From medical gaze to statistical person: Historical reflections on evidence-based and personalised medicine

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Background

The nineteenth century saw the rise of what historians of medicine have termed the 'medical gaze'. Physicians used instrumentation and trained senses to locate the site of disease within the patient's body. This change in practice went alongside changes in the physician's power and how diseases were understood. In the twenty-first century, the rise of high-throughput biomedical experiments, especially in genomics, is leading to equally dramatic shifts in medicine. Increasingly, clinical decisions may be made on the basis of data and statistical associations rather than the particularities of the case at hand.

Objectives

The aim of this commentary iso re-evaluate the status of precision and evidence-based medicine in light of the social, political and economic shifts they entail.

Discussion

Increasingly, the statistical view of diseases and people threatens to take judgment and expertise out of medical decision making. It threatens the centrality of the physician in the relationship between patient and disease.

What was it like to practice medicine in Europe in the eighteenth century? According to historians, it relied a lot on hearing a patient's story of their disease. Consultations began with some variant of the question, 'What's wrong with you?'. Through dialogue and listening to the narrative of illness, the physician then attempted to ascertain the qualities and form of the disease and the individual. The causes of the disease emerged through this dialogue between physician and patient.[1]

The historian and philosopher Michel Foucault famously argued that this scene – doctor and patient in dialogue – changed dramatically during the nineteenth century. Beginning in the Enlightenment, and especially after the French Revolution, the conversation with a physician began not with 'What's wrong with you?', but rather, 'Where does it hurt?'.[1] Now the disease was located in a specific place in the body and it was the physician's job to make a diagnosis based not on a conversation, but rather on evidence. Increasingly, it was understood that there were specific signs and symptoms of disease that could be 'read' on the patient's body.

This change had several important implications for medicine and patients. In the nineteenth century, disease became separate or separable from the patient – it existed as a category that could transcend individual bodies or persons. It was less the case that a patient was ill, but rather that the patient had a disease. Moreover, Foucault associates this change with the development of a particular relationship between the physician and patient: the 'medical gaze'. The physician's role was to penetrate surface appearances and reveal the hidden causes of disease (eg by using new instruments such as the stethoscope). This change was part of a general turn towards empiricism in the nineteenth

century that revolutionised many sciences. It was also part of the increasing specialisation and professionalisation of medicine in the nineteenth century, giving increasing power to physicians and de-emphasising the unique narratives of individual patients.

Many aspects of the 'medical gaze' are still with us. It is still the physician's role to look for the signs of disease, although sophisticated instrumentation and laboratory testing now increasingly mediate the doctor's gaze. Over the past 30 years, however, the medical gaze has been supplemented, perhaps even supplanted, by yet newer kinds of practice. In particular, this period has seen the collection, storage and analysis of vast amounts of biomedical data that are increasingly being put to clinical use. Genomic, protein, metabolic, epigenetic, environmental and clinical data have been mobilised for understanding human disease. All of these have been processed almost exclusively by computers and new fields, such as bioinformatics and computational biology, have emerged precisely to deal with the challenges of making sense of the vast amounts of biomedical data.[2]

One paradigmatic example of how these data are mobilised is through the genome-wide association study (GWAS). Beginning in 2005, researchers began to conduct studies that collected clinical data and information about genomic mutations (or variations) from a large number of individuals (usually using microarrays or deoxyribonucleic acid [DNA] chips).[3] Carefully stratifying and analysing these data showed that some mutations were over-represented in particular clinically significant groups. For example, mutation X might show up 50% of the time in individuals with type II diabetes mellitus (T2DM), but only 10% of the time in individuals without T2DM. This has allowed researchers to generate a large number of statistical associations between genomic mutations and particular diseases. By 2013, there were almost two thousand GWASs conducted on hundreds of different traits and diseases.[4]

These associations can be, and have been, interpreted as risk factors. For example, mutation X seems to bring with it a greater risk of T2DM. This kind of information is what direct-to-consumer personal genomics companies (eg 23andMe) report to their customers. However, studies such as these are justified on the grounds that they will increasingly inform clinical decision-making. Evidence-based medicine, which has been in use for several decades, relies on the notion that decisions should be based on statistical inferences from large numbers of other cases.[5] The notion of 'personalised medicine' proposes to take these ideas further by using more and more biomedical data and GWAS-type analysis to tell us what types of drugs or treatments we should receive when we are sick. GWASs apply, of course, to genomic data. But, in fact, this paradigm is growing to encompass many other kinds of biomedical data, including environmental data. New approaches, such as environment-wide association studies (EWAS),[6] gene-environment-wide association studies (GxE)[7] and phenome-wide association studies (PheWAS),[8] also use statistical approaches to identify over-represented instances within large population groups.

In this kind of medicine, what we have is less 'medical gaze' and more 'statistical person'. The notion of the doctor as expert is, at least partially, replaced by something else – large amounts of data that point to particular risks for particular diseases. Indeed, the patient becomes, in medical terms at least, the collection of a set of risk factors or propensities or probabilities for disease. For the sociologist Nikolas Rose, this construction of the person 'genetically at risk' is a critical part of the way in which we think about our bodies and ourselves in contemporary society.[9] This involves learning to interact and live with risk, and also coming to understand others and ourselves as statistical bodies – bodies characterised by numbers.

What are the consequences of this emerging form of medicine? Why does this shift matter to physicians or patients? Genomic medicine has already brought with it some important successes. Identification of deleterious mutations in the *BRCA1*, *BRCA2* and *KRAS* genes, for instance, has allowed for improved effectiveness in cancer screening. Pharmacogenomic information included on drug labels can help to predict response and minimise adverse events.[10] However, as the use of personalised medicine expands, the issue is not so much a question of whether statistical approaches are 'good' or 'bad'. Rather, like Foucault's 'medical gaze', particular approaches to medicine privilege some individuals, institutions and points of view, while marginalising others. To rephrase, then, what are the potential shortcomings and blind spots of this form of medical thinking?

These approaches are ultimately rooted in a reductionist approach to biology. A GWAS links disease to specific mutations in the genome. As such, this type of study is premised on the notion that the causes of disease are ultimately generated by point-wise changes in DNA, ribonucleic acid (RNA) and proteins. Even studies that examine environmental and epigenetic effects tend to continue to search for individual-level, molecular causes.[11,12] Despite the successes of molecular biology, there are now plenty of good reasons to believe that future successes in understanding organisms will adopt more holistic approaches. The emergence of systems biology, network analysis and integrative biology in recent decades has already begun to suggest the limits of reductionist thinking. Personalised medicine continues to privilege DNA, RNA and protein because they have proved amenable to reading, storage and analysis on a big scale. However, examining these molecules is only giving a partial insight into how bodies and diseases work. In the early twentieth century, many biologists were convinced that endocrinology would reveal the secrets of life. Controlling hormones, biologists believed, would allow us to shape and control people and disease.[13] Of course, we now realise that hormones form only one part of a complex system that regulates our bodies. We need to remain aware that genomes also form only a part of a system that we need to understand as a whole.

These shortcomings seem to be already manifesting in some major problems that have been encountered by GWASs. Of particular concern to biologists is the so-called 'missing heritability' problem. On the one hand, GWASs have revealed hundreds or even thousands of specific genomic loci associated with particular traits. In one widely cited example, height has been associated with over two hundred distinct loci.[14] This is a problem in and of itself – how do we explain what is going on when so many distinct loci seem to be involved? If this is not bad enough, the aggregate contribution of all of these tens or hundreds of loci is insufficient to explain the heritability of the traits with which they are associated.[15,16] Biologists have put forward various theories to account for this 'dark matter' problem (eg rare variants, copy-number variation, epigenetics effects).[17] Whichever turns out to be correct, the problem itself suggests that there is much complexity in the genome that we do not yet understand, and that we should treat the 'associations' generated by the GWASs with circumspection.

Physicians need to interpret evidence based on correlations with great caution. Personalised medicine relies largely on a statistical approach that allows large amounts of data to be processed rapidly into clinically usable information. This approach eschews the more difficult, time-consuming and expensive work of establishing causal and functional connections between molecules and disease, or between molecules and phenotypes. Ultimately, it is such work that allows us to understand how organisms work, and develop effective treatments for disease.

One response to the problems with the GWASs has been to argue that we simply need more data. More DNA sequence, expression profiles and other high-throughput data, some biologists argue, will ultimately reveal all of biology's secrets. However, quantity may not be sufficient. In particular, more of the same kind of data may not generate new insights. The current hype surrounding 'big data' is infecting biology – the exponentially increasing amounts of data (especially DNA sequence) have justified increasing investment in computational resources to analyse it. However, such investments in hardware and software may ultimately lock in specific ways of thinking and doing, rather than producing original and novel solutions or approaches. Of course, GWASs and related 'high-throughput' approaches are not the only methods being used in biomedicine today. However, the amount of data they produce often seems to be justification in and of itself for their increasing significance.

Even putting aside the problems of reduction, missing heritability and seductions of big data, the kinds of information we get from these approaches are also of limited use for making clinical decisions. The US Food and Drug Administration's (FDA's) concerns about the personal genomics company 23andMe certainly suggest that information about 'risks' may even be dangerous for consumers.[18] Ultimately, statistics or 'risks' cannot tell us how to act. Such numbers are often ambiguous and difficult to interpret, even for professionals. Deciding what to do in given circumstances depends on a range of individual and situational factors.

One aim of evidence-based and personalised medicine is to reduce reliance on doctors' judgement. However, statistics without interpretation are just statistics – they cannot tell us anything. In the end, physicians still need to rely on knowledge of anatomy, physiology and pathology, as well as knowledge about patients themselves. Indeed, physicians may be best placed to weigh statistical evidence against the personal and particular circumstances of a patient and weigh statistical evidence against 'narrative' evidence. As Gunn and Palmer have argued, we need to retain the role of the generalist in medical practice.[19] Generalists have the ability to interpret biomedical data in light of population needs, social contexts and 'the whole person'. This means we need to acknowledge that data itself cannot solve problems or give us answers, but must be properly interpreted by 'local' experts. The statistical view of diseases and people, however, increasingly threatens to take judgement and expertise out of medical decision making; unlike Foucault's 'medical gaze', it threatens the centrality of the physician in the relationship between patient and disease. 'Statistical personhood' represents a displacement of power away from doctors and towards a wider biomedical–data complex into which doctors (and patients) are increasingly drawn.

Finally, this is also becoming an issue of social justice. As biomedical data become more and more critical for healthcare, the 'owners' and aggregators of these data become increasingly well placed to extract value from it. Companies such as 23andMe and other personal genomics companies – even Google, Amazon and Cloudera – are gaining more and more control over biomedical data and their analyses. This is contributing to the increasing privatisation of healthcare and the increasing inequities that entails. Physicians have an important role to play in ensuring that patients are protected not only from breaches of privacy, but also from the exploitation of their data by these regimes. In the future, this will mean understanding more about where patients' data are going, and how and for what purposes they may be used and re-used.

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