

End of the Beginning and Public Health Pharmacogenomics: Knowledge in ‘Mode 2’ and P5 Medicine

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“The old paradigm of scientific discovery (‘Mode 1’) – characterized by the hegemony of theoretical or, at any rate, experimental science; by an internally-driven taxonomy of disciplines; and by the autonomy of scientists and their host institutions, the universities – was being superseded by a new paradigm of knowledge production (‘Mode 2’), which was socially distributed, application-oriented, trans-disciplinary, and subject to multiple accountabilities.”

Nowotny et al. [1]

“To the extent that for public health, the nineteenth century was the age of the sanitary engineer and the twentieth century of the social engineer, the twenty-first century may well see the information engineer as the key public health worker.”

Ron L. Zimmern [2]

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1. A HUMBLE BEGINNING: PHARMACOGENETICS FROM 1957 ONWARD

Advances in human biochemical genetics in the first half of the 20th century set the stage for pharmacogenetics, the study of genetics in relation to person-to-person and population differences in drug efficacy and safety. In October 1957, Arno G. Motulsky proposed in a seminal article the idea of genetic contribution to adverse drug effects [3]. Two years later in Heidelberg, Germany, Friedrich Vogel coined the term pharmacogenetics (i.e., long before ‘personalized medicine’ became a popular term and research topic) [4]. Werner Kalow, another trailblazer well known in the field of personalized medicine, published the very first book on pharmacogenetics in 1962 in Toronto, Ontario [5]. The *New York Times* ran both an article and an editorial on the subject that same year [6].

Still, pharmacogenetics from the 1950s to 1990s was considered an eclectic academic interest [7, 8] and did not have the popularity or institutionalization it enjoys today [9]. Indeed, the boundaries between popular and marginalized or disenfranchised subject matters in a given discipline are highly fluid, fiercely contested and socially constructed. In the span of a few years (or months) a research topic can transform from fringe to mainstream scientific discourse, and vice versa (see further discussion on pharmacogenetics [10–12] and data-intensive ‘omics history’ [13]). To graduate students familiar with the current popularity of ‘pharmacogenomics’ and personalized medicine in 2012, this long history of pharmacogenetics as a former ‘subject matter outsider’ within classical pharmacology and biomedicine might perhaps come as a surprise.

2. END OF THE BEGINNING

2.1. The Changing Scope of Pharmacogenomics

Two of us (VÖ, MM) had the good fortune to be mentored by Werner Kalow and experience first hand his unassuming quiet curiosity and creative intellect. But times have changed since the three founders, Motulsky, Vogel and Kalow, created the seminal ideas of our current profession—pharmacogenomics and personalized medicine—more than five decades ago. On the one hand, we continue to investigate the salient drug-related ‘variability questions’ and their mechanisms [9, 10]. After all, were it not for the large person-to-person variations in drug pharmacokinetics and pharmacodynamics, there would be no need for pharmacogenomics or its allied postgenomics sister fields such as pharmacoproteomics [14]. Predictive, preventive, personalized and participatory (P4) medicine now represents the basic tenets of pharmacogenomics R&D. In order to achieve P4 medicine, most biotechnology and pharmaceutical firms, research funders and academic investigators have long subscribed to the classic model of bench-to-bedside drug development, or the maxim ‘discover-then-translate’. With the introduction of next generation sequencing (NGS) technologies, we are witnessing a merger of the long-separated discovery/translation phases of pharmacogenomics R&D. Enabled by NGS, biobanks and other types of infrastructure science (e.g., cloud computing), as well as sophisticated bioinformatics and statistical analyses, discovery and translation research can now be conducted in tandem.

On the other hand, the field of personalized medicine is currently broadening in scope towards population health in four crucial dimensions that are much different than its

previous narrow focus on clinical medicine. First, counter-productive ‘nature versus nurture’ debates are being replaced with a keen recognition that genomics/biological, social and environmental factors act not in isolation, but in concert, to create the large variability we routinely observe in drug efficacy and safety as well as in susceptibility to common complex diseases [9, 15, 16]. Second, personalized medicine is impacting not only drug therapy, but also gaining traction in preventive medicine. Here, the ability to stratify populations into subgroups according to risk, often using genotype as part of the risk assessment, can allow public health programs to be fine-tuned to maximize benefit and minimize harm [16]. Though grouped under the general rubric of personalized, or stratified medicine, such activities may include pharmacological therapies, or more likely other prevention modalities such as screening (for example, mammography testing) and lifestyle interventions. Third, personalized medicine R&D has become truly global in scope over the past few years [9, 17]. This demands scholarship and innovation analysis beyond the developed countries as the populations likely to benefit the most may also be the most challenging to collaborate with because of logistical issues, cultural barriers, and difficulties conducting research studies in real-world settings [18]. Fourth, the theme of ‘personalization’ is being applied not only to variable drug effects but also to other health interventions such as vaccines (vaccinomics) [19].

2.2. Public Health Pharmacogenomics: A Subset of Public Health Genomics

Public health genomics is a multidisciplinary field concerned with effective and responsible applications of genome-based knowledge and technologies to improve population health, as outlined in an international meeting held in Bellagio, Italy in 2005 [20]. Such applications encompass technologies used in health services as part of the public health focus on the ‘organized efforts of society’ [21]. Thus, pharmacogenomics — which uses genomics knowledge to improve outcomes of drug treatments for individuals and groups of individuals with particular conditions — is legitimately part of this field. Moreover, as the core of pharmacogenomics relates to personalized medicine, and as this theme embraces personalized preventive and treatment strategies other than drug treatments, the two areas of study and activity become intertwined. Though closely related, however, examination of the differences in the two fields may be instructive and may provide the basis for an emerging field of ‘public health pharmacogenomics’.

Public health genomics has tended to focus on the role of genomic variation for rare and common human diseases, the prevention of these through the identification of people at high risk, and the use of genetic testing to improve diagnostic accuracy and fine-tune treatments. Additionally, P4 medicine tells us that there is a need to examine the role of genomics for health interventions such as drug therapy (pharmacogenomics), nutrition science (nutrigenomics), vaccines (vaccinomics), not to mention the neglected tropical diseases (NTDs) along similar lines [17]. Public health genomics integrates the many social, legal, regulatory and ethical aspects that accompany genetic testing in global society in order to ensure that testing is used responsibly to maximize benefit and minimize harm. All of these areas are relevant to pharmacogenomics. Finally, and most importantly, public health genomics embraces an important theme that is not yet evident in the growth of pharmacogenomics: the focus on *change management* to deliver improved health. Public

health genomics is not in itself a traditional academic pursuit, but a process. It explicitly includes the gathering and analysis of knowledge, from a wide variety of academic domains including basic science, population sciences and epidemiology, social sciences and law, to name but a few. Through a process of multi-stakeholder engagement (for example, with professional experts, patient groups, voluntary organizations and policy makers in various fields), this knowledge is used to develop and implement strategies for improved health. An emerging field of public health pharmacogenomics should embrace this commitment to change management.

The reader is encouraged to read recent work and analysis on responsible integration of genomics to public health by Zimmern [2], Brand *et al.* [22] and the CPPM interview with Dr. Muin J. Khoury [23].

2.3. The CPPM March Issue

Consistent with these emerging novel strands of personalized medicine, this CPPM March issue directly responds to the growth and application of pharmacogenomics in public health—public health pharmacogenomics—with original research and expert analyses by an international set of scholars. These authors report from both developed countries and low- and middle-income country (LMIC) resource-limited settings on recent advances and current and future challenges in the field.

Dandara *et al.* provide fascinating insights and analyses on current genomics applications in Africa and the emerging role for an *African Foresight Observatory on Genomics Medicine and Data-Intensive Global Science*. The editorial analysis truly brings together a ‘dream team’ for global pharmacogenomics and personalized medicine. With the launch of the H3Africa Initiative and rapid globalization of genomics biotechnology applications, the editorial is timely and fills a substantive void in postgenomics life sciences literature that addresses the responsible applications of genomics in Africa. Moreover, it also sets a laudable example for LMICs in other regions.

Yun *et al.* take us to another original context: the convergence of genomics with Traditional Chinese Medicine (TCM), and further propose a critical path for this integration. This is an area of postgenomics personalized medicine with enormous potential to benefit global health in both LMICs and developed industrialized countries where publics increasingly utilize (or are exposed to) TCM. A genomics-TCM merger is a promising field of postgenomics R&D for young researchers to undertake as they develop their careers. Furthermore, other forms of traditional medicine, such as those found in Africa, stand to benefit if similar endeavors are undertaken to integrate modern molecular science with these disciplines.

Diaz *et al.* turn our attention to hitherto neglected statistical random-effects linear models and explain their remarkable characteristics that allow simultaneous description of patient populations as a whole and as individuals.

In an original report, Park *et al.* caution us that pharmacogenomics has long neglected the non-drug related environmental factors such as ambient temperature change, and the ways in which they can interact with global gene expression in the host genome. Using an *in vitro*

model, this study from South Korea informs future biomarker research design so as to better control and account for ever-present dynamic environmental exposures such as ambient temperature.

Swart *et al.* continue with original findings from South Africa. They report on genetic polymorphisms in two Bantu-speaking populations from Cameroon and South Africa in relation to global pharmacogenomics and personalized medicine. Their research indicates that, interestingly, the two Bantu-speaking African populations were separated from each other and from other African populations. These findings reiterate the need to conduct pharmacogenomics studies in diverse population samples and for researchers and relevant stakeholders to form global pharmacogenomics consortia.

Jain *et al.*, reporting from India, present the first transcriptional analysis for almost all candidate genes, regulators and potential interactors of JAK/STAT pathway in glioblastoma multiforme (GBM), the most commonly occurring brain tumor with survival for the majority of suffering individuals being less than a year. The field of GBM therapy is advancing rapidly with personalized genomic approaches that identify tumor subtypes that differentially respond to combined chemo- and radiotherapies [24]. The findings presented in this original article contribute to efforts for novel diagnostics for early intervention in GBM.

In an appropriately provocative and insightful article entitled “*Prostate Cancer Prevention in the Developing World – What are We Waiting for?*”, Bishop *et al.* underscore that prostate cancer rates are increasing in LMICs. They identify the risk factors for prostate cancer in LMICs and developed countries, with a view to personalizing health interventions in preventive medicine.

Kampira *et al.* conclude our March issue with a much-needed focus on Malawi and the current status of genomics/pharmacogenomics research in this landlocked, southeastern African country. They report on gene-centric knowledge gaps that must be addressed if the field of public health pharmacogenomics is to advance in a country that for too long has been among the world’s least developed and most health deprived.

3. KNOWLEDGE IN ‘MODE 2’: P5 MEDICINE

The changes in pharmacogenomics practice over the past five decades are not merely limited to technology breakthroughs such as NGS and an expansion to a global public health context. The very process of pharmacogenomics knowledge production has also transformed, with a greater emphasis now placed on large-scale collective innovation, infrastructure science, population biobanks and data/biocommons [25, 26]. This brings the social study of science to the fore [27] and renders it a role as important as the genomics biotechnology itself.

Science policy discussions are increasingly embracing the concept of ‘knowledge society’, whether because of hopeful expectations for a prosperous ‘knowledge economy’ [28, 29], or in recognition that urgent social and environmental challenges, including the need to more effectively address tensions between public and expert viewpoints, require more nuanced

understanding of the complex lineages between science, technology and society [30]. For example, the American Association for the Advancement of Science (AAAS), a global non-profit organization founded in 1848 and dedicated to advancing science around the world, held its 2012 Annual Meeting in Vancouver, Canada, with participation from more than 50 nations [28]. One of the questions posed at the meeting was — *why is it that so many around the world remain unconcerned about global challenges such as climate change, water scarcity and polluted oceans?* In response to this pressing challenge, a panel led by AAAS President Nina V. Fedoroff discussed ways in which scientific experts and publics can engage to these ends.

In order to appreciate the current ‘socio-technical’ transformation of pharmacogenomics and personalized medicine and its role in the making of 21st century knowledge societies, it is helpful to recall just how much some of the founding tenets of the modern scientific project have themselves become unraveled.

It is generally recounted that before the 17th century, human inquiry was underdeveloped and verged on the status of being an intellectual vice. Curious persons were labeled ‘strange’, illicit or useless: “seventeenth-century projects for the advancement of learning had to distance themselves from curiosity and its dubious fruits” [31]. Francis Bacon and other empiricists laid out the pillars of modern science in the 17th century that transformed curiosity from vice to virtue over the course of the ensuing centuries. Moreover, in the 17th century—we have been taught to believe—Francis Bacon heroically asserted that knowledge comes from observations and experiments, an idea encapsulated by the modern day aphorism ‘*knowledge is power*’. Less celebrated is the logical counterpart to the phrase, namely, that *ignorance is weakness*. This dubious proposition gives rise to overly simplistic and binary understandings, evident not only in counter-productive tensions such as that above referenced “nature versus nurture” debate, but also in institutionalized standoffs between expert and experience-based ways of knowing. We are now at the point where we need to add, however, more pillars to the social architecture of science and its public extensions.

Indeed, the early origins of pharmacogenetics in the 1950s owe much to the ‘*knowledge is power*’ dictum and were typified by knowledge production in ‘mode 1’ [1, 13] in the academy by experts and within narrowly defined disciplinary boundaries. But as we in the life sciences field have moved towards the realization of P4 medicine [32], the practice of pharmacogenomics R&D increasingly takes place in hitherto unprecedented locales outside the ‘academy’, contributing to knowledge production in ‘mode 2’. This shift replaces what was once described by the previous scientific metaphors of the 20th century, such as the belief that scientific practice is a value-free intellectual activity often limited to the physical confines of the laboratory ‘bench-space’. Now, a much greater diversity of actors is contributing to postgenomics knowledge production [13]. Importantly, societies are recognizing the political dimensions of science and medicine (a P5 medicine) and publics, no longer relegated to a *post facto*, narrowly framed and passive ‘product uptake’ role, are being invited—and in crucial cases, inviting themselves—to collaborate in scientific ‘design’ to steer the innovation trajectory as ‘co-pilots’ with technical experts. Together, publics and experts work to solve fundamental questions, e.g., *which hypotheses should scientists*

pursue?; what type of research should have priority for limited research funds?; how can or should one determine which type of evidence is to be used to adopt new diagnostics for personalized medicine? [33–35].

Frequent contacts and integration between knowledge generators (e.g., scientists and technology designers) and end-users (e.g., citizens, individual patients, policy-makers and the public health community), as well as the creation of mechanisms between *supply* and *demand* of knowledge, are necessary components of Mode 2 knowledge production. Such interactions are also necessary to ensure that issues arising from genomics research (e.g., adequate informed consent and genetic counseling, privacy issues, etc.) are addressed in real-time while the science is still in the making. These components contribute to the creation of innovations that are meant to be better attuned to societal norms, contextually sensitive and thus, socially robust and sustainable. Along these lines, Lavis *et al.* [36] recommend that:

Researchers (and research funders) should create more opportunities for interactions with the potential users of their research. They should consider such activities as part of the ‘real’ world of research, not a superfluous add-on.

While some may view Mode 2 as a departure from ‘pure knowledge’ production, we submit that the boundaries between natural/technical and social systems are highly porous, and have always been, since the existence of human kinds [13, 29]. Social systems such as human values and ways of knowing – *what we choose to know and how we know it* – expressly impact what gets to be produced as scientific knowledge. The choice and framing of scientific hypotheses, experimental methodology and interpretation of data can all be influenced by experts’ and their institutions’ value systems that often remain *implicit* in scientific decision-making [27, 29, 33]. Mode 2, as a concept, both elucidates and broadens the process of knowledge production, synthesis and dissemination beyond the laboratory benches and ivory towers in postgenomics personalized medicine. It recognizes the power of highly specialized and ‘disciplined’ ways of knowing; but it also deploys new tools to address the vast social complexities and uncertainties that can confound well-intentioned yet by now outmoded visions of how knowledge functioned in modern societies. Equally important, it firmly recognizes the inherently political nature of knowledge in its production, use and social shaping of evidence [29, 34].

Indeed, since Francis Bacon and other early empiricists, science, knowledge and technical evidence have been treated by many as value-free entities hermetically insulated from human values and social and cultural systems. Mode 2 knowledge production, with its focus on applied knowledge, brings about new opportunities but also responsibilities for collaborating natural and social scientists, humanists and bioethicists alike. Such responsibilities are truly shared, and do not merely apply to technical experts and natural scientists. While moral philosophers and social scientists, for example, have taken up the task of social critique and study of the social construction of science and technology, their normative conclusions (e.g., ethical/unethical technology), as with natural scientists, are also subject to influences by their own value systems and personal career motives, not to mention the material aspects of technology, that often remain implicit or unchecked. In Mode 2 knowing, no human agent is *automatically* ‘above the fray’ by virtue of disciplinary

affiliation. Moreover, the strong emphasis within the social sciences community for social *deconstruction* of science and technology has not been accompanied by a parallel and crucial effort for socio-technical *integration*.

Knowledge in Mode 2 invites a multitude of actors to be more reflexive and cognizant of how their own existing values and unchecked political and social assumptions – their *habitus* – might affect their field [37, 38]. Rather than hiding behind the protective shelter of disciplinary tradition in order to defend moral and political conclusions about the ‘ethical/unethical’ status of technology (or persons, institutions, etc.), we should cultivate greater reflexivity to bridge longstanding divides and uneasy relationships between the hitherto autonomous spheres of the life sciences, social sciences and humanities [27, 29, 39]. Indeed, Nowotny *et al.* make the point that:

‘Mode 2’ is not only a concept, inherently open to manipulation or exploitation by others (even in ways of which we may disapprove); it is also a project, an example of the social distribution of knowledge, which it seeks to describe. (...) Closure of the ‘Mode 2’ debate is neither possible nor desirable. The project has many of the characteristics of the much more open knowledge production systems that it is attempting to analyse – wide social distribution, trans-disciplinarity, the need for social robustness, and the creative potential of controversies. [1]

To a large degree, reflexivity entails recognition by actors of their ability to not only be shaped by, but also actively shape, their social and political environments. Ilona Kickbusch has persuasively written how the expansion of reflexivity of health is causing us to acknowledge that the choices we make in health “are political in their own right and have political consequences not only of a local but of a global nature” [40]. We therefore suggest that in order to foster better sustainability of postgenomics innovations, and openly acknowledge reflexivity’s purpose in Mode 2 knowledge production, another ‘P’ (the political science dimension of knowledge and evidence) must be appended to the extant P4 medicine framework to create a truly holistic *P5 medicine*. Thus, P5 medicine would merge predictive, preventive, personalized, participatory medicine with an integrated study of the political science aspects of knowledge societies and innovations.

CONCLUDING REMARKS: CPPM 2008 – 2012 AND BEYOND

As with Mode 2 knowledge, the CPPM readership is globally distributed and appropriately demands to stay ‘current’ with nuanced and ‘situated’ knowledge of postgenomics personalized medicine innovations. The CPPM editors have long recognized that editing is a labor of love and comes with a large responsibility to serve, to the best of our abilities, global society including those who live in LMICs and impoverished regions of the world, the life sciences community and patients and citizens in need of personalized medicine [14, 15, 17, 41]. We welcome this responsibility and trust that the March issue presents a stimulating and cutting-edge read!

We will continue to canvass for both recognized senior expert authors and the ‘best unknown’ promising young authors, particularly those in LMICs, whose voices and original ideas deserve to be brought to a global audience. After all, Mode 2 knowledge production is

in part based on the tenet of ‘extended peer review’, including and beyond the realm of developed countries. We wish to ensure that our readership and contributing authors are represented inclusively in the emerging global personalized medicine discourse. We do not have an alternative—if we are to be truly serious about postgenomics and globalized public health pharmacogenomics in Mode 2.

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ABBREVIATIONS

AAAS	American Association for the Advancement of Science
GBM	Glioblastoma Multiforme
LMIC	Low- and middle-income country
NGS	Next generation sequencing
NTDs	Neglected tropical diseases
P4 medicine	Predictive, preventive, personalized and participatory medicine
P5 medicine	Predictive, preventive, personalized, participatory medicine, with integrated study of the political science aspects of knowledge societies and innovations
TCM	Traditional Chinese Medicine

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