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SAPIENT

Going Beyond the Genome in Rare Disease: The Value of a Multi-Omics Approach

Introduction

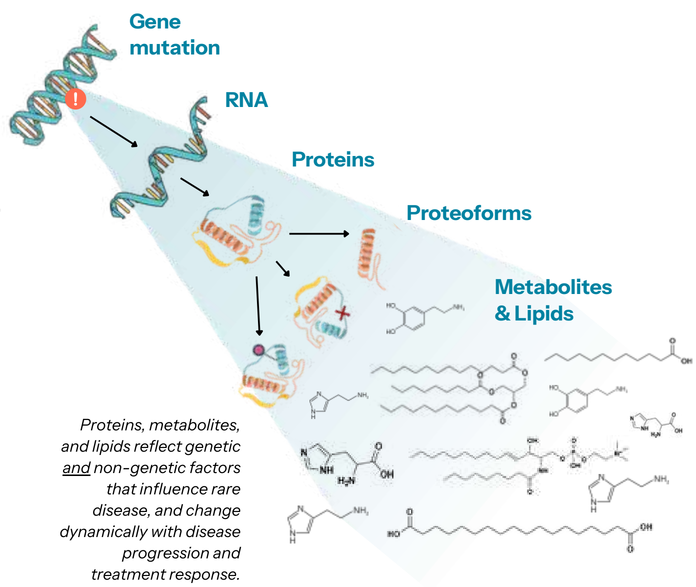
Approximately 80% of all rare diseases are genetic in origin and are often Mendelian in nature, resulting from a single gene alteration involving its loss of function, gain of function, or dysregulated expression. Monogenic diseases may appear deceptively straightforward to diagnose and study with genomic approaches, but **to fully understand systemic pathology requires researchers to look beyond genetic sequence alone.**

Genetic perturbations can have ripple effects across multiple biological pathways, ultimately manifesting as metabolic disruptions, altered protein expression, or compensatory lipid signaling cascades. In this context, **multi-omics approaches – including proteomics, metabolomics, and lipidomics – are proving essential to layer onto genomic data** to fully characterize underlying rare disease biology, develop non-invasive diagnostics, and guide optimal therapeutic intervention.

Assessing Rare Disease Biology through a Multi-Omics Lens

Genomics can identify primary disease-causing DNA variants, but phenotypes can vary in patients with the same causal gene mutation – even among those who are closely related (such as twins or siblings). This variability suggests that **genotype alone may not fully explain rare disease manifestation or progression.** Genetic modifiers, environmental exposures, and downstream molecular effects on proteins and metabolic processes can all influence disease severity and therapeutic response.

By taking a multi-omics approach that integrates protein, metabolite, and lipid profiling data with genetic readouts, we can **elucidate the varied cascading effects that a single gene alteration can have across metabolic and signaling networks,** and uncover critical insights into disrupted pathways and disease mechanisms that can be targeted to correct the pathological state.



Proteins, metabolites, and lipids reflect genetic and non-genetic factors that influence rare disease, and change dynamically with disease progression and treatment response.

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Developing Non-Invasive Diagnostics for Rare Diseases

Trial recruitment can be particularly challenging for rare disease studies as they typically have small, geographically dispersed populations that often include fragile or pediatric patients. Non-invasive diagnostics are therefore critical to minimize patient burden and support decentralized clinical trial approaches. This is where metabolite and protein biomarkers prove particularly valuable, as they not only **provide functional readouts of disease biology influenced by a specific genetic mutation – they can also be readily captured in blood.**

In cases of enzymatic loss-of-function, metabolomics can be used to detect the accumulation or absence of enzymatic products in plasma, providing a **direct and minimally invasive diagnostic readout.** Similarly, proteomics allows for direct, quantitative measure of proteins and their isoforms that are lost or overexpressed as a result of a gene mutation, and can serve as **disease biomarkers or drug targets.**

Guiding Therapeutic Intervention & Monitoring Response

Many new therapies for rare diseases, from gene editing to RNA-based modalities, aim to restore or compensate for a missing or dysfunctional protein. Traditionally RNA sequencing has been used to infer protein expression levels, but studies have shown that **mRNA levels are actually often poorly correlated with protein levels,** particularly in diseased or treated states. This discordance arises from post-transcriptional regulation, differential translation efficiency, and protein degradation dynamics.

Proteomics methods enable the direct quantification of proteins, providing a more accurate readout of biological activity and therapeutic effect. By directly profiling proteins rather than relying on indirect surrogate DNA or RNA measures, we can **better assess target engagement, pharmacokinetics/pharmacodynamics (PK/PD), and potential off-target effects –** helping to inform patient stratification, dosing strategies, and safety profiling.

Sapient's Multi-Omics Platform:
Delivering Deeper Insight into Rare Disease to Enable Better Outcomes

Sapient's multi-omics approaches leverage next-generation mass spectrometry to provide some of the most comprehensive views into human biology, **capturing more than 15,000 metabolite and lipid biomarkers and over 5,400 proteins and their isoforms in a single plasma sample.** This depth and breadth of coverage is especially valuable in rare disease programs, where cohort sizes are small and every sample must yield maximal biological insight.

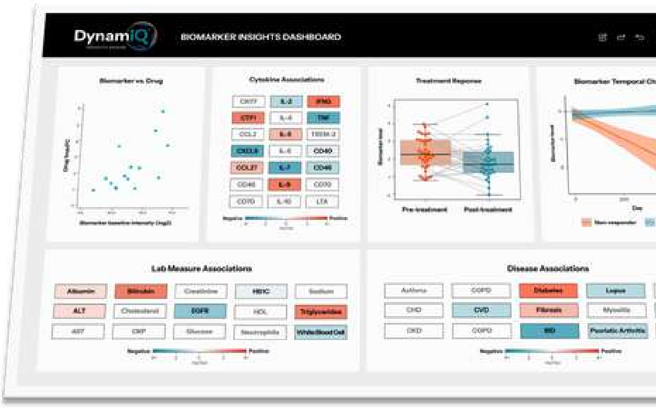
Discovery Proteomics	Metabolomics & Lipidomics	Cytokines & Chemokines	Genomic Measures	Quantitative Protein Assays
5,400+ protein groups	**15,000+** metabolites & lipids	**350+** cytokines & chemokines	**Single-Cell** and bulk RNAseq	**Bespoke** single assays & panels

This level of molecular resolution **builds upon critical RNA sequencing insights and allows for better understanding of how an individual's genotype associates with their disease phenotype.** Using our mass spectrometry systems in a nontargeted, discovery workflow, we can uncover dynamic protein, metabolite, and lipid perturbations across key signaling pathways and biological processes that represent important biomarkers of rare disease pathobiology and drug response. We can also employ targeted workflows to robustly measure and follow specific metabolites and proteins of interest in later phase clinical settings.

For instance, in Duchenne Muscular Dystrophy (DMD) – a monogenic disorder in which dystrophin proteins are either absent or severely reduced due to mutations in the dystrophin gene – Sapient has **developed a targeted plasma assay for dystrophin that enables quantification of this critical muscle protein *and* its isoforms in circulation.** This facilitates both disease diagnosis and monitoring of gene and exon-skipping therapies aimed at restoring dystrophin expression.

Validating Rare Disease Discoveries with DynamiQ™

Sapient's DynamiQ™ Insights Engine adds another powerful layer of value to rare disease research by **enabling rapid contextualization of biological findings from even the smallest cohorts.** The DynamiQ database integrates multi-omics and real-world data (RWD) from tens of thousands of deeply phenotyped biosamples across diverse populations, ages, and disease states – including a number of rare diseases.



Through guided analyses that reference this data, we can help **validate novel biomarker discoveries, prioritize targets with therapeutic relevance, and assess the specificity, prevalence, and clinical significance** of molecular changes seen in rare disease states.

Conclusion

Though most rare diseases are genetic in origin, their phenotypic manifestations – the symptoms, severity, and progression observed in each patient – are largely read out by the proteome and metabolome. **Proteins and metabolites are the functional outputs of genes and the key drivers of biological activity,** making them essential to understanding how a genetic mutation translates into disease.

Sapient **enables multi-omics beyond the genome, adding new layers of insight to enhance and expand upon our understanding of rare diseases,** driving earlier diagnosis, improved patient stratification, and faster therapeutic development.