

Personalized Medicine in Context: Social Science Perspectives

Richard Tutton
Senior Lecturer
Department of Sociology
Lancaster University
Lancaster
r.tutton@lancaster.ac.uk

Kimberly Jamie
Research Fellow
Science and Technology Studies Unit (SATSU)
Department of Sociology
University of York
York
kimberly.jamie@york.ac.uk

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Introduction

In the 1990s, the scientific and popular press heralded the emergence of a new paradigm in drug discovery and development called pharmacogenomics (pgmx). This science would produce a new generation of ‘personalized medicines’ utilizing information about individuals’ genotypes to make more effective and safer drugs. As well as capturing the interest of scientists, policymakers and journalists, the field of personalized medicine has also been of immense interest to social scientists who research new innovations in health and biomedicine. Social science has mapped industry involvement in pgx and ‘personalized medicine’ since the 1990s, identifying the visions that have guided development in this field and reflected on the broader social and economic contexts in which pgx has appeared. The clinical adoption and the challenges of pgx testing becoming a standard healthcare service have also been documented by careful examination of clinicians’ own practices, and social science has also explored public perspectives on pgx and the potential implications of patient stratification. The purpose of this article is to review this research and its contribution to an understanding of personalized medicine. It will summarize some of the most important findings to date, and reflect on the future research agenda.

Personalized Medicine as a Vision

One of the key roles of social science research has been to map the construction of scientific fields of inquiry over time and the means by which these fields attract their supporters. Central to this undertaking has been the study of language not for its own sake but for understanding its practical significance. Hedgecoe argues that the adoption of the term pmx did not describe an area of research distinct to that of pharmacogenetics (pgx) which had been in existence for forty years, but served as a rhetorical device to gain support and investment by linking it to the Human Genome Project (1). This is not to deny that important technical changes had taken place such as the development of SNP databases and chips to genotype individuals to identify genetic variation. However, it is of note that the term pmx only first appeared with the announcement of an alliance between Genset and Abbot Pharmaceuticals in 1997

and so became associated more closely with the commercial potential of the study of the role of genetic variability in drug response in drug development. The two terms *pgx* and *pgmx* have continued to be used and their exact meanings disputed and debated by scientists and others (2).

The potential contribution of *pgmx* was described as producing ‘a new generation of personalized medicines’ -- drugs aimed at the individual as opposed to the ‘average person’ (3). Since that time, ‘personalized medicine’ (in the singular now) has proven to be a highly popular term that easily conveys to a range of audiences what genomics has to offer medicine and healthcare in the twenty-first century. However, clinicians had used the term personalized medicine since the early 1950s to describe a patient-centred practice that focused on the ‘art’ of clinical judgement and was often hostile to technology in medicine (4). The term personalized medicine has also been controversial: some claim that it promises more than can be delivered because individualized therapy can only be truly realized in a biopsychosocial paradigm while *pgmx* is a biomechanistic concept that is instead concerned with the stratification of patient populations (5). Recently, certain actors have preferred other expressions such as stratified medicine as a more accurate description of how drugs are targeted at groups as opposed to individuals (6).

Building on this interest in language, social scientific analysis of emerging biotechnologies has also proceeded with understanding that the visions of social actors such as scientists can shape technological outcomes by attracting allies and their resources to support work to realize these visions. Therefore the study of visions has been central to a thorough examination of how a technology is constructed and then translated into everyday use. This approach has been adopted by social scientists in relation to *pgx* (7, 8). Smart and Martin show that there were multiple and potentially competing pathways for pharmacogenetics to develop, which included: (i) discovering new ‘*pgmx*’ drugs aimed at genomic sub-populations; (ii) the identification at later clinical development stages of ‘good responders’ for new drugs; (iii) use of efficacy data in the marketing of both new and existing drugs; (iv) pre-prescription screening to identify patients at risk of ADRs; and (v) pre-prescription screening to identify ‘good responders’ (8). Smart and Martin’s study investigated the level of support from the biotech and pharma industry for each of these ‘visions’ in

order to assess their prospects, interviewing industry leaders and analyzing published data on publicly announced collaborations. They conclude that there was significant interest in the potential of pharmacogenetics to aid in new drug discovery and development (i, ii), but there were barriers to applying pgx in relation to already licensed drugs. However, there were some exceptions, most notably the HIV/AIDS drug Abacavir (Ziagen) developed by GlaxoSmithKline; it was also clear that some specialist diagnostic developers saw opportunities to develop and market diagnostic tests for existing drugs.

Recent analysis of FDA data indicates that just over 10% of the 385 drugs licensed in the period 1998-2011 had pgx biomarker data included in their labels at the time of their approval (9). Only three drugs – Herceptin®, Xalkori® and Zelboraf® – were approved by the FDA as ‘combination products’ of co-developed drugs and companion diagnostics. Of the drugs listed by the FDA as having pgx biomarker data in their labels the majority are already licensed drugs for which this data is included in the main to improve their safer use by clinicians and patients (9). Therefore, the evidence is that significant headway has been made on pre-prescription screening on drug safety grounds. Where drugs have been approved with biomarker data to guide their use by clinicians, the majority have been cancer therapies. The wider application of pgx to other therapeutic areas is for now unclear.

Personalised Medicine in Clinical Practice

Social science research has followed personalised medicine into clinical practice to document how pre-prescription testing is mobilised to identify patients who are likely to respond well to particular drugs and those that are at increased risk of adverse drug responses (10, 11). At present, this approach is almost exclusively limited to secondary care where the increased complexity, cost and toxicity of therapies makes a trial-and-error model of prescribing inappropriate. Oncology is of particular note as a clinical specialism in which pharmacogenetic approaches to medicines and patient bodies have become fairly well routinised. As noted above, 42% (n=36) of the current 117 biomarker associations identified in FDA-approved drugs pertain to this therapeutic area. Within this field, the breast cancer drug Herceptin® has repeatedly been drawn on as an example of the highly successful integration of personalized

medicine into routine clinical use. Herceptin is only effective in the 25-35% of breast cancer patients whose tumours over-express the human epidermal growth receptor 2 (HER2) protein as a result of gene amplification. Given this, pre-prescription testing of the breast tumour for HER2+ status can determine whether Herceptin is an appropriate therapy option. Notwithstanding the debate as to whether Herceptin ought to be considered pgx drug at all (since it is targeted at the tumour not the genotype of the patient), its adoption is noteworthy for a number of reasons. For example, the media played a central part in debates about the extension of Herceptin's license for the treatment of early stage breast cancer (12; 13). Moreover, by funding HER2 tests prior to Herceptin's approval, Roche gained widespread professional support from oncology practitioners and overcame the previously conservative British oncology testing culture. This experience provides a useful insight into understanding the nuances of testing cultures across different clinical specialisms in Britain and elsewhere (14;11).

Further research on clinical cultures has shown that the divergent adoption of pgx testing across different clinical specialisms is less about conservatism or resistance than the perceived 'clinical usefulness' of tests in specific clinical settings. Four social aspects of clinical practice which contribute to understandings of pgx tests as useful or otherwise; (i) the differences between disease classifications in scientific research and clinical practice; (ii) the potentially wide ranging familial implications of test results; (iii) complexity around which clinical department is liable for financing pharmacogenetic tests and/or care for adverse events; and (iv) the precedence given to clinicians' diagnostic opinions over tests results where these two differ (15,16, 17). This final point has also been discussed in relation to familial hypercholesterolemia where researchers found that practitioners involved in diagnosis understood genetic test results as less useful than other information, namely cholesterol tests (18).

As an example of this clinical usefulness framework in practice the Alzheimer's drug Tacrine is commonly mobilised as an example antithetical to Herceptin where the integration of pgx testing has been significantly stalled. Briefly, during the 1990s variations in response to Tacrine were linked to changes on the APOE gene (APOE4) which was also linked with increased risk of late-onset Alzheimer's disease. Within the scientific community, however, conflicting results were presented with some

researchers understanding APOE4 as central to Tacrine response and others being more sceptical about the links between Tacrine and genotype (19; 20). Moreover, pre-prescription tests for Tacrine would also highlight a genetic susceptibility to Alzheimer's which clearly has wide-ranging familial implications. Pgx tests for Tacrine response were, then, considered limited in their clinical usefulness given that the scientific community could not produce quantifiable conclusions about the APOE/Tacrine link for use in clinical practice and given the familial implications of identifying the presence of an increased Alzheimer's risk factor (15).

Social science has shown how the cases of Herceptin and Tacrine highlight the complex nature of the integration of pgx testing into clinical practice where the 'micro' world of everyday work, politics and cultures of clinical practises become as important as, and intertwined with, the 'macro' politics of medicine vis-à-vis regulation and funding. In bringing the importance of these social and cultural issues to the fore, questions of personalized medicine in clinical practice become somewhat more complex than simply seeing clinician education and resources as the principal 'barriers' to the uptake of pgx in clinical practice (21;22).

Personalised Medicine and Patients

As well as clinicians' perspectives on the clinical usefulness of pgx testing, public understandings of their clinical usefulness are also central to their uptake and routinization within healthcare practices (23).

Patient Expectations: Social scientific research has indicated that there can be a disjuncture between patients' high expectations of pgx and practitioners' relative reluctance to deliver pgx services (24). A study of lay peoples' perspectives on pgx found that whilst most respondents were generally positive about the potential improvements to patient outcomes and experiences, its perceived preventative, rather than curative, nature could weaken the chances of pgx being adopted (25).

Privacy and Confidentiality: Surveys of public perception highlight concerns around privacy and confidentiality of results as a factor which could restrict the clinical usefulness of pgx from the patient's perspective (26). This concern is echoed

by qualitative research which found that although Australian consumers were anxious about, and keen to minimise, side effects of drugs, they were sceptical about whether their genetic data could be securely stored (27). Questions of insurance and employment discrimination also features prominently in social scientific analyses of (pharmaco)genetics. Although anti-discrimination legislation has been passed such as Genetic Information Non-discrimination Act (2008) in the US which prevents insurers and employers using genetic information in a discriminatory way, American employers can still request all health records as a condition of employment (28).

Familial Nature of Genetic Information: The familial aspect of privacy and confidentiality in p_gx practice has also been examined. Although the decision to undergo any (pharmaco)genetic test should be the decision of the individual patient alone, the results are necessarily familial and, as such the potential risks to other family members ought to be taken into consideration during any genetic testing process (29). Others have identified the nature of medicine itself as family or community medicine in that individuals cannot easily be separated from their social or cultural environments given the genetic ties (and responsibilities) with which they are bound (16; 30; 31). In a seminal report of the ethical challenges of p_gx, the Nuffield Council on Bioethics (2003) noted that such decisions around informing family members cannot be arbitrarily legislated against and, instead, recommended that decisions about informing family members of potential genetic risks identified by test results should be taken by the healthcare practitioner based on the circumstances of each individual case (32).

Implications of Patient Stratification: Another issue that has been prominent in social scientific analyses of p_gx is the extent to which stratification practises risk replicating issues of social injustice and healthcare inequality that have been a central concern of medical sociology. Social scientists have also contemplated whether stratification may also lead to the emergence of therapeutic ‘orphan populations’ with limited access to new and more effective treatments (10, 33, 34). This may be a result of their genetic make-up falling outside of the most common genotypes where discovering effective therapies is challenging using available technology or because the genetically-defined subpopulation to which they belong is too small to be economically attractive as a potential market for pharmaceutical companies. Where

drugs are developed for these small patient subpopulations, the probability is that they will be extremely expensive, thus reproducing questions of equality and access (33).

While pgx offers a way to stratify patients by genotype, fears have been expressed about using proxies such as race/ethnicity to target the development and marketing of drugs (35, 36). Central to many of the sociological debates about race and pgx has been the congestive heart disease drug BiDil®, which was licensed by the FDA in 2005 for use in (self-identifying) African-American patients only. Its appearance prompted concerns that by characterizing drugs and drug responses along racial lines, health differences would be attributed purely to biological factors and thus marginalize social inequalities, such as education and housing, which can have significant effects on health (37).

On a global scale, it has been questioned how useful pgx practises will be for low- and middle-income countries where access to basic healthcare provision is limited (38). Given that subscription to pgx medicine will involve a ‘sophisticated’ testing and medical information technology infrastructure, the extent to which it can be successfully integrated into medical practice in poorer countries is questionable (33). In this way, current global inequalities of access to contemporary biomedicine may be reproduced where patients in the wealthy developed world routinely use genetic information to increase the safety and efficacy of medicines whilst healthcare in the developing world remains characterised by risk (38).

Future Research

To conclude this short review, we highlight a number of new directions for social science research. We endorse the suggestions made by Hogarth et al for further study of the role of drug regulators and activities in biomarker patenting (39). To that we would add the following: (i) Further investigation of the different professional roles in delivering pgx as a healthcare service both now and in the future; at present there is something of an implicit assumption that doctors are, and will be, the primary practitioners carrying out pgx testing. We suggest that it is important for social scientists to examine this assumption more fully and explore the potential role of other professional groups like nurses and pharmacists. (ii) To develop the

opportunities offered by ‘big data’ to research more fully the patterns of pgx uptake in healthcare services and (iii) to engage in an interdisciplinary dialogue with health and biomedical scientists on how personalization could be elaborated in a way that encompasses biomechanistic and biopsychosocial aspects of patient care and the structural determinants of health inequalities in society. Such an interdisciplinary approach to the multiple biological and social determinants of health inequalities seems apposite given the increasing interest in epigenetics.

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