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WHITE PAPER

The proteomics revolution - Using proteomics to personalize medicine across the continuum of care

For many years we've been told that a wave of precision and personalized medicines based on the intricate, molecular details of patient biology is just over the horizon. Unfortunately, except for niche cases like drugs targeting specific mutations in cancer (Morash et al 2018) or genome editing for rare diseases, this wave has not come.

Biologists have long sought technologies that will make personalized medicine possible and many hoped that advances in genetics and genomics were the key to unlocking this new era. Indeed, new DNA sequencing technologies have revealed genes associated with disease, and full genome sequencing can tell individuals about their potential susceptibility to certain ailments. Yet, genomes do little to inform people about their current health or if their lifestyle choices have increased or decreased their disease risk.

To truly achieve personalized medicine, we need to look beyond DNA and instead focus on the molecular machines that scientists have long recognized as fundamental units of biological activity. We need to look to proteins.

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Introduction

Proteins carry out the vast majority of cellular processes and a cell's "proteome," the dynamic composition of its full set of proteins and their associated distribution throughout the cell, determines cellular identity, form, and function. "Proteomics" technologies aim to reveal the abundances and locations of all proteins in cell samples right now. The dynamic patterns of these ever-changing proteomes comprise thousands to millions of fluctuations in protein levels and distribution, and can reveal whether we are healthy, sick, or have enhanced potential to become sick.

Below we cover how caregivers can apply proteomics technologies across the continuum of care. We dive into the ways physicians can use proteomics to better serve patients when they are sick, when they are healthy, and everywhere in between.

Personalized measures of baseline health

Physicians often use average health metrics to determine if a patient is sick, but this is problematic because even basic metrics like body temperature can vary significantly from person to person (Obermeyer et al 2017). Every biologist knows that no two cells or organisms behave in exactly the same way. Even a single cell will behave differently in different environments. No matter how hard we try to make measurements in controlled settings, biology is complicated and differences will manifest. To provide patients with more meaningful measures of their health, we need to embrace biology's complexity and move beyond average population metrics to personalized, time-dependent measures. Proteomics enables us to do so.

By regularly assessing how an individual's protein levels and cellular distribution change from day-to-day, minute-to-minute and comparing these changes with other measures of health, we can associate particular patterns of protein production with individual patient wellness. Rather than look at crude population measures, physicians can then assess whether a patient's proteome deviates from a personalized "normal." In doing so, they can prevent unnecessary worry when other metrics are out of step with population averages but normal for the individual.

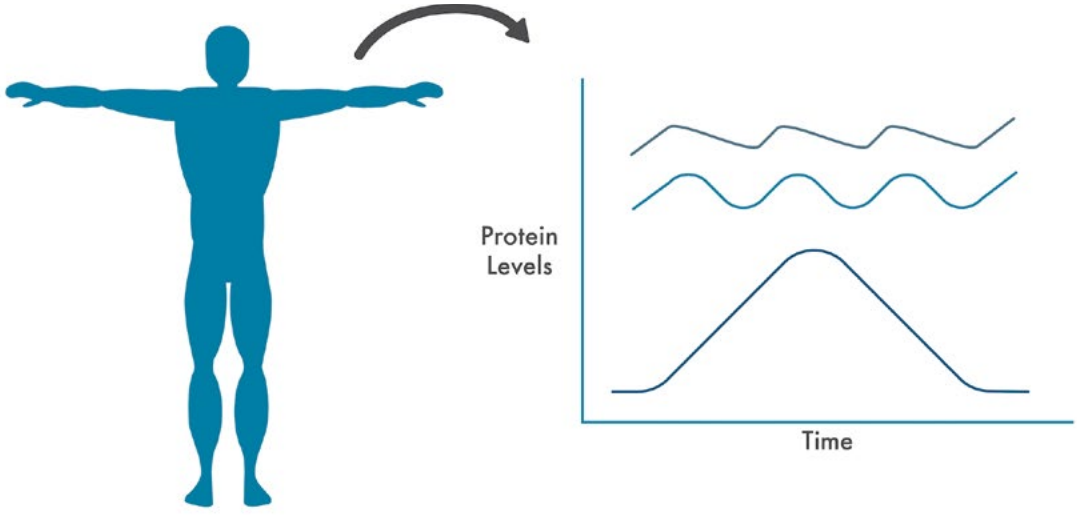

Figure 1. Using proteomics to get a baseline measure of good health

Capturing protein fluctuations when a patient is well provides caregivers with a dynamic baseline indicative of good health.

Screening for potential problems and pinpointing their causes with diagnostics

With a proteomic baseline in place for an individual patient, a physician has a holistic way of screening that patient for many ailments at once. Under the current status quo, many men and women regularly undergo specialized screens for common diseases. We have mammograms for breast cancer, colonoscopies for colon cancer, glucose tests for diabetes, and much more. These screens are useful because they help physicians detect diseases early - when they can be most effective. However, screens can be expensive, anxiety inducing, and even physically harmful.

With proteomics, on the other hand, physicians have the potential to screen for protein changes associated with many different diseases at once. If a physician noticed that a patient began to deviate from their normal proteomes, they could dig into the data to determine which specific proteins were altered from the baseline. There may be known associations between these altered proteins and a particular disease or, if enough patients regularly measure their proteomes, researchers could begin linking additional changes with specific diseases. In this way, proteomic measurements taken at a standard visit to the clinic could automatically act as screens for a wide variety of diseases. This would get patients the treatments they need quickly and improve therapeutic effectiveness.

This type of proteomic screening could also complement other diagnostics measurements. For example, caregivers might see that proteins involved in responding to viral infections are surging. To pinpoint the precise problem, they could order further diagnostic tests that look for viral proteins indicative of specific viruses. Rather than prescribing a treatment based on symptoms alone, proteomics can guide physicians to the most useful diagnostic tests, avoid wasting time, and give them the confidence to prescribe therapeutics that precisely target a patient's illness.

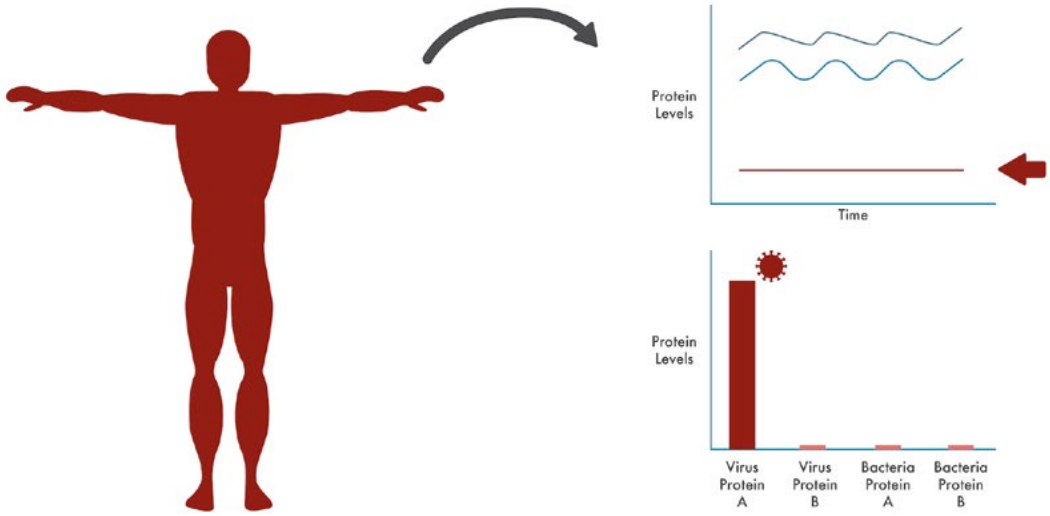

Figure 2. Screening for potential problems and pinpointing their causes with diagnostics

Changes from baseline protein fluctuations can provide caregivers clues as to the cause of a disease. Refined measurements of additional proteins (like viral and bacterial proteins) can diagnose the cause of the disease.

Developing and using effective treatments

Clinical researchers spend much of their time establishing objective measures of effective treatments. From experiments in cells growing in petri dishes, to experiments in animals, to clinical trials, they need means of measuring whether experimental drugs actually (and preferably specifically) treat or cure their target diseases.

Given the differences between cells, animal models, and humans in the real world, it can be very difficult to choose metrics that confidently predict success across all levels of drug development. This is part of the reason why only ~13% of drugs make it through clinical trials (Wong et al 2019).

To solve this problem, many researchers are developing experimental systems that better mimic human biology (Walsh et al 2017), but proteomics offers a complementary solution. Rather than look at potentially superficial phenotypes associated with disease, researchers can use proteomes as objective biological measures of disease, as "biomarkers."

For example, if a particular change in the proteome is known to be associated with heart disease, researchers could look to see if this change is copied across their various experimental systems. Given the intricate, molecular association between the change in the proteome and the disease, it's likely that at least some of the proteins involved would have something to do with the mechanism of the disease. If a treatment returned the proteome to normal across experimental models, researchers could have more confidence that it would do so in patients.

After approval, physicians could use proteomics to continue to monitor treatment efficacy. If physicians failed to see a patient's proteome begin to return to normal, they could take action and alter the treatment quickly.

For example, if a patient gets a bacterial infection, they may be prescribed an antibiotic. Unfortunately, this selects for the growth of other bacteria that are resistant to the antibiotic and is a particular issue with people who suffer from chronic infections such as those with cystic fibrosis (Hahn et al 2018, Scialo et al 2021). Proteomics could give physicians a leg-up on the bacteria by enabling them to monitor patient samples for the presence of proteins indicative of antibiotic resistance. Before these bacteria accumulate in the patient, physicians could prescribe new antibiotics and stop the resistant bacteria in their tracks.

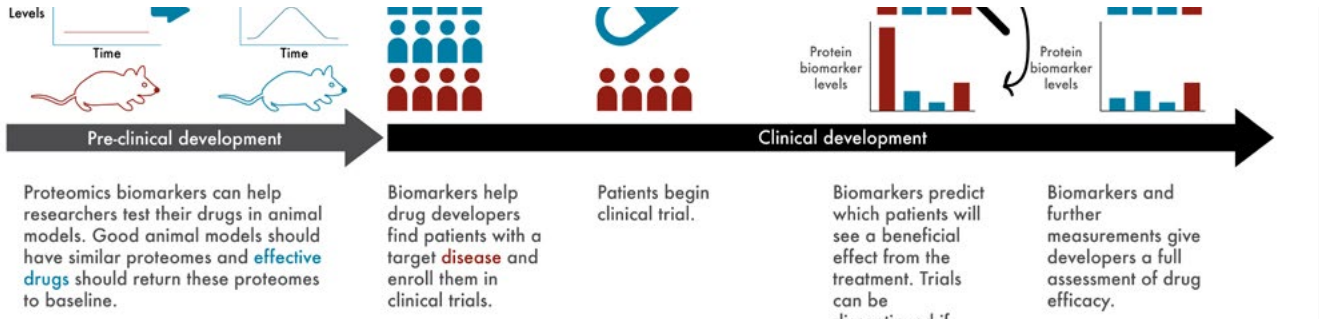

Figure 3. Using biomarkers for drug development

Using proteomics to forecast changes in patient health

Even if a patient doesn't feel sick yet, changes in their baseline proteome could alert physicians to future problems. This would help physicians prevent the development of a serious illness.

For example, if a patient has a family history of heart disease, physicians could pay special attention to protein changes associated with their heart health. Physicians might begin to see changes in these proteins before something catastrophic like a heart attack occurred and could act on these early warning signs. Given that over 650,000 people die of heart disease annually in the US alone, physicians could potentially save hundreds of thousands of lives by pre-emptively putting at-risk patients on preventive heart medications in this way.

Similarly, proteomics measurements can complement the disease susceptibility information provided by genomics. Genetic information may altert a physician to a patient's pre-disposition for heart disease. This physician could then pay more attention to changes in the patients' proteome associated with heart health and prescribe preventative measures as soon as they see things begin to deviate from normal.

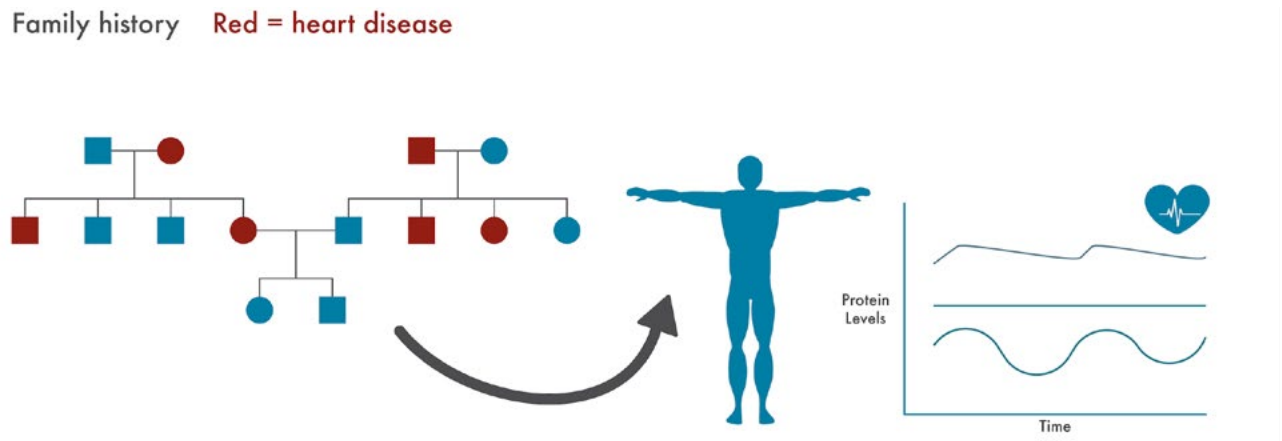

Figure 4. Using proteomics to forecast changes in patient health

If a patient has a family history of a disease with a genetic component (heart disease here), caregivers can specifically monitor changes to the proteome associated with that disease. Doing so, they may identify issues and prescribe preventative treatments before serious health issues arise.

The proteomic gold standard in precision medicine

Proteomics will soon become the gold standard for technologies that make personalized medicine possible for all. Through proteomics, we can establish critical, personalized baseline measures of patient health and associate changes from this baseline with the molecular causes of sickness. This will make it much easier to diagnose ailments, prescribe appropriate treatments, and develop new therapeutics. Advances in proteomics will finally give biologists and physicians the tools they need to probe the depths of protein biology in near real time and make the long-hoped-for era of personalized medicine a reality.

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