Personalized medicine: something old, something new

"At the level of clinical practice, personalized medicine is in fact nearly as old as recorded history."

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"That which has been is that which will be. And that which has been done is that which will be done. So there is nothing new under the sun."
– Ecclesiastes 1:9

'Qohelet', the author of the biblical book Ecclesiastes [1], was a kill-joy of the first degree. He, or perhaps (though unlikely) she, argued that basically all human activity was futile and repetitive, that 'progress' was an apparition, and all that mattered was what came after the welcome embrace of death. Hardly the first person that comes to mind for a quote in an editorial on personalized medicine.

Yet there is something about Qohelet's observation that we should take to heart before we trumpet the matins of a new medical revolution. In fact, when we step back from the attendant hype, it becomes clear that at least part of what is commonly called 'personalized medicine' is fundamentally 'nothing new'. Rather, what seems to me to be the primary 'newness' of personalized medicine resides in the new language that is emerging. This new language attempts to give us the ability to speak more authoritatively about the phenotype of disease based on our growing knowledge of biology. Furthermore, this new language is very much in its infancy, and the phrases and words that we manufacture to mean one thing today will inevitably change as the language is eventually codified by clinical practice. But at the level of clinical practice, personalized medicine is in fact nearly as old as recorded history.

"That which has been is that which will be"

Personalized medicine – in the sense of the 'right treatment for the right patient at the right time' – has been practiced for millennia. One has to take the term 'right' in this context with a grain of salt. However, within the limitations of the knowledge and language of the time, the therapy certainly appeared right to both physician and patient.

In a wonderful manuscript published in 2005, Sykiotis *et al.* argue that the pharmacogenetics principles underlying our current understanding of personalized medicine are in fact traceable to the writings of Hippocrates, the 5th century BCE 'father of western medicine' [2]. Although the authors push the comparison a bit, the article does raise questions about our use of personalized medicine as the phrase to capture what is happening in our time.

Hippocrates worked with the philosophical and scientific language of his time, provided by the pre-Socratic philosopher Empedocles, to define sickness as dyscrasia, or an imbalance of the four humors. The goal of the physician was to restore the patient to 'eucrasia' or good balance (i.e., wellness) by addressing the cause of the disease as revealed by the phenotype.

Let me offer a theoretical case study. Pythagoras comes to Hippocrates' clinic complaining of sadness and low energy, his usual excitement about his mathematical pursuits overcome by a terrible depression. Hippocrates determines, both from Pythagoras' self description and by visual inspection of the patient's presenting phenotype, that Pythagoras is suffering from an overabundance of black bile, or melancholia. The treatment doled out is precise to Pythagoras, including changing his dietary habits, a temporary spate of abstinence, and a harsh purging of his bowels. Following treatment, Pythagoras is better, though whether that is due to the efficacy of the treatment or his relief that it is over is unclear.

What has happened? From one perspective, the right treatment was given to the right patient at the right time. Again, the notion of 'right' is within the context of the knowledge of the time (the humors), but the treatment was certainly personalized and even effective.

The four humors as the basis of medical practice continued to reign for two millennia, and even a bit beyond. It grew increasingly embellished with other phenotypic markers – every bodily fluid became fair game for testing in ways

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that are best left undescribed here – and newer therapeutic interventions were employed to restore balance with mixed results (e.g., the over-eager blood-letting of George Washington may have led to his untimely demise [3]). Although humors-based medicine as a way of phenotyping individual patients was acknowledged to be incomplete, there was simply no other organizing principle at hand, apart from a resurgence of metaphysics-based beliefs and practices.

Making the old new again: expanding the language of phenotype

Interestingly, some of those very metaphysical practices were the seed bed for the beginning of the end of the humors as the medical paradigm. Parcelsus, nee Phillip von Hohenheim, grew up in Einsiedeln (near Zurich) in the late 15th century CE and followed his father in becoming a physician [101]. His particular familiarity with miners, the ores they mined, and the unique sicknesses caused by the coming together of the two led him to question the reigning medical beliefs of his time, and his deep training in alchemy, at the time a highly mystical enterprise, was steered by his observations away from its spiritual underpinnings to a more rational foundation.

Paracelsus pronounced, much to the chagrin of the keepers of established medical wisdom, that human disease could be traced to the interaction of the individual with his/her individual environment, and that chemical imbalance lay at the root. He also believed that chemicals given in a proper dose could most effectively treat this imbalance, earning him the title of 'father of toxicology', and ushering a new language of chemistry into medical practice. The notion that external forces were as critical as internal ones in determining disease seems obvious to us, but was revolutionary at the time. Indeed, this is perhaps the first example of the ongoing debate about nature versus nurture, though it would not have been cast in such terms. Paracelsus also broke open the possibility that the phenotype of disease was far more complex than could be accounted for by the humors, even in their most nuanced understanding.

But what were those external forces if not metaphysical? A bit more than a century later, a potential answer came from the Netherlands by way of a hobby. Antoine van Leeuwenhoek, a haberdasher and chamberlain of the sheriffs of Dellf, decided he could improve on the 3× magnifying glasses used by textile merchants to closely examine their stock in trade. His lens-crafting techniques, which he carefully guarded [4], opened up an entire world of external life, much of it living in frightening and a bit disgusting proximity to the human body. Suddenly there was external life everywhere beyond the naked eye's ability to take it in. And some of it directly relevant to disease states, especially certain types of bacteria. Subsequently, a new language of phenotype flooded the medical literature, at least for infectious diseases and other diseases that affected the human cells or tissues that could now be seen under the microscope.

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Despite these amazing breakthroughs, the notion that the individual patient presenting in the clinic had an individual phenotype from which to make a diagnosis and prescribe a treatment did not change. Clinical knowledge may have been changing, but clinical practice – in its most basic incarnation of treating the right patient at the right time in the right way – was not.

There are many other historical breakthroughs, to be sure: my goal is not to write yet another history of medicine, but to help understand just how different – or not – things are today.

The 21st century: evolution versus revolution

In July 2000, announcing the relative completion of the Human Genome Project, US President William Clinton stated: "With this profound new knowledge, humankind is on the verge of gaining immense new power to heal. Genome science will have a real impact on all of our lives — and even more, on the lives of our children. It will revolutionize the diagnosis, prevention, and treatment of most, if not all, human disease" [5].

Revolutionary stuff, indeed. And the explosion in the past few years of genome-wide association studies finding genetic linkages to a host of human afflictions seems to bear the President's superlatives out. Yet what is really happening?

I believe that the new language of genomics, as applied to medicine, is less a revolution than an evolution: the ability to more precisely describe phenotypes has allowed us to change the specifics, but not the fundamental practice of medicine. Thanks to our increased knowledge of genetic and genomic variation, we have gone from a diagnosis of 'blood disease' in 1900 CE to over 38 leukemia and 51 lymphoma subtypes (and more to come) in 2008 [6]. If you are suffering

from chronic myelogenous leukemia as a result of the rare Philadelphia chromosome translocation, we have a drug that addresses that phenotype, at least temporarily. If your form of breast cancer is overexpressing a specific gene, we have a drug that may work better for you than for others without that genetic variation. And so forth. However, for most of the diseases for which we are gaining insight, we are still struggling with therapeutic options. But there is real hope, buried within the confusing new genomics-based language emerging from the lab bench into the clinic, that we may find more effective new treatments. This evolutionary change, perhaps a period of punctuated equilibrium, is still in line with all that has gone before.

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By no means am I trying to belittle the progress made. Like the early rise of toxicology and drug treatments in the 15th and 16th centuries, and the ability to see beyond the limitations of the human eye in the 17th, the toolbox of medicine will undoubtedly be changed in profound ways in the 21st as well, thanks to our ability to ever more precisely define phenotype with genomic tools and insights. Personalized medicine, which has been around a long time, will be ever more exquisitely personalized based on better phenotype definitions, though perhaps not as fast as suggested in the President's words or by the various groups that have formed to promote this 'new' old field. I believe that the primary challenges we face are threefold, in decreasing order of urgency:

- Sorting out meaningful phenotypes from irrelevant ones;
- Incorporation of this knowledge and language into medical practice itself;
- Incorporation of this refined diagnostic ability into healthcare and regulatory systems built around older medical paradigms.

Previous (r)evolutions went through similar steps, and there is no reason to believe the current one is any different.

We particularly need to be cautious about what our current state of genomic knowledge tells us – and does not tell us – about human disease and its treatment. Much of our current knowledge is based largely on a few complete genomes and a lot of genome-wide association studies. As heady as that information is, it is a long way from being completely or even adequately descriptive for diagnostic, much less therapeutic purposes. One need look no farther than the uproar that followed the founding of genomic information companies such as Navigenics and 23andMe: although questions were loudly raised about privacy and ownership of genomic information, the real question is whether this information in its current woefully incomplete form is worth anything from a medical perspective. I suspect not, or at best its worth is minimal and is largely misunderstood by patients and their doctors [7–9]. Perhaps most telling is the blind faith of some customers of these companies, who have, in essence, replaced rational knowledge with an odd kind of genetic determinism metaphysics, mirroring the surge of spiritual and mystical practices that arose in response to the incompleteness of the humors paradigm.

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Incorporation of new findings into regular medical practice requires that the language of the omics be translated into clinically relevant and meaningful terms, and be tied to some actionable outcome. Driven to date by molecular biologists (for the most part), there remains a significant gap between genomic knowledge and clinical practice. At its heart is the silence that meets the most common question from practicing physicians: what difference does this make in how I treat patient X? There are a few examples of answers for some diseases, but that fundamental medical question is still unanswered in the vast majority of cases. This must be acknowledged, even as many academic centers are racing to focus on the translational research needed to drive bench findings to the bedside, making genomic knowledge relevant to practicing physicians and their patients. And by relevant, I mean that it has to be more than a statement of molecular phenotype; in other words, it has to be accompanied with an option for addressing the problem.

One particularly interesting potential effect of this new knowledge in driving clinical practice may be the shift of focus away from traditional medical divisions based on organs and organ pathology towards a more mechanistic disease description based on cellular pathways [10]. It is not too far a stretch to think about doctors

who specialize in, say the TGF-β pathway-associated diseases rather than the organs or systems affected. But such a shift will require a more complete catalogue of the meaningful molecular phenotypes and their effects than we currently have. And it won't change the fundamental goal of medical practice; just the means by which that goal is reached.

Finally, plenty of ink has been spilled about the woeful inadequacy of our current healthcare and regulatory systems to deal with the new information flowing from postgenomic laboratories, and a lot of hand-wringing happens at a growing number of annual personalized medicine meetings about how the current system may slow or even prevent the advent of the new personalized medicine. There are undoubtedly some tough transitions ahead, but until the new language of phenotype is more complete, codified in meaningful ways and incorporated more integrally into regular medical practice, substantial changes in the regulatory or healthcare structures may prove ineffective at best and counterproductive at worst: it is very hard to prepare a new system to handle a surge of new data that are not yet well-understood and a language that has not settled into a common tongue. Before we demand that the system accommodate us, we need to be sure we know what it is we are asking the system to take on in as concrete a way as possible.

So what's new?

Despite the curmudgeonly admonitions of Qohelet, there is indeed something new under the sun in medicine. But it is not personalized medicine *per se*. Rather, it is our ongoing eking out through the finer lenses of new postgenomic technologies the molecular phenotypes that contribute to or even directly cause a range of human diseases. It is exciting stuff, both intellectually and in its potential for better medical care. However, the flood of new data we have produced in such a short time is really only a trickle compared to what we have yet to generate before we can speak about a revolution of medicine with any kind of authority beyond reading genomic tea leaves.

Lewis Thomas is credited with saying that "the great thing about human language is that it prevents us from sticking to the matter at hand". Using the term personalized medicine to cover the potential flowing from the postgenomic research world appeals to the gut and the ear, but ultimately misleads. And I suspect that physicians from Hippocrates to your current GP would be appalled to learn that they have not practiced personalized medicine.

> *"We have to acknowledge that personalized medicine as a clinical approach is indeed nothing new under the sun."*

Yet it is hard to construct some other terminology that works. 'Molecular medicine' or 'genomic medicine' are perhaps more accurate to the real novelty of what is happening, but may not be as attention grabbing. 'Individualized medicine' suggests more variation in the human species than evolution would actually allow. Thus, I suspect we are stuck, at least for now, with the term personalized medicine. But at least let us agree that we have to be clear about the meaning it carries: an evolutionary growth in our medical lexicon of disease phenotype and treatment. And we have to acknowledge that personalized medicine as a clinical approach is indeed 'nothing new under the sun'.

Conclusion

'Personalized medicine' as a term is attention grabbing, but may be incorrect. As long as it refers specifically to our increased molecular knowledge of human biology and its application to diagnostics and therapeutics, it is acceptable, if incomplete. If it is used to denote a change in the fundamental practice of medicine, it is a poor choice of words.

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