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Personalized Medicine: Motivation, Challenges and Progress

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Abstract

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 an inevitability, especially as relevant assays and deployment strategies become more efficient and cost-effective.

Keywords

Precision medicine; biomarkers; patient monitoring; genomics

Introduction

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

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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 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 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 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, e.g., 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 that “...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 (i.e., 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 disease 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) Essentially, 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 vs. 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 (i.e., 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 (e.g., 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. These 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, e.g., environmental exposures, developmental phenomena and epigenetic changes, and behaviors, all need to be taken into account when determining the optimal way to treat an individual patient (see Figure 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 that the authors believed that in order to determine an optimal course of action for an individual patient in the absence of any *a priori* understanding of how best to treat that patient given his or her characteristics or profile, a number of items would need to be obtained. Thus, greater information about that patient would have to be gathered, a plan to vet the utility of an intervention chosen on the basis of that information would have to be pursued, and a strategy for incorporating the results of the patient-oriented study into future care would have to be crafted. Although simple in theory, the practical issues surrounding gathering more information about a patient and pursuing an the empirical assessment of a personalized intervention can be daunting. For example, questions surrounding how one can know that a chosen intervention works unless meticulous patient follow-up information is kept, how one would know if a patient satisfied with what they are experiencing with the intervention, and how one could assess the difference between other interventions that could have been chosen and the chosen personalized intervention, would all need to be addressed. In fact, practical issues surrounding the implementation of personalized medicine that Hogben and Sim considered are often overlooked in contemporary discussions about personalized medicine, especially since different technologies for profiling patients are constantly being developed and refined, and more and more evidence for inter-individual variation in factors associated with diseases (from technologies such as DNA sequencing, proteomics, sophisticated imaging protocols, etc.) is emerging.

Early Examples of Personalized Medicine

There have been a great many examples of interventions tailored to individual patient profiles, virtually all of them based on genetic profiles. Before providing a few classic examples, it should be emphasized that personalized medicine can be practiced not only for the treatment of disease, but also for the early detection and prevention of disease. We provide some historical examples of personalized disease treatments here and consider early detection and prevention in the next section, as developments in personalized disease detection and prevention are much more recent.

The human body deals with traditional pharmacotherapies (i.e., drugs) to treat disease in two general ways. Initially, the body must respond to a drug. This response occurs in steps, with the first step involving the absorption of the drug by the body. The drug must then be distributed throughout the body (during this process the drug might be 'biotransformed' or metabolized into useful components) and then begin to elicit effects. Finally, any remaining drug or drug components are excreted. These processes are often lumped under the heading of 'pharmacokinetics' and collectively referred to as the 'ADME' of a drug (Absorption, Distribution, Metabolism and Excretion). Pharmacokinetic activity is often under the control of a unique set of genes (e.g., drug metabolizing enzymes) that could harbor naturally-occurring genetic variants (or 'polymorphisms') that influence their function and hence how the body ultimately deals with a particular drug. Once a drug is within the body, how it interacts with its target (typically a gene or protein encoded by a gene) to elicit an effect is known as its 'pharmacodynamic' properties. These properties include the 'affinity' the drug has for its target(s), the drug's ability to modulate the target(s) (or its 'efficacy'), and the 'potency' of the drug, or how much of the drug is needed to induce a certain change in its target. Pharmacodynamic properties of a drug are also under genetic control.

Many early examples of personalized medicines were associated with genetically-mediated pharmacokinetic aspects of drugs. This was due in part to the biomedical science community's understanding of drug metabolizing enzymes and the role they play in the body's response to drugs. An excellent introduction to pharmacogenetic properties of drugs, as well genetic variants in genes that influence the efficacy and side effects of drugs (especially with respect to genetic variants in drug metabolizing enzymes) is the book by Weber.(20) Warfarin is a widely used blood thinning medication that, if not dosed properly, could cause a potentially life-threatening adverse drug reaction. Warfarin targets a particular gene, VKORC1, and is metabolized in part by the gene CYP2C9. Naturally-occurring genetic variation in both the VKORC1 and CYP2C9 genes leads to variation in the pharmacodynamic and pharmacokinetic properties of Warfarin across individuals, ultimately creating variation in individuals' responses to warfarin. The US Food and Drug Administration has therefore recommended that dosing for warfarin take into consideration an individual's genotype (i.e., the dose must be personalized to an individual based on the specific genetic variants they possess in the VKORC1 and CYP2C9 genes).(21)

Another classic example of a drug that should only be provided to individuals with a certain genetic profile is primaquine (PQ). PQ has been used to manage malaria with some success in parts of the world where malaria is endemic. However, military doctors working in the past observed that some of the soldiers they treated for malaria that were provided the drug became jaundiced and anemic, and ultimately exhibited symptoms of what would later be termed 'acute haemolytic anaemia (AHA)'. It was later shown that the individuals exhibiting AHA after PQ administration carried variants in the G6PD gene.(22) Current clinical practice with PQ therefore calls for the genotyping of individual patients to see if they carry relevant variants in the G6PD gene that might discourage PQ use for them.

A final, often-cited example of a personalized medicine is the drug imatinib.(23) Imatinib is used to treat chronic myelogenous leukemia (CML). Imatinib inhibits an enzyme, tyrosine kinase, that is increased by the formation of a fusion of two genomic regions, one

encompassing the Abelson proto-oncogene (abl) and the other the breakpoint cluster region (bcr). This fusion event arises in many tumors contributing to the development of CML and is referred to as the 'bcr-abl fusion' or 'Philadelphia chromosome.' However, not all individuals with CML have tumors harboring the bcr-abl fusion mutation. Therefore, imatinib is typically given only to individual CML patients with this fusion event.

Contemporary Examples Of Personalized Medicine

Drugs like warfarin, PQ and imatinib that appear to only work – or only work without side effects – when a patient possesses a certain genetic profile, have generated tremendous interest in identifying factors, such as genetic variants, that influence an individual patient's response to any number of drugs and interventions. This interest in crafting personalized medicines to treat diseases has expanded into personalized disease surveillance (i.e., early detection protocols) and personalized disease prevention strategies as well. We briefly describe a few very recent examples of this activity.

Mutation-Specific Therapies

Instead of developing a drug and then identifying factors that mitigate its efficacy or side effects through observational studies on individuals provided the drug, as with warfarin, PQ and imatinib, there are now attempts to identify, e.g., genetic profiles possessed by patients and then craft therapies that uniquely target those profiles. For example, the drug ivacaftor mentioned earlier was designed to treat individuals with cystic fibrosis (CF) that have very specific pathogenic mutations in the gene CFTR.(4) The CFTR gene has many functions, but one set of functions is dictated by a 'gate-like' structure in the CFTR gene's encoded protein that can open and close to control the movement of salts in and out of cells. If the CFTR gene is dysfunctional, then the gate is closed, causing a build-up of mucus and other material in the lungs. Different mutations in the CFTR gene cause different types of dysfunction. For example, some mutations simply cause the CFTR gene to not produce anything, whether the gate is open or not. Other mutations cause the gate mechanism to dysfunction. Ivacaftor is designed to open the gate for longer periods of time in the presence of certain mutations that tend to cause the gate to be closed. Therefore, ivacaftor is only useful for the small subset of CF patients whose CFTR mutations lead to this specific gating problem. Connections between genetic variants and drug efficacy and side effects are growing in number, and in fact the US FDA provides a list of approved drug-based interventions that require a test to determine their appropriateness for an individual: <https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm>. Other publications consider the practical implications of approved personalized medicine interventions, such as the report produced by the Personalized Medicine Coalition (PMC).(24)

A second example involves the emerging set of cancer treatments known as immunotherapies.(25) Although there are many types of immunotherapies, all of them seek to prime or trigger an individual's own immune system to attack a cancer. One type of immunotherapy exploits potentially unique sets of genetic alterations that arise in a cancer patient's tumor cells, known as 'neo-antigens,' which are often capable of raising an immune response if recognized properly by the host's immune cells. Essentially, this type of

immunotherapy works by harvesting cells from a patient that mediate that patient's immune reactions, such as T cells, then modifying those cells to specifically recognize and target the neo-antigens found to be present in the patient's tumor. These modified cells are then put back in the patient's body so these cells can attack the tumor cells giving off the neo-antigen signals. Cytotoxic T cell therapies like this, as well as immunotherapies in general, have had notable successes, but can be very patient-specific for two reasons. First, the neo-antigen profile of a patient might be very unique, such that cytotoxic T cells made to recognize and attack a specific set of neo-antigens will not work in someone whose tumor does not have those neo-antigens. Second, if 'autologous' constructs are used, then the patient's own T cells are modified, and hence not likely to work as well in another patient, although attempts to make 'allogeneic' constructs in which one individual's T cells are modified and introduced into another patient's body are being pursued aggressively.(25)

Personalizing Early Detection Strategies

If an individual is susceptible to a disease, or susceptible to recurrence of a disease, then that individual should be monitored. It is now believed that such monitoring should be pursued with use of 'personal thresholds,' as opposed to 'population thresholds,' to make claims about evidence or signs of disease or a pathogenic process.(26) Population thresholds are derived from epidemiologic data and population surveys and include, for example, cholesterol levels > 200 being an indicator for risk of heart disease, or systolic blood pressure > 140 being an indicator of hypertension, risk of stroke or heart disease. Personal thresholds are established from legacy values of a measure collected on an individual over time that used to gauge how deviant future values of that measure might be for that individual. Significant deviations from historical or average legacy values are taken as a sign of a health status change, irrespective of whether or not those values are beyond a population threshold.(27) As an example, Drescher et al.(26) explored the utility of personal thresholds applied to longitudinal CA125 levels collected on a number of women, a subset of whom developed ovarian cancer. The authors found that in all but one instance, the application of personal thresholds would have captured the presence of ovarian cancer at the same time as, or importantly earlier than, the application of population thresholds. Further, the authors showed that the use of personal thresholds could have captured the ovarian cancer almost a year earlier, on average, than the use of population thresholds. As the costs and convenience associated with monitoring assays and technologies improves (i.e., they become cheap and non-intrusive, if not transparent, to an individual user, say through an easily implantable wireless device), then the use of personal thresholds will likely become the rule rather than the exception in health monitoring protocols.

Personalizing Disease Prevention

The use of genetic information to develop personalized disease prevention strategies is now well established in the scientific community, but not yet widely adopted in clinical practice. There are many excellent examples of how the use of genetic information can lead to both a decreased risk of disease development as well as decreased complications from standard treatment and screening strategies. A prime example relates to colorectal cancer, which remains the third leading cause of cancer deaths despite being a highly preventable illness. In 2012 Liao et al. reported an improvement in overall survival and a decreased risk for

cancer-specific deaths in patients taking postoperative aspirin if they exhibited a somatic mutation in the PIK3CA gene in their colorectal cancers compared with patients whose cancers had the wild-type PIK3CA gene.(28) In 2015, Nan et al. reported varying effects of aspirin use on risk for development of colorectal cancer depending on an individual's genotype, with individuals possessing different genotypes having either lower, higher or no change in their risk of colorectal cancer development with aspirin use.(29) Given that aspirin use can have serious side effects associated with intestinal and intracranial bleeding, it would be ideal to limit the use of this medication for those individuals predicted to have a side effect, based on genotype.

As another example, in 2018, Jeon et al. reported the use of expanded risk prediction models for determining when to begin colorectal cancer screening. Currently the guidelines use only age and family history as variables. Jeon et al. showed that by using information about an individual's environmental exposure and genetic profile, specifically the presence of colorectal cancer associated genetic variants, recommendations for when to start screening could change by 12 years for men and 14 years for women.(30) The accuracy of relevant predictions about an individual's risk for colorectal cancer has been studied and suggests that the area under the curve (AUC) value for a model including environmental and genetic factors, where an AUC of 1.0 would suggest a model with perfect predictive accuracy, was 0.63 for men and 0.62 for women. This is compared to an AUC value of 0.53 (men) 0.54 (women) when only family history information was considered. Although there is still room for improvement given the AUCs were only ~0.62 for the model with patient environmental exposure and genetic information, the considerable improvement over models that did not include genetic or environmental information justifies their use.

Testing Personalized Medicines

Although we have argued that personalized medicine is rooted in a great number of legacy insights and historical precedents, mostly related to genetics and rare diseases, its recognition as a paradigm that should be embraced broadly by the biomedical research and clinical communities is relatively recent. This suggests that not enough time has elapsed since the time of this recognition for researchers to show that personalized medicine actually works in a wide enough variety of settings to motivate its broad adoption. In this light, questions of how the community can vet or test the utility of personalized medicine arise. We describe three emerging strategies for vetting personalized medicines below, including N-of-1 clinical trials, intervention-matching trials, and adaptive clinical trials, and argue that although these strategies borrow elements from traditional randomized clinical trials (RCTs), they deviate significantly from historical population-based RCTs that were prominent in the past.

N-of-1 Clinical Trials

If there is no reason to believe that any one of a set of different interventions matches an individual's profile (e.g., genomic, behavioral, etc.) better than others, then there is 'equipoise' among those interventions. In this case it becomes an empirical question as to which intervention might be optimal for the individual in question. Trials focusing on an

individual's response to different interventions to determine an optimal intervention are referred to as 'N-of-1' or single subject trials. N-of-1 trials often exploit a simple cross-over design or even a repeated crossover designs, such as 'ABABAB' designs, where 'A' and 'B' refer to different interventions, and the sequence 'ABABAB' refers to the order in which the interventions are provided to a patient. Alternating interventions, and collecting data on the individual's response to those interventions, allows comparisons of those interventions (for example between a test intervention and a comparator, or placebo, intervention). Randomization, blinding, washout periods, multiple endpoints, and many other design elements can be used in N-of-1 trials.(27, 31, 32)

N-of-1 trials involving the provision of different interventions in sequence to an individual and evaluating outcomes for each, need to accommodate serial correlation between the observations, as well as possible carry-over effects from one intervention to another, but these issues can largely be overcome with appropriate analytical methods and study design. (32) Cross-over based N-of-1 trials are impractical, if not unethical, in settings where an individual is suffering from an acute or life-threatening condition, since switching from one intervention to another may exacerbate that individual's condition. However, sequential N-of-1 designs, in which measures are continuously monitored in real time to determine if an intervention is causing harm or working, have been proposed for these situations.(27) Given that the focus of an N-of-1 trial is on the identification of an optimal intervention for an individual, rather than on the average response to an intervention in the population at large (which is often the focus of traditional RCTs), they may be most appropriate to conduct in actual clinical practice when a physician is faced with equipoise, as considered by Hogen and Sim.(33, 34)

Intervention Matching Trials

If evidence is found that certain features in individual patients' profiles can be used to identify interventions that might work for each of them, then a question arises as to how to test that the hypothesis that providing interventions to those individuals based on these 'matches' leads to better outcomes than providing those individuals interventions based on some other scheme or strategy. One could test each individual match, but this may require pursuing many small clinical trials, which may be logistically complicated and hard to find financial support and infrastructure to implement. As an alternative, one could test an entire matching strategy against an alternative way of providing interventions (e.g., giving everyone the same intervention). This is more or less the motivation behind 'basket' and 'umbrella' trials currently in use, primarily in oncology settings.(35, 36) In oncology contexts, basket and umbrella trials enroll multiple individual patients into a trial knowing that they each might have unique features in their profile that could indicate that different interventions are appropriate. Basket trials enroll individuals without regard to the specific tissue affected by cancer (e.g., lung, breast and colorectal cancer patients can be enrolled) whereas umbrella trials only consider a single tissue (only lung cancer patients are enrolled). Each patient's tumor is profiled, usually via DNA sequencing. The tumor genome is analyzed to see if there are actionable 'driver' perturbations in the tumor, such as mutations affecting particular genes, that are likely contributing to the growth of the tumor. If the mechanisms of action of a group of interventions (i.e., cancer drugs) are understood well

enough, it may be possible to match those drugs to the perturbations in the tumor (e.g., if the EGFR gene is mutated and overexpressed in the tumor, then using a drug like cetuximab, which inhibits the EGFR gene, would be logical). Thus, each patient is steered towards a particular intervention basket (e.g., the EGFR inhibitor basket). The trial then seeks to test the hypothesis that the use of the different intervention baskets based on the matching scheme results in better outcomes than interventions provided to individual patients based on some other scheme that does not involve tumor profiling and matching.

If the trial is a failure (i.e., the matching scheme doesn't lead to better outcomes than something else), then an argument could be made that the matching scheme was flawed and not necessarily that the interventions considered in the trial are flawed. It would also be wrong to assume that the concept of personalized medicine is flawed as a result of a failure of a basket or bucket trial if in fact the matching scheme was found to be flawed. Some basket trials only have a single basket and no comparison group, but rely on determining which patient profiles appear to be associated with better outcomes for the intervention being tested.⁽³⁷⁾ Intervention matching schemes are likely to become the rule rather than the exception in medicine, especially since the introduction of computational environments like IBM's 'Watson' system. Essentially, Watson is a system that includes a very large database extracted in part from the vast medical literature, providing links between information about a patient (e.g., genetic profiles, age, sex, etc.) to outcomes (such as drug response). These links have been enhanced by leveraging statistical methods to further assess relationships between patient profiles and outcomes. For example, Watson has been 'trained' to identify and establish links about perturbations often observed in a tumor and how those perturbations might be combated by available drugs and interventions generally. Thus, if Watson was provided a patient profile, it could look up the best possible intervention given the current state of the science reflected in the literature and Watson's methods for establishing links between profiles and outcomes. The use of IBM's Watson system in actual clinical settings has led to discussions about how best to test and deploy such a system as a way of supporting, as opposed to replacing, physicians' decisions about an intervention choice for individual patients.⁽³⁸⁾

Adaptive Clinical Trials

Adaptive and sequential clinical trials have been used for decades but their consideration and use in personalized medicine contexts is much more recent.⁽³⁵⁾ Essentially, adaptive trials have as one of their focal points a desire to minimize the amount of time a patient is on what is likely to be an inferior therapy. In the context of personalized medicine, if there is equipoise with respect to available interventions or between an untested and a conventional intervention for an individual patient, then the evaluation of the effects of each intervention on an individual to determine the best one for that individual (as in a very elaborate N-of-1 study) might be impractical or cause more harm than good. This is the case because some, if not all, of the interventions might not actually benefit that individual. In this light, it makes sense to implement studies in which biomarkers reflecting response or adverse effects are collected on an individual trial participant and monitoring of those biomarkers is pursued to determine if there are signs an intervention is not working. If there are, e.g., signs that an intervention is not working, the individual could cross-over to a new intervention. Although

adaptive designs can be difficult to implement given their real-time evaluation and updating components, and can also produce data that might be more complicated to analyze than data from fixed, non-adaptive trials, they are often seen as more ethical. In addition, adding adaptive components to N-of-1 and aggregated N-of-1 trials as well as intervention-matching trials is possible. Although there are a growing number of papers describing adaptive trials, the work of Murphy and colleagues has received a great deal of attention because of its focus on minimizing the amount of time a patient is on an inferior treatment. (39-41)

Emerging and Next-Generation Personalized Medicine Strategies

There are a number of very recent research and clinical activities that are charting new territory for personalized medicine. We focus on four of these activities in the following, providing a brief overview of each. These activities include the use of patient-derived cell and organoid ‘avatars’ for determining the best therapies for that patient, the use of intense individualized diagnostic and monitoring protocols to detect signs of disease, the development of personalized digital therapeutics, and the use of personalized medicine approaches in treating patients with fertility issues.

Patient-Derived Cellular Avatars

It is now possible to harvest cells from individuals and use pluripotency induction (i.e., induced pluripotent stem cell or ‘iPSC’) methods on those cells to generate additional cell types of relevance to a patient’s condition without having to directly biopsy the affected tissue. This allows researchers to essentially develop a ‘disease in a dish’ cellular model of a patient’s condition.(42-44) These *in vitro* cellular ‘avatars’ can be studied to identify key molecular pathologies that might give an indication as to how best to treat an individual patient of interest. The use of iPSC technologies in this manner can be extended with a few additional, very recently developed, technologies to create even better models of an individual’s condition. For example, if the patient has a known mutation causing his or her condition, it is possible to use assays based on, e.g., Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and related constructs to create isogenic cells in which some cells have the mutation in question and some do not. Comparison of these cells allows direct insight into the effects of the mutation while controlling for all relevant genetic background effects associated with the patient’s genome.(45, 46) In addition, it is possible to create partial organs or ‘organoids’ from cells obtained from an individual.(47) Organoids can provide greater insight into molecular pathologies associated with an individual patient’s condition since they can model cell:cell interactions and more global tissue function.(48)

To achieve truly personalized medical care, the use of patient avatars derived from their own cells could be integrated with other pieces of information about a patient, as well as protocols for acting on that information. Schork and Nazor describe the motivation and integration of different aspects of patient diagnosis, intervention choice, and monitoring, using, among other things, patient avatars.(49) One important aspect of the use of cell-based patient avatars in personalized medicine is that they can accommodate personalized drug screening: literally testing thousands of drugs and compounds against a patient’s cells (or

organoids, possibly modified with CRISPR technologies) to identify drugs or compounds that uniquely correct the patient's molecular defects. If the drug or compound has actually been approved for use, possibly for another condition, then it could be tested for efficacy with the patient in question under an approved drug 'repurposing' protocol. The use of patient-derived cells in personalized drug screening initiatives has shown some success in cancer settings, as tumor biopsies can yield appropriate material for drug screening.(48, 50) The biggest concern with this approach revolves around the question of whether or not the *in vitro* models capture relevant *in vivo* pathobiology and drug response information that may impact a patient's response to a chosen drug. A more direct strategy for *in vivo* experimental cancer intervention choice could involve implanting a device into a patient's tumor *in vivo* and then delivering different drugs through that device to see which ones have an effect.(51, 52)

Intensive Personalized Health Monitoring

The availability of inexpensive genotyping and sequencing technologies is allowing individuals and their health care providers to assess their genetically-mediated risk for disease and/or make a genetic diagnosis if they are already diseased. In addition, given the availability of health monitoring devices, online-ordered blood-based clinical assays, inexpensive imaging devices, etc. it is possible to continuously, or near continuously, monitor aspects of an individual's health (see Figure 1 and see the articles associated with the 'quantified self' movement: <http://quantifiedself.com>)(53, 54). With this in mind, combining genetic risk or diagnostic assessment with intense health monitoring makes sense. A number of individuals with unique diseases and conditions have benefitted from a genetic diagnosis, as it uncovered potential genetically-mediated pathogenic mechanisms or revealed potential targets for pharmacotherapies for them.(49) In addition, a number of individuals have monitored their health intensely for the express purpose of identifying signs of a health status changes, some of which might be attributable to genetic susceptibilities. (55) Table 1 lists examples of published studies exploring the utility of genetic assays in generating a diagnosis for individuals with idiopathic conditions (or what have been referred to as 'diagnostic odysseys') as well as published studies exploring the utility of near continuous monitoring to identify evidence for a health status change in an individual. Such diagnoses and monitoring are highly personalized by definition.(15, 16, 56)

Monitoring individuals for health status changes is not trivial, however, if the measures being collected have not been evaluated in a population. This is because there will be no established norms that can be contrasted to the measures collected on an individual to know if those measures are abnormal. However, the community is quickly recognizing the utility of establishing 'personal thresholds' for measures as opposed to 'population thresholds,' as discussed in the 'Personalizing Early Detection Strategies' section above (26, 27) As noted, population thresholds are established from epidemiologic and population survey data and include often-used thresholds for determining disease status such as a cholesterol level greater than 200 for heart disease or a systolic blood pressure greater than 140 mmHg for hypertension. Personal thresholds are established from longitudinal or legacy values of a measure collected on an individual and may be unique to the individual in question and their use in some settings suggests that they work better than population thresholds.(26)

Digital Therapeutics and Personalized App Content

The ubiquity of smart phones has attracted the interest of many researchers in the health professions as a vehicle for not only collecting health data through various ‘apps’ but also to provide advice, feedback, coaching, imagery, music, text-messages, or connections with other resources, that could benefit an individual with a particular condition or disease. This has led to the emergence of the concept of a ‘digital therapeutic:’ a smart phone app designed to treat and bring relief to an individual affected by a medical or psychological condition.(57) The content provided by a digital therapeutic app to an individual could vary depending on what is learned about that individual and his or her response to content provided in the app. In this way, the app can be personalized.(58) Many digital therapeutics have undergone evaluation for their ability to engage users and benefit them.(59) The US Food and Drug Administration (FDA) has created guidelines for registering digital therapeutics as bona-fide, insurance-reimbursable, approved health technologies, and has begun evaluating and approving many of them. The first approved digital therapeutic – an app for substance abuse – was approved by the FDA in 2017.(60) How easily digital therapeutics will be assimilated into the care stream is an open question.(61)

Personalized Interventions Involving Fertility and Sterility

Personalized medicine strategies and approaches can be applied to treatments for fertility, as many researchers have proposed. For example, it has been suggested that one could leverage ‘real world’ data of the type collected routinely on patients visiting reproductive medicine and fertility clinics (from, e.g., Electronic Medical Record (EMR) systems established at many hospitals and clinics), and use these data to in analyses exploring patterns, patient subgroups and individual patient profiles that could shed light on variation in fertility rates, responses to interventions to enhance fertility, etc. The results of these analyses could then guide future care for patients with fertility issues.(62) In the context of the use of digital medicine, proposals to develop smart phone apps that could provide personalized coaching content to enhance pregnancy have been put forth.(63). Genetic variants known to influence fertility have also been identified and could be used to support diagnoses or personalized intervention plans.(64)(65) Finally, adaptive trial designs have been proposed that could be used to assess the utility of personalized approaches to raising awareness about time to conception and fertility.(66)

In addition to these more traditional approaches to personalizing fertility interventions, there are a number of emerging strategies to enhance fertility in women that go beyond traditional ways of stimulating ovaries.(67) For example, it is now possible to cryopreserve a set oocytes and ovarian tissue samples from a woman and then implant them in her at a later time that may suit her desire to become pregnant.(68) Such a procedure would be highly personalized, since it would work with an individual's own cells and accommodate her preferences for becoming pregnant. However, this procedure would only work if the preserved tissues were viable and not damaged, although relevant cells in those tissues could, in theory, be corrected for genetic defects using gene editing techniques.(69) A more futuristic and controversial personalized fertility intervention, involves the concept that one could use cell reprogramming technologies to generate sperm and egg cells from other cells

obtained from an individual (e.g., skin cells) that could be edited to generate *de novo* gametes for fertilization – a concept known as ‘*in vitro* gametogenesis.’(70)

Conclusions

Personalized Medicine, or the practice of characterizing an individual patient on a number of levels (e.g., genomic, biochemical, behavioral, etc.) that might shed light on their response to an intervention, and then treating them accordingly, is a necessity given the fact that clinically meaningful inter-individual variation has, and will continue to be, identified. The availability of modern biomedical technologies such as DNA sequencing, proteomics, and wireless monitoring devices, has enabled the identification of this variation, essentially exposing the need for the personalization of medicine at some level. The future challenges associated with this reality will be to not only improve the efficiency in the way in which individuals are characterized, but also in the way in personalized medicines are crafted and vetted to show their utility. This is not to say that interventions that work ubiquitously (i.e., the traditional single agent ‘block buster’ drugs) should be ignored if identified, but rather that they might be very hard to identify going forward.

There are a few other issues associated with personalized medicine that may hard to overcome in the near term. For example, the need for large data collections in order to identify factors that discriminate groups of individuals that might benefit more from one or another intervention, could create concerns about privacy and the data about those individuals possibly being used for nefarious purposes.(71-73) Fortunately, this issue is not necessarily unique to health care settings, whether current or future, as it has plagued many other industries including the banking, marketing, and social media industries. Strategies exploited in these other industries could be used in health care settings as well. In addition, developing more efficient ways of developing personalized medicines (for example, with respect to cell replacement therapies or mutation-specific drugs that work for a small fraction of patients) is crucial to meet the demands of all patients. Also, paying for personalized medicine practices in the future may be complicated given that they might be initially more expensive.(74) Finally, in order for various stakeholders to embrace personalized medicine, better strategies to educate and train health care professionals about personalized medicine must be developed and implemented.

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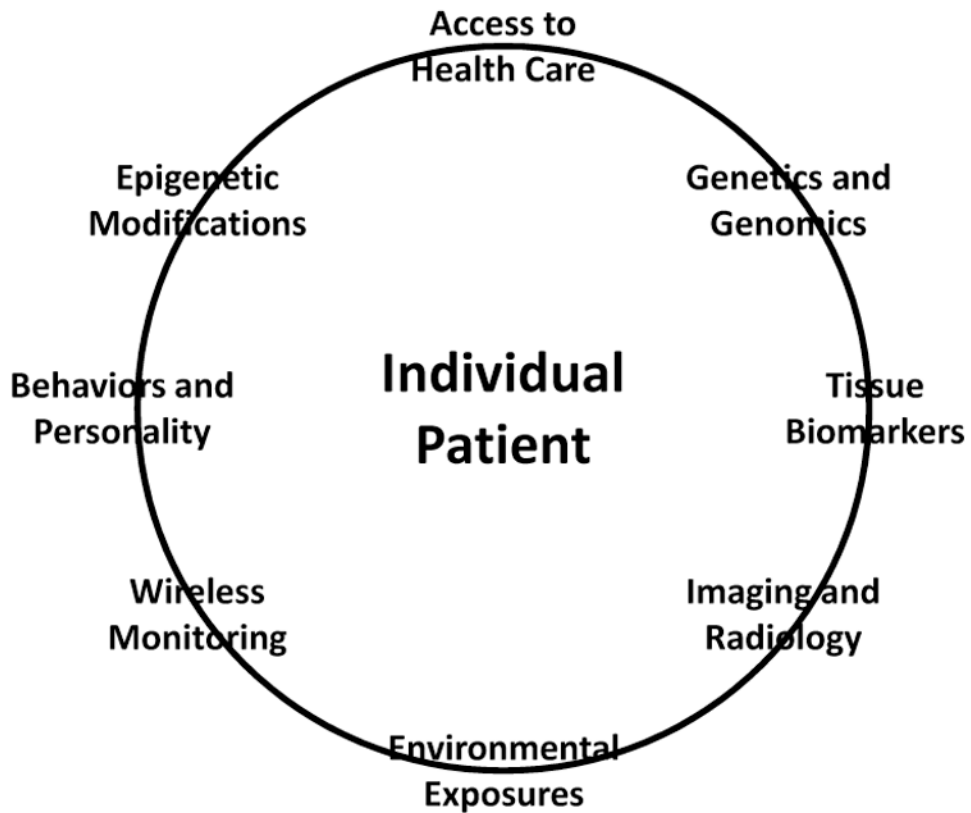


Figure 1. Graphical depiction of elements in need of integration and assessment in pursuing truly personalized medicine. Access to health care is important since some individuals may not be able to access expertise and technologies due to geographic or economic barriers and therefore interventions might need to be crafted for those individuals with this in mind. Inherited genetic information is really only predictive or diagnostic in nature however somatic changes to DNA can provide valuable insight into pathogenic processes. Tissue biomarkers (e.g., routine blood-based clinical chemistry panels) are useful for detecting changes in health status, as are imaging and radiology exams as well as data collected routinely via wireless monitors. Environmental exposures and behaviors can really impact the success of an intervention and exhibit great inter-individual variability. Epigenetic phenomena reshape gene function based on exposures and developmental or stochastic phenomena and should be monitored as well as indicators of a health status change.

Table 1
Recent Examples of Genetically-Guided Diagnoses for Rare and Idiopathic Conditions ('Diagnostic Odysseys') as well as Published Individual Monitoring Studies for Detecting Early Signs of Disease ('Intensive Monitoring')

Category	Source	Subject	Significance	Purpose of study	Variables/Endpoints	Results
Diagnostic Odyssey	Worthey EA et al. 2011 (75)	15 month old boy with intestinal illness similar to Crohn's disease	The first successful use of whole exome sequencing to identify a disease-causing genetic mutation.	Whole exome sequencing of a single subject with refractory inflammatory bowel disease.	Identification of the specific mutation causing severe intestinal inflammation.	A missense mutation was identified in a gene that played a role in the inflammatory response. A stem cell transplant cured the subject of the disease.
	Bainbridge MN et al. 2011 (76)	14 year old twins with a complex movement disorder	Further evidence of the benefits of whole genome sequencing in treating complex disease.	Whole genome sequencing of twins with a complex movement disorder.	Identification of genetic mutations responsible for the debilitating neurologic disease.	A compound heterozygous mutation was identified in a gene responsible for dopamine and serotonin synthesis. Supplementation with a serotonin precursor resolved symptoms.
	O'Rawe JA et al. 2013 (77)	37 yo male with severe obsessive compulsive disorder (OCD).	Highlights the use of whole genome sequencing in neuropsychiatric disease.	Whole genome sequencing of a single subject with refractory OCD.	Identification of genetic markers associated with neuropsychiatric illness.	Genetic variants were discovered in at least three genes associated with neuropsychiatric disease. No actionable variants identified.
Intensive Monitoring	Chen YZ et al. 2014 (78)	2 children with childhood onset autosomal dominant familial dyskinesia with facial myokymia (FDFM)	Identification of a new missense mutation as a contributing factor to this debilitating complex movement disorder	Whole exome sequencing of two children with FDFM.	Identification of a likely causal mutation for the debilitating neurologic disease.	Both subjects had a similar mutation identified in the ADCY5 gene.
	Wartman LD 2015 (79)	20+ yo male with acute lymphoblastic leukemia (ALL)	One of the first instances of using whole genome sequencing to identify a drug target for ALL.	Whole genome sequencing of a single subject with recurrent ALL.	-Identification of genetic mutations that could be used as targets for chemotherapy drugs. -Remission of acute lymphoblastic leukemia.	Subject did go into remission after a targetable mutation was identified. He was then able to receive second stem cell transplant.
	Chen R et al. 2012 (80)	54 yo healthy male	First report of an integrative personal omics profile (iPOP) with genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles	Longitudinal monitoring of multiple omics profiles to assess health and disease states over a 14 month period	Multiple factors analyzed and correlated with subject's activity levels, diet, ingestion of medications, and development of infections or other disease	Disease risk could be assessed from genomic sequencing based on development of infections then Type 2 diabetes. Dynamic changes noted in omics that could be useful for early disease detection and prevention
	Smarr, L. 2012 (81)	60+ yo male with intestinal disease	Comprehensive monitoring for a full decade, highlighting a systems biology approach.	Quantified self approach to disease detection and tracking of treatment.	Genomics plus longitudinal monitoring of standard biomarkers, lifestyle, and microbiome assessment.	Time series measurements of inflammatory markers and stool microbiome led to diagnosis of subject's Crohn's Disease, thus proving clinical utility of the quantified self approach.
	David LA et al. 2014 (82)	Two healthy males, ages unknown	One year of daily gut and saliva microbiome analysis	Investigation of how lifestyle can affect an	Diet, exercise and travel data were measured, in addition to	Microbial communities were stable overall except during

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	Forsdyke DR 2015 (83)	60 year old male with hypertension	Discovery of seasonal changes in sensitivity to antihypertensives in a single individual.	Determine if blood pressure changes in the summer time would be significant enough to warrant adjusting dosages of various antihypertensive medication.	Daily or twice daily blood pressure measurements were correlated with outdoor temperatures for over 12 years.	Summertime sensitivity to the angiotensin II receptor blocker losartan was identified requiring dosage adjustment to prevent side effects of hypotension.
	Trammell SA et al. 2016 (84)	52 yo healthy male	First clinical trial of the pharmacokinetics of nicotinamide riboside (NR) in humans	Determine bioavailability of NR when taken as a precursor vitamin of nicotinamide adenine dinucleotide (NAD+)	Subject took daily doses of NR then had multiple measurements of blood levels of NAD+ and its metabolites.	NAD+ levels did rise after ingestion NR and a new metabolite, nicotinic acid adenine dinucleotide (NAAD), was identified in the NR to NAD+ pathway.
				individual's microbial communities.	the daily evaluation of gut and saliva microbial communities.	periods of enteric infection (food poisoning) and travel out of the United States, when profound changes were observed.