease. For example, GWAS have found strong association of mutations in the region of the gene *FTO* with obesity [10,11]. A recent study used further omics data to show that a causal variant in this region leads to derepression of important bioenergetic genes [12••]. This work represents an exciting move towards understanding the mechanism behind heritable obesity.

Most GWAS findings, however, tend to be common genomic variants with very small effects on the probability of disease. A recent model proposed by Boyle et. al. suggests that variants in almost any gene expressed in disease-relevant cells may contribute to disease, and that these small effects add up to account for most of the heritability of diseases [13]. This hypothesis, which they call the omnigenic model, could be true because of the highly interconnected nature of genes and other molecules in the cell; expression changes of nearly any set of genes can work through these interactions to affect important disease pathways. Their findings emphasize the need for detailed integrative models to uncover functional insights in cases where the mechanisms of disease-driving variants or pathways are not obvious.

Disease classification and prediction

Omics data can lead to further subdivision beyond a binary classification of healthy vs. diseased that can prove to be hugely beneficial in the clinic. Such approaches can lead to better treatment for patients based on the actual biology of their specific disease, by placing patients within subtypes or along a spectrum of their disease. Pirhaji *et al.* recently showed that even relatively crude ordinal classification of disease severity can be used effectively to find disease-related pathways [14•]. Finding the best methods for subtyping [15] and for improving