The Twin Questions of Personalized Medicine: Who Are You and Whom Do You Most Resemble?

Commentary

The twin questions of personalized medicine: who are you and whom do you most resemble?

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Abstract

Personalized medicine is typically described as the use of molecular or genetic characteristics to customize therapy. This perspective at best provides an incomplete model of the patient and at worst can lead to grossly inappropriate practices. Personalization of medicine requires two characterizations: a well-grounded understanding of who the patient is and an equally robust understanding of the subpopulation that most resembles that patient in the context of the decisions at hand. These characterizations are readily represented probabilistically and can be used to drive decision-making in a rational manner that maximizes the positive outcomes for the patient.

Wikipedia [1] defines personalized medicine as the "use of information and data from a patient's genotype, or level of gene expression to stratify disease, select a medication, provide a therapy, or initiate a preventative measure that is particularly suited to that patient at the time of administration." Other data types are then mentioned as being equally important. A more conventionally authoritative source [2] defines personalized medicine as "The use of genetic susceptibility or pharmacogenetic testing to tailor an individual's preventive care or drug therapy." This apparent primacy of molecular or genetic measurements obscures the fact that they are both only one of many clinical characterizations, and often not the most important one.

An alternative definition, arising from more than 50 years of clinical decision science [3], holds that personalized medicine is the practice of clinical decision-making such that the decisions made maximize the outcomes that the patient most cares about and minimizes those that the patient fears the most, on the basis of as much knowledge about the individual's state as is available. To be able to contemplate such a personalized medicine practice, two fundamental questions have to be answered. First, what are the relevant patient characteristics? Second, which clinically distinct subgroup of patients does this patient most resemble?

The second question defines the knowledge that we have about how a group of clinically relevant patients are likely to respond to a given intervention or what the accuracy and specificity of a particular test are when applied to that subgroup. The first question is important because the deeper our understanding of who the patient is, the more accurately we can identify which subgroup or subgroups (s)he might belong to, and the more accurately we can assess the level of confidence that the match to that group is relevant. Stated differently, information about the patient is of very limited utility without the knowledge derived from experience or measurements of a group of similar patients and evidence as to which is the best comparison group. The mapping of that knowledge from one or more circumscribed groups to the patient's information is what defines the personalization of medicine. Therefore, I argue here that answering these two questions is central to a safe, effective, and sustainable delivery of personalized medicine.

So, who are you? What are your personal characteristics so that we can define personalized medicine? What about your race? Is that a relevant characteristic? And if so, how do we measure it [4]? Should we ask an individual what their racial background is? Or should we simply perform a genome-wide scan and use common polymorphisms to identify, with very

high accuracy, the continent of origin of a given individual on the basis of as little as 50 random single nucleotide polymorphisms [5]? Is this genomic characterization sufficient and does it obviate the need to ask the individual what is their race or continent of origin?

On brief reflection it becomes obvious that the genome is not sufficient. An African American of Yoruban origin might be genomically very similar to a number of Yorubans living in Nigeria, but as a result of different exposures, cultural practices, and availability of medical services, the individual's self identification may be just as important as their shared genetic background with individuals in Africa. Whereas individual genotypes can be known with a high certainty [6], other characteristics such as knowledge of one's average blood pressure, caloric intake or family history are known with much less accuracy and with varying degrees of certainty. Nonetheless, all the characterizations of an individual, ranging from the genomic to the behavioral, are observations that each have a probabilistically expressible degree of certainty [7,8].

Now what about group membership: whom do you most resemble? Most medical knowledge about treatment response and diagnostic categories and physiologies rests on observations made on groups of patients. Take, for example, the effect of glycemic control on retinopathy of type 1 diabetes patients as a function of their glycohemoglobin [9]; the time to recurrence of HER2-positive breast cancer patients [10]; or the degree of shared allergenicity of various insulin-derived antibiotics [11]: all these pieces of knowledge are based on characterization of subgroups of patients defined as having some shared characteristics that define their group within a formal study or by anecdote. Here, again, the characteristics of the group can range from genetic to behavioral characterizations, and for each subgroup of patients there is a set of medical characterizations, whether they be therapeutic susceptibility or prognostic course, that are known with varying degrees of certainty. Therefore, these assertions can be expressed probabilistically too.

Without a well grounded estimate of who you are, and therefore which group you are most likely to resemble, some significant misassignment and erroneous personalization can occur, even despite the availability of genetic information, or sometimes, as in the following well documented case, because of it.

Hemochromatosis is an iron-storage disease with multisystem effects that eventually lead to premature death, and it is known to have a genetic basis. A homozygous G845>A mutation in the *HFE* gene is found in 80% of patients with inherited hemochromatosis in genetic clinics [12,13] and has been thought of as a classically Mendelian inherited, highly penetrant mutation. However, a group of investigators screening over 40,000 patients in an outpatient setting found that, of the 152 patients that were homozygous for the G845>A mutation in *HFE*, only one of them had any historical, physical, or biochemical evidence of hemochromatosis [14]. These results suggest that this mutation, rather than being highly penetrant, is in fact a relatively common mutation whose penetrance is not 100% but closer to 1%.

How could so many genetics clinics be wrong about the value of this test? In the two instances, the patient subgroups being identified and the patients being identified were very different populations. In a genetics clinic, the patients usually evaluated are already under a high suspicion for having hemochromatosis, either because of family history, or because of biochemical or clinical evidence of iron overload. These characteristics are essential parts of the 'who are you?' question of personalized medicine. A personalized medicine would and must distinguish patients who may be homozygous for the same mutation of the *HFE* gene but who otherwise differ in other important characteristics; they therefore should be given very different risk profiles because of the consequent different answers to the question 'who do you most resemble?' Some hints as to what these other characteristics may be, in this instance of inherited hemochromatosis, are pointed to by several reports. These include a French study [15] that showed that the penetrance of the *HFE* mutation is a function of alcohol consumption. Other studies suggest sex-dependent modifier genes [16] that also change the patient's physiology and therefore affect their correspondence to subgroups with different risk profiles.

What, then, does this imply for a safe and effective practice of genomic medicine? How can we avoid an avalanche of alarming false positive diagnostics and prognostics (that is, the 'incidentalome' [17])? Given that more and more genetic testing will occur in the outpatient setting or even in the direct-to-consumer setting, the preceding discussion suggests that what is called for is increased precision and quantification of the individuals' complete health state, and increased precision and breadth with which populations are characterized. Institutional electronic medical records provide some promise for characterization of a patient's complete health state, as do personal health records, depending on how these evolve in the future [18]. The efficient characterization of populations will require systematization of epidemiology augmented by genomics, involving the harmonization of data standards, new analytical methods and marshalling of populations to a level that dwarfs all previous epidemiological efforts [19]. The representation of all these data in the aforementioned probabilistic framework will enable the application of time-tested and rigorous methods for personalized decision-making in a readily computable manner [20-22] to maximize the utility of health outcomes. Whose utilities are being maximized, society's or the patient's, is a crucial policy discussion in the development of funding models for personalized medicine [23].

In summary, the key to successful fulfillment of the expectations for the personalized medicine era will not be driven primarily by finding new molecular targets with which to direct customized therapy. As illustrated above, a too narrow focus on genetic variation fundamentally blinds us to the personalized information that can and should guide our clinical decision-making for individuals. Personalized information should extend to observables such as the environment and physiology, which cannot be easily inferred from examining genome-scale variation. We have to revisit what the best clinicians have always done: gather together as comprehensive a perspective on the individual patient's condition as possible, and see the extent to which that patient's perspective fits into the sets of similar patients that were previously encountered. Fortunately, unlike the expert physicians of previous eras, we now have the automated means with which to do this on an industrial scale. However, to use this automation effectively will require the incorporation of computer-assisted decision-making throughout medical practice and the education of our clinicians in the effective use of such assistive devices. These goals are likely to stand as two of the most challenging of personalized medicine.

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