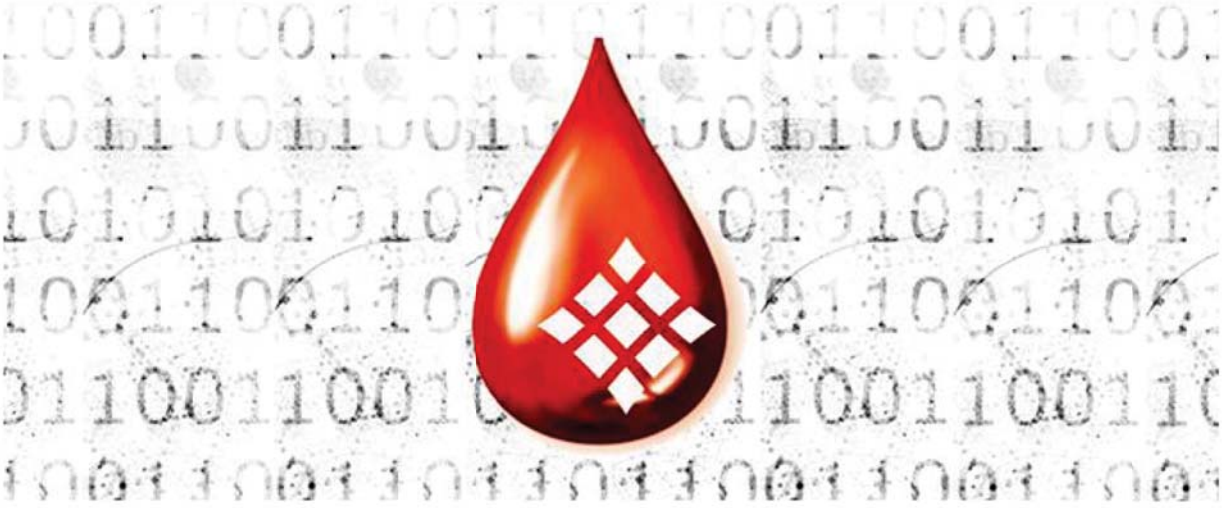
Swiss Re
Centre for Global Dialogue



Biognosys: The future of blood-based diagnostics

Dr. Matthias Inauen, Dr. Yulia Butscheid, 12 Sep 12

The prospect of a full proteome analysis – scanning all bodily proteins for any potential disease - is fast becoming a reality. The implications for diagnostics and subsequent therapies are considerable.

From genetic predisposition to personal health status

The desire to understand the underlying mechanisms of pathologies has always been the driving force behind advances in diagnostics and treatment. In 2003, after more than a decade of research, the Human Genome Project sequenced the human genome for the first time at a cost of approximately USD 4 billion. As the result of technological advancements, the sequencing of an individual human genome for less than USD 1000 is within reach today.

Genomics has established itself over recent years in applications that range from basic research to end-user genetic testing. However, the promised benefits for diagnostics and more individualised healthcare have thus far largely failed to materialise[1]. Genes, encoded by DNA, are the blueprints for the proteins that make up the body and execute all cellular functions. Whereas an individual's genomic information is *static*, the proteome (the entirety of all proteins) reflects the current state of the body. Genetic risk is, in the majority of cases, nota diagnosis of a disease and only provides information as to what *may* occur; proteins, however, reflect what *is currently happening* in the body at a given moment. Therefore, information about individual proteins and potentially the full proteome is the key to comprehensive health assessment and relevant medical intervention. A representative subset of proteins that reflect the body's current state is easily accessible through a simple blood sample.

The monitoring of all proteins – the proteome – is a logical extension of long-established diagnostic approaches. Whereas current methods measure single, isolated parameters, novel technologies provide insight into the patient's condition at unprecedented resolution and thus provide physicians with the whole picture of the processes occurring in the patient's body. On the level of individual humans, this high level of resolution enables an entirely new level of quality in health monitoring and diagnostics: proteomic data for individuals can be collected over time, and a personal baseline for any protein can be established. Currently, diagnostic protein levels are

measured against the normal range for the population and individual fluctuations are not taken into account. The comparison of a patient's protein levels with his or her individual baseline is the basis of personalised medicine.

The emergence of targeted proteomics

Historically, the field of proteomics has developed more slowly than the field of genomics, primarily because proteins are more complex biological molecules than DNA. Proteins consist of up to 22 different amino acids, compared with only 4 building blocks (nucleic acids) for DNA. Moreover, proteins can undergo various modifications and can be present in different confirmations, which makes measurements of the concentrations of these biomolecules challenging.

Proteomics relies on the analytical method of mass spectrometry. In this method, biomolecules are accelerated by strong magnets and the time required to reach the detector varies characteristically for individual molecules based on their electrical charge and weight. This technique thereby allows the identity and quantity of a molecule to be determined. The principle of mass spectrometry itself is well established and can be traced back to the 1960s, when it was used for the first time to detect amino acids and peptides (fragments of proteins). The crucial steps necessary to bring proteomics to the clinic required another fifty years to complete. Instrumental in the development of proteomics was the recently developed technique known as *targeted proteomics*. In contrast to classical approaches, which are commonly referred to as *shotgun proteomics*, targeted proteomics allows the detection of proteins with high sensitivity, quantitative accuracy and, most importantly, in a reproducible way. Advances in genomics have enabled predictions and computations of unique specific patterns (protein assays) for each of the more than 20,000 human proteins, thereby providing the basis for the targeted detection and quantification of any conceivable protein.

In contrast to established methods like ELISA (enzyme-linked immunosorbent assays), targeted proteomics does not rely on the development of specific reagents, such as antibodies. This universal applicability of targeted proteomics offers a significant competitive advantage.

The new area of digital biobanks

The ETH Zurich-based Institute of Molecular Systems Biology, led by Professor Ruedi Aebersold, one of the founding fathers of modern proteomics, is the epicentre of novel proteomic approaches. The institute's spin-off company, Biognosys, has revolutionised targeted proteomics. Biognosys' high-throughput technology allows the analysis of thousands of proteins in a single run, which means that this technology enables the use of *one test for all diseases*. This patented technology has been used to create a so-called protein map that digitally captures the quantities of individual proteins in the sample and potentially represents the entire proteome. The protein map contains information about all proteins that are detected in the sample at the point in time when the sample was taken. This map can be analysed at any time with the help of Biognosys' unique protein coordinates (fingerprints orassays) and the company's sophisticated software tools. The data contained in these digital protein maps make the conservation of blood for protein analysis redundant because all information can be stored digitally on a server. Such digital biobanks also enable retrospective analyses of biomarkers whose significance is not yet known.

The benefit for the patient

The need for high-throughput protein identification and quantification is already clear in cancer proteomics. The aim is to identify novel drug targets, discover biomarkers that indicate early-stage cancer, predict therapeutic efficacy and the severity of side effects. In collaboration with the research group of Professor Aebersold, Biognosys has recently released a milestone paper on high-throughput biomarker validation in the prestigious journal *Science Translational Medicine*. In this study, assays for more than 1000 cancer-associated proteins were developed and validated. These assays enable the reproducible detection of target proteins in plasma and urine from cancer patients and healthy controls. The highly accurate and sensitive quantification of 34 biomarker candidates that allow the diagnosis and differentiation of cancer across 84 patient

plasma samples was demonstrated[2].

In current medical practice, diagnostics is primarily used to confirm the suspicion of an underlying pathology. Future diagnostics will allow the detection of abnormalities before visible symptoms occur. The benefit for patients is already clear today; an ovarian tumor, for example, can be detected while still small and potentially curable. In an ongoing internal study performed by Biognosys, plasma biomarkers for the sensitive and specific differentiation of benign and malignant ovarian tumors were discovered. A unique 5-protein biomarker signature was identified and validated not only in the mouse model but also in patient samples. The panel provides higher sensitivity and significantly outperforms existing tumor markers. In a similar study, the company identified plasma biomarkers that allow the sensitive and specific differentiation of high- and low-risk breast cancer patients.

Economic aspects of diagnostics

Healthcare costs have exploded over the last several decades. In the US, the fraction of GDP spent increased from 5% in 1965 to 17.9% in 2010[3]. Novel diagnostic approaches can help ease the economic burden of healthcare by ensuring that treatment is provided early and selectively to patients who will respond to novel costly drugs.

From an economic perspective, two primary factors determine a diagnostic test's cost effectiveness: (1) the per patient savings, which is the difference between the cost of treating a disease and the cost of the intervention indicated by the test; and (2) the likelihood that a test suggests an intervention for any particular patient[4]. Tests that help avoid the use of expensive therapies or minimize costly adverse events can be enormously cost effective. These tests, called companion diagnostics, increase the probability that a new drug will be approved by regulatory authorities because these tests help to stratify patients during the clinical trial phase, thus improving the trials' outcomes and ensuring that, later on in clinical practice, the sub-population of patients who will respond to the drug can be identified.

However, today's procedure-based reimbursement system for diagnostic tests presents the biggest challenge for companies bringing companion diagnostic tests to the market. On the one hand, the development and regulatory approval of companion diagnostics requires a substantial financial investment. On the other hand, neither payers nor pharmaceutical companies, whose drug can be prescribed only if such a test is performed and is positive, are incentivised to support value-based pricing for companion diagnostics. In addition, how the potential value should be shared among several companion diagnostics tests that are required as part of therapy selection is unclear if more than two options exist.

Targeted proteomics, however, can solve the reimbursement challenge because it provides *one test for all diseases* and simultaneously quantifies all detectable proteins in a sample. The performance of an additional diagnostic test will not require another physical measurement of a sample but only an additional computational analysis. This fact pushes the marginal cost for another test to almost zero because the captured digital protein map already covers information on all possible markers. For health insurance companies, this lower marginal cost will allow better control of the costs associated with blood-based diagnostics. Pharmaceutical companies will benefit by being able to avoid the pricing trade-off for the drug-test bundle. The relevance of the information extracted from this *all-in-one test* will constantly grow with new discoveries and trials that contribute to the interpretation of protein levels for the purpose of health monitoring, the detection of disease onset and treatment selection.

Furthermore, the systematic collection of data on individual protein levels provides an entirely new level of quality for health monitoring and diagnostics: proteomic data for individuals can be followed over time, and a patient's personal baseline for any protein can be established, thereby enabling truly personalised diagnostics and treatment.

Future outlook

According to PricewaterhouseCoopers' estimates, the total US market for personalised medicine

is currently USD 232 billion and is projected to grow 11% annually, nearly doubling in size by 2015, to a total of USD 452 billion[5]. The key to successfully bringing personalised healthcare into mainstream medicine depends on whether the scientific discoveries in genomics and proteomics can be translated into customised tests and treatments whose costs can be borne by society.

A paradigm shift in medical practice is on its way. The growing amount of data arising from both genomics and proteomics sheds light onto the molecular mechanisms of disease. Today, targeted proteomics is transitioning from a basic-research tool toward a routine clinical technique, bridging the gap between genomic pre-disposition and actionable information. This shift toward personalised medicine is already leaving its footprints among the pharmaceutical industry and regulatory authorities. Currently, more than 70 prominent examples of personalised drugs, treatments and diagnostics products are available, and the numbers are increasing rapidly[6]. Soon, the sampling of every patient's protein map may become an integral part of routine examinations.

Despite rapid developments in recent years, personalized proteomics is still in its infancy. Today, techniques are readily available for basic and pharmaceutical research; however, crucial steps still have to be taken before patients can fully benefit from these techniques. After clinical development, protein maps will have to be introduced to routine clinical use, and a transition period will be needed to establish the concept that a single assay can potentially replace the majority of common blood marker tests. Finally, healthcare providers will have to ensure that novel techniques are available for all patients.

In this regard, Biognosys provides unique and best-in-class technology for the monitoring of personal protein profiles from a single drop of blood and the preservation of information for future advances in diagnostics and treatment. Although targeted proteomics can revolutionise healthcare by eliminating tensions in the pharma–diagnostics–payers triangle, the maximum added value for personalised medicine will emerge only through an open innovation relationship with other key players, such as regulators and clinicians. By emphasising the transferability of its methods to other labs, Biognosys ensures broad accessibility and acceptance of its techniques.

---

[1] The Economist (2009), Getting personal – the promise of cheap genome sequencing, Apr 16th 2009, available at http://www.economist.com/node/13437974.

[2] Hüttenhain, R. et al. (2012), Reproducible quantification of cancer-associated proteins in body fluids using targeted proteomics, Science Translational Medicine 4 (142), 142ra94.

[3] Congressional Budget Office and Henry J. Kaiser Family Foundation.

[4] Davis, J. et al. (2010), The microeconomics of personalized medicine, McKinsey Quarterly, February 2010.

[5] PWC PricewaterhouseCoopers (2012), Personalized medicine, available at http://www.pwc.com/us/en/alumni/keyword/vol4/personalized-medicine-pg2.jhtml.

[6] Personalized Medicine Coalition (2012), Personalized medicine by the numbers, available at www.personalizedmedicinecoalition.org/sites/default/files/files/PM_by_the_Numbers.pdf.