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Personalized medicine beyond genomics: alternative futures in big data—proteomics, environtome and the social proteome

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Abstract No field in science and medicine today remains untouched by Big Data, and psychiatry is no exception. Proteomics is a Big Data technology and a next generation biomarker, supporting novel system diagnostics and therapeutics in psychiatry. Proteomics technology is, in fact, much older than genomics and dates to the 1970s, well before the launch of the international Human Genome Project. While the genome has long been framed as the master or "elite" executive molecule in cell biology, the proteome by contrast is humble. Yet the proteome is critical for life—it ensures the daily *functioning* of cells and whole organisms. In short, proteins are the blue-collar workers of biology, the down-to-earth molecules that we cannot live without. Since 2010, proteomics has found renewed meaning and international attention with the launch of the Human Proteome Project and the growing interest in Big Data technologies such as proteomics. This article presents an interdisciplinary technology foresight analysis and conceptualizes the terms "environtome" and "social proteome". We define "environtome" as the entire complement of elements external to the human host, from microbiome, ambient temperature and weather conditions to government innovation policies, stock market dynamics, human values, political power and social norms that collectively shape the human host spatially and temporally. The "social proteome" is the subset of the environtome that influences the transition of proteomics technology to innovative applications in society. The social proteome encompasses, for example, new reimbursement schemes and business innovation models for proteomics diagnostics that depart from the "once-a-life-time" genotypic tests and the anticipated hype attendant to context and time sensitive proteomics tests. Building on the "nesting principle" for governance of complex systems as discussed by Elinor Ostrom, we propose here a 3-tiered organizational architecture for Big Data science such as proteomics. The proposed nested governance structure is comprised of (a) scientists, (b) ethicists, and (c) scholars in the nascent field of "ethics-of-ethics", and aims to cultivate a robust social proteome for personalized medicine. Ostrom often

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noted that such nested governance designs offer assurance that political power embedded in innovation processes is distributed evenly and is not concentrated disproportionately in a single overbearing stakeholder or person. We agree with this assessment and conclude by underscoring the synergistic value of social and biological proteomes to realize the full potentials of proteomics science for personalized medicine in psychiatry in the present era of Big Data.

Keywords Precision medicine · Big data · Proteomics · Technology foresight · Futures studies · Innovation management systems

> "Watch out for the fellow who talks about putting things in order! Putting things in order always means getting other people under your control."
>
> Denis Diderot (1988)

Next generation biomarkers for psychiatry

Big Data and the biological proteome

Big Data is an emerging phenomenon that is a consequence of the discrepancy between the *exponential* increase in our ability to generate data and the *linear* increase in our capacity to store and analyze data in the new century (Dove and Özdemir 2015). Big Data has multiple meanings; it refers not only to the enormous size of contemporary datasets, but also to the rapid rate by which data are able to move around different locations, time zones and application contexts worldwide. Big Data include a diverse array of unprecedentedly large datasets created by omics biotechnologies (genomics, proteomics, metabolomics, metagenomics), biosensors, electronic health records, simulation experiments, social media, crowdfunding platforms and the Internet, to mention but a few (Dimitrakopoulou et al. 2014; Jain et al. 2015; Higdon et al. 2015; Özdemir et al. 2015a; Calimlioglu et al. 2015).

Science, technology and innovation policy is rapidly changing in the era of Big Data. There is no scientific or medical field untouched by Big Data and psychiatry is no exception. What do futures hold for personalized medicine biotechnologies (Pavlidis et al. 2015)? The answers rest, in part, in the long social history of cell biology and omics biotechnologies (e.g., genomics, proteomics) (Thoreau and Delvenne 2012; Ozdemir et al. 2014).

Proteomics is a Big Data science and a next generation biomarker platform supporting novel system diagnostics and therapeutics in psychiatry. Proteomics offers new hope for psychiatry and postgenomics medicine by providing a functional read on biological complexity underlying common complex mental health diseases and variable drug responses (Sokolowska et al. 2015; Ma et al. 2014; Özdemir 2014). Biological dogma is a key concept taught to all life sciences and neuroscience students interested in protein research. It describes the *unidirectional* flow of biological information from the genetic code in DNA to the messenger RNA to proteins. Seen through the lens of biological dogma, the genome is the master or "elite" executive molecule of biology. By contrast, the proteome is humble; it is essential for life as it ensures the daily *functioning* of cells and whole organisms. Proteins are, in other words, the blue-collar workers of biology, the down-to-earth molecules that we cannot live without.

Perhaps it is partly the influence of this entrenched subconscious ethos and collective psychology associated with the teachings of biological dogma that explains why genomics technology, and the Human Genome Project in particular, have received greater international publicity than other omics disciplines over the past two decades. Additionally, it may explain why large capital investments were made to the then-nascent field of bioethics and the Ethical-Legal-Social-Issues (ELSI) project starting in the early 1990s with the express aim to understand the ethical, legal and societal impacts of the Human Genome Project and genomics technologies (López and Lunau 2012; Özdemir et al. 2015b).

Big Data-driven fields such as proteomics bring about vast uncertainties about their societal trajectory and how social systems might in turn influence the development of proteomics science. Taking the insight offered by the philosopher Denis Diderot in this article's epigraph, we need new governance mechanisms, however, so as not to fall into the trap of "solving" societal complexities of proteomics innovations in psychiatry by simply "contracting out" or delegating them to the ELSI researchers as was done in the case of genomics biomarkers (López and Lunau 2012; Petersen 2013; Dove and Özdemir 2014; Özdemir et al. 2015b). For a variety of reasons discussed in the sections below, proteomics science presents a wider range of societal dilemmas and opportunities that demand innovation not only in new technology governance, but also in research over the socio-ethical dilemmas attendant to proteomics diagnostics in psychiatry.

The social proteome

The allure of the biological dogma persists. Consider that even though the Human Proteome Project was launched relatively recently in 2010 under the leadership of the Human Proteome Organization, in fact proteomics technology is much older than genomics and dates back to 1970s, long before the launch of the Human Genome

Project. Indeed, Norman G. Anderson and N. Leigh Anderson, a father and son team, proposed to develop an index of all human proteins (the Human Protein Index) in 1970s, a visionary initiative akin to the modern day omics scale systems science. Unfortunately, the idea was ahead of its time as they failed to receive funding at that time in history (Anderson et al. 2001). Reflecting on their early experiences in the field of protein science, the Andersons offered the following insights:

> Because DNA sequencing technology is inherently simpler and more scalable than protein analytical technology, and because the finiteness of genomes invited a spirit of rapid conquest, the notion of genome sequencing has displaced that of protein databases in the minds of most molecular biologists (Anderson et al. 2001).

That these scientists suggest how a *perceived finiteness* of the genomes and the *metaphor* of "rapid conquest" played a role for the more meteoric rise of genomics than proteomics suggests that new technologies do not come to being in a vacuum; rather, they are tightly embedded in, and socially constructed by social and political power-laden systems that co-produce (or hinder) their emergence.

Yet, the study of the societal aspects of proteomics, i.e., the efforts to map the *social proteome*, has worrisomely lagged behind. Proteomics innovation trajectory is co-produced by both technical and socio-political systems; the latter dimension and its influence on translational neuroscience are often underappreciated. We define the social proteome as shown in Box 1.

BOX 1: The missing concept and examples of the "social proteome" to enable the next generation personalized medicine in psychiatry

The *social proteome* refers to the societal aspects of proteomics science and technology, including the presence of a highly porous boundary between proteomics technology and society, and the two-way exchange and interaction between proteomics science and social systems.

The social proteome, encompasses, for example, new reimbursement schemes and business innovation models to govern the emerging proteomics diagnostics that depart from the "once-a-life-time" genotypic tests, the biotech industry that may have an enthusiastic uptake for dynamic ongoing proteomics testing instead of the single measure genotype based diagnostics, and the anticipated hype attendant to context and time sensitive proteomics Big Data.

As we note below, proteomics science and emerging biotechnologies can benefit from truly independent social science and humanities-driven research (Haffeld and Siem 2013; Dove and Özdemir 2014).

Mapping the social proteome

There are ample socio-technical reasons to believe that the past lessons learned from social studies of genomics are not directly transferable to the social proteome. The distinctly adaptive capacity of the proteome to capture the dynamic changes in biology and function within an individual means that proteomics test results fluctuate within a given person, either due to disease, drug treatment or baseline physiological within-person variations (Hogan et al. 2006; Kasthuri et al. 2006; Jehmlich et al. 2013; Wood et al. 2013; Mehta et al. 2015; Reddy et al. 2015). Such *dynamic* biological characteristics of the proteome, however, are likely to translate into certain social consequences such as hype, uncertainty and individuals' perceptions of their future health risks, in ways distinct from the *static* genotype-based risk assessment models (Table 1).

Social media, business and innovation policy, also integral to the social proteome, deserve a fresh look (Zhao et al. 2014). Historically, insofar as the genotype-based static diagnostics are concerned, the traditional "single-test-per-life-time" business model has had limited growth and interest within the diagnostic industry, not to mention the moderate attractiveness of the reimbursement schemes as perceived by the biotechnology industry. With the repeated testing necessary to monitor the function of cells and living organisms using proteomics, new diagnostic innovation and business models may become more akin to pharmaceuticals that require repeated prescription fillings (Ghidoni et al. 2013). Whether the proteome-based biomarkers and diagnostics will face acceptance by the biotechnology and pharmaceutical industries, global society and psychiatry research and clinical community are questions that are in need of empirical social science research, as with other candidate issues listed in Table 1.

Looking at the social proteome on a global scale, the availability of mass spectrometry will be a decisive factor socio-technically; the scientists, institutions and countries with access to mass spectrometry will excel in mapping out the biological proteome. The social proteome, too, will be influenced by the availability of mass spectrometry, for this equipment is expensive, thereby holding substantive potential to shape the professional values, professional competition and cooperation within the proteomics science community. Technologies situated at the epicenter of proteomics such as mass spectrometry can thus shape both the biological and the social proteome; by tracing mass spectrometry as a "socio-

Table 1 Translating the biological proteome to social proteome and innovation management instruments

Biological proteome examples	Social proteome examples
Proteomics is a dynamic biomarker	*A highly porous boundary between health and disease*
Proteomics test results *vary over time and place* in a given person, and between-populations	Risk assessment models will change; there will be ongoing continuous real-time monitoring of health and disease using proteomics tests
	Fluctuating diagnosis of disease; there will no longer be fixed point estimates of future risks
Within-person variability of the proteome is not clearly established	*Hype*
	Compared to genetics/genomics, will there be greater or lesser hype associated with proteomics-based imaginations of future health status?
	How do we ascertain if a change in proteomics result is over-and-above physiological intra-individual variation in the proteome? Absent this information, the promise of the proteomics biomarkers may conflate with positive or negative hype. As proteome varies within- and between-persons, hype and expectations will also show a dynamic range
Mass spectrometry at the epicenter of proteomics data production	*Re-thinking the mass spectrometry instrument as a locus of social power*
	Those scientists, institutions and countries with access to mass spectrometry will forge ahead readily. How might this influence within-team and between-team collaborations, conflicts, professional jealousy, and synergies among scientific communities?
	It would be naive to conceptualize the social dimension of proteomics knowledge co-production practices without due attention to the materiality of the mass spectrometry as a socio-technical object
Repeated testing is required for proteomics unlike the one-time genotype-based tests for familial disease	*New business and innovation models are needed for proteomics*
	Reimbursement mechanisms are needed for serial proteomics tests over time and context; business models from "once-a-life-time" genotypic tests will likely not transfer successfully to proteomics diagnostics
	Industry investment may (potentially) be more enthusiastic for dynamic ongoing biomarker testing instead of the single measure genotype based diagnostics
	Equity and fair pricing/reimbursement issues?
Anticipatory governance of proteomics technology trajectory	Fostering national innovation systems for proteomics-in-psychiatry

material" object, one might better understand the emergence of new socio-technical configurations of proteomics science and its diffusion (or lack of access to proteomics diagnostics in certain regions) around the globe.

The social proteome, no doubt, deserves much greater attention than it has received to date. As we highlight in Table 1, the scale, quality and multiple application contexts of proteomics technology suggest that the emergence of proteomics science has distinct social, economic, political and medical impacts on society, thus creating a social proteome that is in need of rigorous empirical and normative analyses in the future.

Conversely, changes in the social proteome, for example, in the ambient social context of a human host, can alter the biological proteome. It has been shown that social medicine services such as provision of thermal therapy at saunas or hot baths has the potential to improve impaired insulin sensitivity and boost endothelial expression of the "constitutive" isoform of nitric oxide synthase (McCarty et al. 2009). The latter impacts on the biological proteome, produced by changes in the social proteome, appear to be akin to that induced by aerobic training for control of diabetes. This means that patients with diabetes who lack access to a sauna or communal hot tub in their social proteome will have correlate signatures or imprints in their biological proteome. As psychiatric illness and therapies are in a state of dynamic interaction between the individual, society and the social systems such as those noted above and in Table 1, it would be beneficial to study in the future the bidirectional impacts of the social proteome on the biological proteome and vice versa.

But who should map the social proteome?

Looking back at the Human Genome Project, which was completed more than a decade ago, there has been a latent and at times overt tendency by scientists to contract out the "societal aspects work package" to bioethicists. Such outsourcing or co-opting of aspects of science, technology and medicine need not, and perhaps should not, be foregone conclusions. Moving forward to map the social proteome, there is much that can be done by proteomics scientists themselves. The

contours between the biological and the social proteome are more porous than what we are led to believe within the scientific community (Özdemir et al. 2015b).

Proteomics scientists could enhance their reflexivity (cognizance) of the social proteome by taking an active role to map it because they often know quite well the local context in which proteomics technology is emerging, for context is everything when it comes to the social proteome. By situating the context of knowledge co-production and applications of proteomics technology, scientists can help create a "socialized proteome" whereby the social, political, economic and ethical dimensions are surfaced transparently. Conceivably, both the chromosome-centric and the disease-centric teams who are contributing to the HPP around the world could take up the task of mapping the biological proteome and the social proteome in parallel.

This is not to say mapping the social proteome (Table 1) is a task cut out solely for scientists, technology experts or clinicians. Social scientists and humanists play critical roles in developing a sociology of bio-knowledge (De Vries 2004; Petersen 2013). On the other hand, Elinor Ostrom, Nobel Laureate in Economic Sciences in 2009, underscored the importance of *nested* governance *systems* for checking on, and making transparent, the power systems that contribute to the intractable problems in modern day societies and ecology such as biophysical spillovers, discrimination, and intergroup conflicts (Ostrom 1990). Scholars embarking on the journey to map the social proteome might consider a "code of ethics for the ethicists" whereby a nested governance system is established to make all knowledge workers, be they on the biological or the social proteome side, made accountable in terms of their own motivations, and the ends to which they are developing proteome related contextualized knowledge (De Vries 2004; López and Lunau 2012; Dove and Özdemir 2014; Özdemir 2014; Özdemir et al. 2015b). Further building on the "nesting principle" previously outlined by Ostrom (1990, 1999), we propose a 3-tiered architecture for proteomics knowledge co-production. As illustrated in Fig. 1, under this nested technology governance scheme, three autonomous and independent groups of knowledge workers co-produce proteomics knowledge and innovations while cross-checking independently each others' behavior, power, accountability and transparency of motivations.

Ostrom often noted that such nested designs to govern society and ecosystems (in our case, proteomics technology and innovations) offer assurance against professional blind spots and so the power is distributed more evenly and not concentrated exclusively in a single stakeholder such as scientists or ethicists and other regulators. A nested architecture permits questions both "in frame" (how do we translate proteomics technology to innovation?) and "on frame" (should we invest in proteomics or alternative

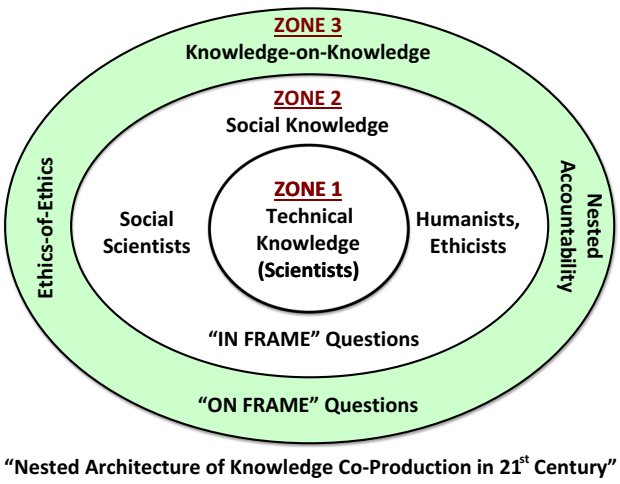

Fig. 1 Proposal of a multi-layered technology governance and innovation management system as proteomics transitions to applications in psychiatry and society. Proteomics science and technology experts (knowledge work in *Zone 1*), ethicists (knowledge work in *Zone 2*) and scholars examining independently the ethics-of-ethics (knowledge-on-knowledge in *Zone 3*) autonomously work together so as to develop robust accountability and more even and just distribution of *power* attendant to science, technology and innovation. Nested designs as proposed also help sort out genuine experts from those who rise by unjustified charisma or pseudo-science and social networks, be they in the developed or developing world

biotechnologies? what are the opportunity costs given the limited resources of financially strained world governments and global society?).

The nesting principle also brings about the opportunity of prompt correction of errors, biases or discrimination in the scientific knowledge commons and helps exclude untrustworthy individuals (Diderot 1988; Ostrom 1999; Özdemir 2014; Özdemir et al. 2015b).

The way forward: realizing proteomics in psychiatry

Protein science is not new (Al Awam et al. 2015; Patel 2014; Anderson et al. 2001). However, proteomics as a systems science is being revitalized and finding new meanings and broad research and clinical applications (Reddy et al. 2015). This is materializing in part by the availability of robust high throughput technologies such as mass spectrometry and the deployment of the Human Proteome Project in 2010. We have also come to appreciate that there is a wide gulf between genomics structure, cell function in the brain and human behavior in mental health disorders (Domschke et al. 2015). Proteomics offers the missing functional link between structure and behavior, and thus complements genomics biomarker platforms.

But how do we respond to the inherent unknowns on the proteomics technology innovation trajectory en route to

personalized therapies in psychiatry (Sclove 1989; Miles 2010; Taleb 2010)? At this early stage of globalization of proteomics science in the developed and developing world alike, it would be prudent to pause, reflect and learn from the lessons learned from genomics and other emerging technologies in twentieth century. We may want to adopt the view that early engagement with emerging technologies can accrue important social, ethical, economic and policy gains that responsibly benefit many stakeholders. Yet such anticipated gains from new technologies are *not* automatic; they demand multi-layered governance/accountability systems and complex adaptive responses at the scale of innovation systems (Haffeld et al. 2013).

Notably, the interaction between environment and human biology or behavior has traditionally been conceptualized one-factor-at-a-time (e.g., smoking, blood cholesterol), but rarely by the *entire* complement of the environmental factors that enact on the genome or the proteome. Unlike the systems approaches to study genome and proteome, systems thinking to enlist the full range of environmental/exogenous factors enacting on living organisms has not been envisioned to date. This would then seem an incomplete approach, particularly in the current era of Big Data, to adopt systems science for the study of *endogenous* variations, and yet neglect the systems architecture of the *exogenous* factors or the environment (physical, financial, social, political and ethical) in which humans, and for that matter, all life, are situated and sustained.

A systems vision of the environment: the environtome

The biological proteome is unique in a given person, time and space. So is the social proteome. Indeed, both are subject to dynamic forces that are endogenous (internal) such as endocrine feedback systems, persons' psychology and reflexive knowledge of the self as well forces that are exogenous (external) to the human host or the "environtome" (Fig. 2). We define "environtome" as shown in Box 2.

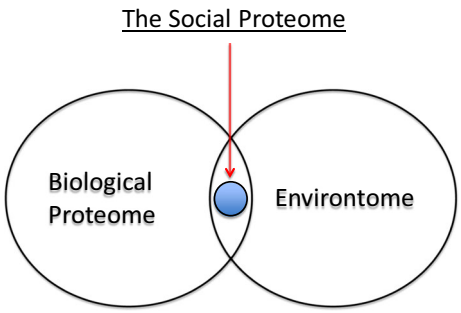

Fig. 2 The environtome interacting with the biological proteome. The social proteome is a subset of the environtome, and situated at the intersection of the biological proteome and the environtome. The social proteome impacts on, and is impacted by the biological proteome

Box 2: The concept of "environtome" for the next generation personalized medicine in psychiatry

The *environtome* refers to the entire complement of elements external to the human host, from microbiome, ambient temperature and weather conditions to government innovation policies, stock market dynamics, human values, political power and social norms that collectively shape the human host spatially and temporally. The social proteome is a subset of the environtome that enacts on the biological proteome (and vice versa) and thus is critical to translating proteomics technology to innovation in psychiatry.

A final thought: doing away with the "conquest metaphor" of innovation

Returning to the Andersons, the father and son team of protein scientists quoted in the introduction, the concept of "conquest" often expressed within the scientific community is perhaps best revisited, in a context of evaluation of scientific discovery and emerging technologies. The problem with the conquest metaphor of scientific progress is that it can "lock in" scientists' and publics' imaginations on a given particular technology, forego the opportunity costs or alternative technologies that may be as effective. As we move towards new frontiers in twenty first century science in an age of climate change and global warming, we will face greater uncertainties on innovation trajectories. Keeping an open mind and thinking through the diverse scenarios in which innovations materialize can permit us to be more flexible, adaptive and take into account multiple societal dimensions as they emerge.

We are currently poised at the confluence of genomics and proteomics fields. Whether genomics and proteomics are distinct fields or rather a continuum, the personalized medicine community would be well served to forego the deterministic metaphor of conquest in science (Miles 2010; Ravetz 1971). The complexities of the proteome teach us to be humble and appreciate that *for every first order action, there is always a second order consequence*; this is especially so in biology that represents an interconnected web of interactomes.

Looking forward, we might be able to move towards developing a "systems sociology" approach to study "proteomics-in-society". McNally has aptly referred to this systems approach to study society as "sociomics" (McNally 2005). Thus, as we embark on the journey to map the biological and social proteome for psychiatry, we should keep in mind that our goal is not conquest of

complex biology that has preceded the existence of the human kinds, but rather it is more humble to *understand* and explain the complex inner workings of biology and society (Collingridge 1980; Bourdieu and Wacquant 1992). For that, we need to be prepared to be reflective and question multiple elements, including biology, technology, as well as our values and motivations as scientists, social scientists and humanists within a nested governance framework (Fig. 1). In so doing, collectively we can help build sustainable proteomics innovations and a rich intellectual lore for psychiatrists, neuroscientists, clinicians and society at large.

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