Personalized medicine: motivation, challenges, and progress

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There is a great deal of hype surrounding the concept of personalized medicine. Personalized medicine is rooted in the belief that since individuals possess nuanced and unique characteristics at the molecular, physiological, environmental exposure, and behavioral levels, they may need to have interventions provided to them for diseases they possess that are tailored to these nuanced and unique characteristics. This belief has been verified to some degree through the application of emerging technologies such as DNA sequencing, proteomics, imaging protocols, and wireless health monitoring devices, which have revealed great inter-individual variation in disease processes. In this review, we consider the motivation for personalized medicine, its historical precedents, the emerging technologies that are enabling it, some recent experiences including successes and setbacks, ways of vetting and deploying personalized medicines, and future directions, including potential ways of treating individuals with fertility and sterility issues. We also consider current limitations of personalized medicine. We ultimately argue that since aspects of personalized medicine are rooted in biological realities, personalized medicine practices in certain contexts are likely to be inevitable, especially as relevant assays and deployment strategies become more efficient and cost-effective. (Fertil Steril® 2018;109:952–63. ©2018 by American Society for Reproductive Medicine.)
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The application of emerging, high-throughput, data-intensive biomedical assays, such as DNA sequencing, proteomics, imaging protocols, and wireless monitoring devices, has revealed a great deal of inter-individual variation with respect to the effects of, and mechanisms and factors that contribute to, disease processes. This has raised questions about the degree to which this inter-individual variation should impact decisions about the optimal way to treat, monitor, or prevent a disease for an individual. In fact, it is now widely believed that the underlying heterogeneity of many disease processes suggests that strategies for treating an individual with a disease, and possibly monitoring or preventing that disease, must be tailored or 'personalized' to that individual's unique biochemical, physiological, environmental exposure, and behavioral profile. A number of excellent reviews on personalized medicine have been written, including a growing number of textbooks on the subject meant for medical students and clinicians. It should be noted that although many use the term personalized medicine interchangeably with the terms individualized and precision medicine (as we do here), many have argued that there are some important, though often subtle, distinctions between them (1, 2).

There are a number of challenges associated with personalized medicines, especially with respect to obtaining their approval for routine use from various regulatory agencies. In addition, there have been many issues associated with the broad acceptance of personalized medicines on the part of different health care stakeholders, such as physicians, health care executives, insurance companies, and, ultimately, patients. Almost all of these challenges revolve around a need to prove that personalized medicine strategies simply outperform traditional medicine strategies, especially since many tailored or personalized therapies, such as autologous Chimeric Antigen Receptor T cell (CAR-T) cell transplant therapies for certain types of cancer (3) and mutation-specific medicines such as ivacaftor to treat cystic fibrosis (4, 5), can be very expensive (6). In this review we consider the history and motivation of personalized medicine and provide some context on what personalized medicines strategies have emerged in the last few decades, what limitations are slowing their advance, and what is on the horizon. We also consider strategies for proving that personalized medicine protocols and

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strategies can outperform traditional medicine protocols and strategies. Importantly, we distinguish examples and challenges associated with personalized disease prevention, personalized health monitoring, and personalized treatment of overt disease.

ARCHIBALD GARROD AND THE PRECURSORS OF PERSONALIZED MEDICINE

There is much in the history of western medicine that anticipates the emergence of personalized medicine. For reasons of brevity, we will not focus on all of these events, but rather only a few that we feel encompass the most basic themes behind personalized medicine. More than a century ago Archibald Garrod, an English physician, began studying in earnest diseases that would later become known as inborn errors of metabolism. Garrod studied a number of rare diseases with overt, visible phenotypic manifestations including alkaptonuria, albinism, cystinuria, and pentosuria. Of these, his focused work on alkaptonuria led to some notoriety when he observed that some members of families exhibiting alkaptonuria showed measurably outlying values for certain basic biochemical assays (from urine, relative to the values of family members who did not possess alkaptonuria). This led him to conclude that alkaptonuria was due to a specific altered course of metabolism among affected individuals, which was subsequently proven correct (7). Further, in considering other rare diseases like alkaptonuria, Garrod argued, "…the thought naturally presents itself that these [conditions] are merely extreme examples of variation of chemical behavior which are probably everywhere present in minor degrees and that just as no two individuals of a species are absolutely identical in bodily structure neither are their chemical processes carried out on exactly the same lines." This more than hints at his belief that, at least with respect to metabolism, humans vary widely and that these differences in metabolism could help explain overt phenotypic differences between individuals, such as their varying susceptibilities to diseases and the ways in which they manifest diseases (8, 9).

Garrod was working in the backdrop of a great deal of debate about the emerging field of genetics. Although the specific entities we now routinely refer to as genes, stretches of DNA sequence that code for a protein and related regulatory elements, were unknown to Garrod and his contemporaries, he and others often referred to factors influencing diseases possessed by certain individuals that were consistent with the modern notion of genes. Claims about the very presence of such factors were born out of discussions rooted in the findings of Mendel; later, it would be shown that many of the metabolic outliers Garrod observed in people with diseases like alkaptonuria were due to defects in genes possessed by people with those diseases. Mendel observed consistent connections between the emergence of very specific phenotypes only when certain breeding protocols were followed in peas that anticipated the modern field of genetics (10). As discussed in an excellent book by William Provine (11), many in the research community at the time debated how genes or factors of the type Garrod and others were considering could explain the broad variation in phenotypic expression observed in nature. One group of academics and researchers, referred to as the 'Mendelians' in the historical literature, which included William Bateson and Hugo de Vries, focused on the discrete nature of the factors likely to be responsible for many observable inheritance patterns, such as those of focus in Mendel's studies and observations like Garrod's in the context of rare disease. In opposition to the Mendelians were the 'Biometricians,' represented most notably by Karl Pearson, whose focus on continuous or graded phenotypes, like height, gave them concerns about how to reconcile such continuous variation with the overtly discrete (either/or) factors and inheritance patterns considered by the Mendelians and researchers like Garrod.

The Mendelian versus Biometrician debate was resolved to a great extent by the statistician Ronald Fisher in a series of seminal papers. Fisher argued that one could reconcile continuous phenotypic variation with discrete, heritable factors that contribute to this variation by suggesting that many factors, such as genes, might contribute in a small way to a particular phenotype. The collective effect, or sum total of these factors, could then create variation in phenotypes that give the appearance of continuity in the population at large. For example, an individual who inherited only 1 of 25 genetic variants known to increase height would be shorter on average than someone who inherited 10 or 12, and much shorter, relatively speaking, than an individual who inherited 22 or 25 (12). The belief that there might be many genes that contribute to phenotypic expression broadly, some with more pronounced effects and some with less pronounced effects, that interact and collectively contribute to a phenotype in a myriad of ways, has been validated through the application of modern high-throughput genetic technologies such as genotyping chips and DNA sequencing. As a result, much of the contemporary focus on personalized medicine is rooted in the findings of genetic studies, as it has been shown that individuals do in fact vary widely as each individual possesses subsets of literally many millions of genetic variants that exist in the human population as a whole. In addition, subsets of these genetic variants may have arisen as de novo mutations and hence may be unique to an individual. This extreme genetic variation explains, in part, why individuals vary so much with respect to phenotypes, in particular their susceptibilities to disease and their responses to interventions (13). It should be emphasized that although personalized medicine has its roots in the results of genetic studies, it is widely accepted that other factors (environmental exposures, developmental phenomena, epigenetic changes, and behaviors), all need to be taken into account when determining the optimal way to treat an individual patient (Fig. 1) (14–16).

Another, sadly more obscure, publication was also prescient for personalized medicine, although this publication bears more on the need for clinical practices that are consistent with personalized medicine, rather than a scientific justification of personalized medicine. More than 60 years ago Hogben and Sim considered how clinical practice needs to pay attention to nuanced characteristics of patients in order to determine an appropriate intervention for them (17–19). Although more will be discussed about their paper in the section on Testing Personalized Medicines, suffice it to say