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Precision Medicine Is Not Just Genomics: The Right Dose for Every Patient

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Abstract

Genomics has helped to initiate the era of precision medicine, with some drugs now prescribed on the basis of molecular genetic tests that indicate which patients are likely to respond or should not receive a drug because of a high risk of adverse effects. However, for precision medicine to realize its potential, the patient's history, environment, and lifestyle must also be taken into account. Improving precision medicine requires a better understanding of the underlying reasons for the variability in drug response so as to better identify which drug or combination of drugs is likely to be most effective for an individual patient, along with consideration of the optimal dose or doses for that patient. Greater individualization of dose will be an important means to achieve more precise medicine and mitigate significant variability in drug response. Achieving this will require changes in how drugs are developed, approved, prescribed, monitored, and paid for. Each of these factors is discussed in this review.

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type—that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"
President Obama, January 30, 2015

INTRODUCTION

At the launch of President Obama's Precision Medicine Initiative, precision medicine was described as "providing the right treatment at the right time to the right person and taking into account patients' health history, genes, environments, and lifestyles" (1). Today, precision medicine uses molecular genetic tests to identify which patients have the potential to respond to a drug (2, 3). The application of precision medicine has primarily been to patients with cancers, for which subgroups of patients have tumors dependent on driver mutations, overexpression of single genes, or both, and for which inhibiting the abnormal, or abnormally expressed, protein is an effective treatment strategy in those patients (4–7). Recently, this strategy has been extended to other genetic diseases with the discovery that some childhood diabetes is caused by mutations in *KCNJ11* or *ABCC8* genes and is sensitive to sulphonylureas (8, 9) and the approval of ivacaftor for cystic fibrosis patients with G551D mutations in the *CFTR* gene (10). Some mutations predict nonresponse—for example, Kras mutations and epidermal growth factor receptor antagonists in carcinoma of the colon (11)—or a high risk of serious adverse events, such as Stevens-Johnson syndrome after abacavir, which occurs only in patients with *HLA-B*5701* (12). In such cases, the precision medicine test identifies who should not receive the drug. However, precision medicine should also take health history, environment, and lifestyle factors into account (1) and much more than genomic testing will likely be required to enable precision medicine for many diseases.

Furthermore, President Obama's remarks acknowledged the importance of dose. For a drug to be the right treatment, it needs to be provided at the right dose. Often, there is a single dose level selected to balance benefits and the risk of adverse effects in a population. However, some individuals will not respond at all, some will develop adverse effects at the population dose but respond well to lower doses, and others will have little or no response to the population dose yet respond to and tolerate higher doses (**Figure 1**). Dealing with this variability has been a reality of drug treatment for as long as drugs have been available. In many diseases, clinical practice is to adjust doses until a target effect is achieved; informing how best to do this is a cornerstone of the discipline of clinical pharmacology. Much of what is written in a drug label is information needed to guide dose adjustments to take into account differences between patients with regards to age, gender, ethnicity, organ function, concomitant medications, and other factors.

UNDERSTANDING RESPONSE VARIABILITY IS THE KEY TO PRECISION MEDICINE

For most drugs, many patients do not respond well or even gain no benefit at all (13, 14). Overcoming this is the mission of precision medicine. Wider implementation requires better identification of which patients should receive a particular treatment—the right patient—and what dose should be given to each patient with the potential to respond—the right dose. Thus, implementing precision medicine, which can also be termed personalized or individualized medicine, requires understanding the key reasons for variation in response to treatment.

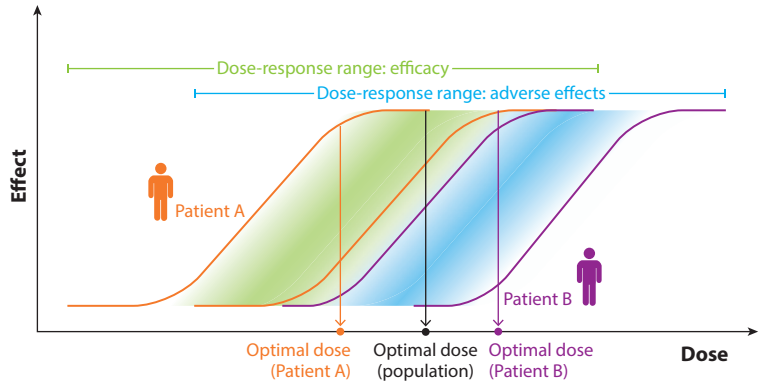

Figure 1

The difference between optimal population and optimal individual dose. The range of dose-responses for efficacy (*green*) and adverse effects (*blue*) in a population is shown, with the optimal dose selected to provide the best efficacy without too many adverse effects. However, patient A (*orange curves*) experiences many adverse effects at the population dose yet responds well to a lower dose, whilst patient B (*purple*) experiences little efficacy at the population dose but can tolerate a higher dose.

Causes of Response Variability

The sources of variability in drug response are generally considered in two main groups (**Table 1**). Firstly, there is pharmacokinetic variability in the relationship between dose and systemic exposure, which describes why different patients require different doses to achieve the same

Table 1 Sources of variability in drug response

	Pharmacokinetic variability	Pharmacodynamic variability
Subject phenotype	Weight Body surface area Age Organ status Ethnicity Gender Microbiome	
Subject genotype	Polymorphisms in metabolizing enzymes or transporters	Polymorphisms in drug target or downstream pathway Off-target polymorphisms indicating risk of adverse effects
Disease phenotype	Expression levels of drug target Disease response or progression over time Indirect treatment effects (for example, derepressing cytochrome P450s)	Heterogeneity of disease mechanisms
Disease genotype		Driver mutations of disease heterogeneity
Lifestyle and environment	Concomitant medications Diet Smoking	
Other	Adherence Drug formulation and route of administration Dosing regimen	

systemic exposure. Secondly, there is variability in the relationship between systemic exposure and effect (i.e., pharmacodynamic variability), which describes why patients respond differently to the same exposure and need different exposures to achieve the same effect. Under these definitions, some pharmacodynamic variability may relate to differences in drug concentrations at the site of action despite the same systemic exposures.

In general, the sources of variability include the following (15):

- Subject phenotype (individual characteristics) and genotype
- Disease phenotype and genotype, including clinical features and outcomes
- Subject lifestyle and environment
- Adherence to the treatment
- Drug formulation, route of administration, regimen, and so forth.

Understanding the sources of response variability guides drug and dose selection between and within patients, as many of the sources vary over time.

Pharmacokinetic Variability

The sources of pharmacokinetic variability, especially related to a person's phenotype and genotype, are usually well characterized, and their impact is addressed in prescribing information. The impact of phenotype is extensively studied for most drugs through population pharmacokinetics analyses and specific studies to address common causes of pharmacokinetic variability, such as age, presence of food, organ failure, and concomitant medication. Recently, the microbiome has been shown to contribute to pharmacokinetic variability (16). Likewise, the impact of genotype is understood for many drugs whose absorption, distribution metabolism, or elimination involves polymorphic metabolic enzymes or transporters. The Clinical Pharmacogenetics Implementation Consortium (CPIC) (17, 18) is an open, international, nonprofit group that creates standard guidelines on how to use genomic data to inform prescribing. Actionable germline variation data are now included in treatment recommendations for 7% of US Food and Drug Administration (FDA)-approved medications, representing 18% of prescriptions (19). Almost all such recommendations relate to the impact of genomic variation on pharmacokinetic variability, with recommendations to adjust the dose or use an alternative drug to avoid treatment failure from inadequate systemic exposure or toxicity from excessive exposure.

Disease factors are important sources of pharmacokinetic variability. The impact of diseases affecting organs of absorption, metabolism, or elimination is well recognized, including indirect effects of disease, such as from cytokines that reduce cytochrome P450 activity (20). However, the disease being treated can also be an important factor altering the pharmacokinetics of drugs used in its treatment. This is most recognized for antibodies, especially those against membrane-bound proteins, that undergo target-mediated drug disposition (TMDD), such that clearance varies depending on the level of target antigen (21, 22). Patients with high levels of antigen may require higher doses than those with lower expression levels to maintain drug exposures, and as the disease activity changes, it may be necessary to alter the dose, increasing it for patients whose disease worsens and decreasing for those whose disease improves (23, 24). TMDD is less common for small molecules but can be important for those with high affinity to their targets and those in which the targets are widely expressed (25).

Pharmacodynamic Variability

In contrast to pharmacokinetic variability, pharmacodynamic variability, which often accounts for the majority of response variability (26), is much less well understood. Subject genotype has

been investigated when there are known polymorphisms in target receptors, but there are very few examples in which this has led to recommendations that impact drug choice or dose selection. The most extensively studied example is warfarin, for which polymorphisms in vitamin K epoxide reductase convertase 1 alter sensitivity to the effects of warfarin and are included in dosing algorithms (27–29). In a few cases, such as abacavir (*HLA-B*5701*) (12), carbamazepine (*HLA-B*1502*) (30), and simvastatin (*SLCO1B1*) (31), an individual's genotype is predictive of the risk of adverse events and identifies who should not receive a drug.

Disease variability is likely to be a highly underrecognized source of pharmacodynamic response variability. Other than currently recognized precision medicine examples, there are very few examples for which the relationship between disease variability and drug effect is sufficiently characterized to impact the choice of a drug. However, the recent example of the interleukin 5 (IL-5) antibody mepolizumab shows that disease variability, other than gene mutations, is an important contributor to response variability. Mepolizumab was clinically ineffective in patients with moderate asthma, despite producing profound reductions in eosinophils (32). More than a decade later, mepolizumab was confirmed to be highly effective in the subset of patients with hypereosinophilic syndrome (33, 34). Presumably the IL-5 eosinophil pathway is less important in most asthmatics, and there is no clinical benefit from blocking it. For many diseases, several mechanisms probably produce similar sets of signs and symptoms (35–37), suggesting that disease heterogeneity will be an important source of response variability in terms of selecting the right treatment.

Variability in disease between patients and over time within a patient can also impact the choice of dose and heretofore has had limited investigation. The best characterized example is omalizumab, an IgE antibody, for which efficacy requires free IgE < 50 μg/ml; dosing is adjusted for body weight and baseline IgE to achieve the necessary reduction in IgE (38, 39). Disease variability can also have an impact on dose-related adverse events. The doses of antibodies to amyloid-β are lower for patients with at least one ApoE4 allele, which reduces the incidence of amyloid-related imaging abnormalities (40). In general, however, the impact of disease severity on drug and dose-response is not well understood and could be an important factor that will improve understanding of the variability of pharmacodynamic response for many diseases.

CHALLENGES AND OPPORTUNITIES FOR GREATER PERSONALIZATION OF THERAPY

The population-based approach to determine drug efficacy and dose is effective for many diseases and patients. Further improvements in understanding response variability, with the goal of better efficacy through more individualized dosing, will require changes in how drugs are developed, approved, prescribed, monitored, and reimbursed (41).

Investigate Dose-Response in the Population

The first challenge in dose individualization is that the population dose-response is often poorly understood despite it being a commonly cited reason for failure in drug development (42). It is not a requirement for approval that the optimal dose be identified. As long as efficacy and safety are demonstrated, failure to optimize dose is not a reason for nonapproval of a new drug (43). Although the dose- or exposure-response relationships for many individuals differ from those for the disease population as a whole, most individual values will be within the range of values for the population. Knowledge of the magnitude of population dose- and exposure-response is thus a useful starting point for identifying how it varies for individual patients.

Take Disease Heterogeneity into Account

For most drugs currently considered as precision medicines, disease heterogeneity is the underlying source of the variability that leads to their precision targeting. Investigations of the underlying mechanisms of the diseases have led to the identification of specific molecular pathways and proteins that are abnormal in subgroups of patients with the disease; drugs have been developed that are active against those targets and pathways. Molecular diagnostic tests are used to exclude patients who cannot benefit from the drug; however, response variability can occur among those with positive diagnostic tests. Vemurafenib, which selectively targets mutated b-raf kinase in tumors with a *V600E* mutation in the b-raf gene, is an effective treatment for melanoma but is less effective in colorectal carcinoma with the same mutation (44). Presumably, additional factors account for greater heterogeneity in colorectal carcinoma and its response than in melanoma. Thus far, for most diseases, extensive genotyping has revealed multiple associations, none of which are able to account individually for substantial variability of disease or are able to predict reliably the efficacy of potential treatments. This bottom-up approach to investigating disease heterogeneity and identifying subgroups of patients who may respond to a treatment is limited as a means to identify the right drug for many diseases, let alone the right dose. Patients with hepatitis C who are homozygous for wild-type IL28B have an 80% response rate to interferon, falling to 25–35% in those heterozygous or homozygous for mutant IL28B (45). Nevertheless, these response rates were still high enough to support dosing all patients with interferon until the advent of newer treatments. The dosing algorithms for warfarin take into account genotypic variation in the molecular pathway of vitamin K metabolism (27–29), but, at this time, apart from driver mutations, there are no CPIC-approved cases of genotypic variation in the disease being used to guide dose selection.

There are other ways to incorporate disease heterogeneity into investigations of drug effect. At the simplest level, treatment trials commonly select patients based on phenotypic characteristics of the disease. This might include indicators of disease severity, such as the extent of specific symptoms or signs, clinical rating scores, or results of lab tests or imaging. Duration of disease, age at onset, previous treatments, and many other factors should also be considerations for understanding disease heterogeneity and its impact on treatment choices. Such factors could be relevant to investigations into which population responds best to a particular treatment or how some disease groups might require higher or lower doses than others. Designing trials that stratify patients based on measures of disease heterogeneity will be useful when there is a good reason to believe that the factor (or factors) being investigated are relevant to understanding response heterogeneity. Such trials can provide confirmatory evidence of the impact of disease heterogeneity on treatment response.

Disease heterogeneity covariates and markers of drug pharmacology should be included in population pharmacokinetic/pharmacodynamics analyses. This may be the most informative approach when there is little prior information regarding which covariates are likely to relate disease heterogeneity to drug and dose-response. The choice of covariates should be informed by the understanding of disease pathophysiology and go beyond the limited disease phenotype data typically included today. Such analyses can generate hypotheses about how disease heterogeneity may be linked to drug and dose-response, but caution is required when trying to confirm causality for associations between markers of disease severity and response. The covariates identified for drug response may simply be prognostic markers for the disease independent of treatment (46). Only after correcting for known prognostic impact is it possible to consider that the covariate (or covariates) are potential predictive markers for drug response (15, 47). Otherwise, an apparently good or bad response to a treatment in patients with a particular set of disease markers may simply reflect that patients with these markers have a good or bad prognosis, with no difference

in the drug effect between them. Even when all known prognostic factors have been taken into account, further studies may be required to confirm that the link between the markers of disease heterogeneity and treatment response is not due to a previously unidentified prognostic effect (46).

Quantitative disease modeling is an important tool to investigate disease heterogeneity. Disease progression modeling (48, 49) has already identified slow- and fast-progressing patient subgroups in Parkinson's disease (50) and in mild cognitive impairment that progresses to Alzheimer's disease (51, 52). Systems models are also useful (53). The failure of mepolizumab in asthma patients was predicted using a systems model that suggested the disease mechanism for most patients involved pathways other than IL-5 and eosinophils (54).

Identify the Underlying Mechanism of Variability

Some covariates associated with response variability may be oversimplifications that do not provide useful information on the mechanisms of variability. Dosing guidelines based directly on such covariates will be of limited use compared to those that take into account the true underlying mechanism of response variability. This may be particularly important when considering the effect of ethnicity on response variability. It is common to study how drug response varies in different populations; identification of differences in subjects with different ethnicities may lead to dose recommendations that take ethnicity into account. Many drugs are approved at lower doses in Japan compared to the United States and Europe (55, 56). However, ethnicity is a poor surrogate for the genes and environmental factors that underlie differences in pharmacokinetics and pharmacodynamics between populations, both those intrinsic to the subjects, such as frequency of different polymorphisms, and those extrinsic, such as diet and differences in medical care. Individual variation in drug response within populations is usually much larger than the difference in average response between populations. Determining the true reason for an apparent difference related to ethnicity allows more informed guidance on drug and dose selection for that ethnicity, patients in other ethnic groups, and those with mixed ethnicity, with the same underlying differences. Ethnic differences in pharmacokinetics may reflect differences in the frequencies of functional polymorphisms in metabolic enzymes or transporters (55), and dose adjustment based on genotype is much more useful to all populations than adjustment based on ethnicity. Ticagrelor appeared to be less effective than clopidogrel in US patients but more effective in Asia and Europe. Further study revealed that the cause of this discrepancy was not ethnicity but rather the higher dose of aspirin given as standard of care in the United States (57).

Study the Outliers

Population analysis can identify sources of response variability and help guide recommendations about how to adjust dose or even use specific drugs to improve benefits and reduce risks for individual patients or groups of patients. A major advantage of population methods is that they are routinely applied to the development of new drugs. During a pharmacokinetic/pharmacodynamic analysis of a population, researchers commonly consider the population as a series of discrete groups, such as above and below a threshold of interest or contained within a percentile range. Comparing such outlying groups within a population can identify trends in the data, and, after correction for imbalances in known prognostic factors between the groups, remaining differences indicate the potential importance of that factor in contributing to response variability.

Investigating individual or small groups of extreme outliers is also important but less widely used. The outliers in a population are those patients most or least sensitive to the effects of the drug. Investigating the outliers in detail can be an important means to define and understand the reasons

for variability in pharmacokinetics and pharmacodynamics. Polymorphic metabolism as a cause of pharmacokinetic variability was discovered when researchers investigated outliers with extreme exposures or responses (58). It has been said that pharmacogenetics started as "tailoring treatment for the outliers" (59). New metabolic enzyme polymorphisms are still being discovered in this way (60, 61). The National Cancer Institute is genotyping exceptional responders to several cancers (62). Detailed investigation of extreme responders is also providing new insights into optimal drug and dose selection in common and mechanistically complex disease such as diabetes mellitus (63); such investigations have the potential to complement population-level surveys that identify risk factors and markers predictive of drug response. In such a way, many nongenomic patient factors that impact therapeutic response can be identified for further investigation.

Poor adherence is a common cause of nonresponse in individual patients (64, 65). Drug concentration monitoring helps to identify which patients actually take the drug, although it is not always a reliable indicator of adherence; additional information may be required to understand the extent to which it contributes to poor response (65–67). Similarly, apparently good treatment response can be confounded by placebo effects, especially for psychiatric disorders (68, 69), settings in which one is evaluating symptoms, such as pain, with subjective, patient-reported endpoints (70), and diseases in which behavioral change can confound interpretation of drug effects, such as (non-protocol-mandated) dietary change in diabetes or obesity.

Therapeutic Drug Monitoring

For a few drugs, therapeutic drug monitoring (TDM) is available to allow doses to be adjusted in individual patients in order to achieve a predetermined target exposure, thereby reducing or eliminating pharmacokinetic variability with some reduction in overall response variability. TDM requires accurate knowledge of the dosing history, including the time of the most recent dose; availability of validated drug assays; knowledge of how to adjust dosing when the measured exposures are different from the target value; and, ideally, evidence for the clinical value and cost effectiveness (71) of the assay. For these reasons, TDM is not widely available and to date has mostly been used for a few small molecules with narrow therapeutic indices or delayed effects in which adjustment of the dose based on clinical response is not a good option. Biologic agents targeting immune system mediators have revolutionized the treatment of immune system–mediated disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Nonetheless, some patients do not respond, and others show decreased response over time. Some of these treatment failures may relate to low systemic exposures of the drugs, perhaps through TMDD or other causes of increased clearance (23, 24, 72, 73). Recent studies suggesting the presence of exposure-effect relationships support the potential value of TDM for biologic agents in rheumatoid arthritis and some cancers; trials are under way to determine if adjusting dose to maintain a target exposure can improve efficacy. TDM could be applied for any drug and disease when dose adjustment improves efficacy, provided simple assays are developed and tools are made available to help physicians adjust the doses in light of the results of the TDM. The devices and diagnostics industry can help with developing simple assays that could be positioned as predictive markers. Methods to help prescribers use the data are discussed in the section titled Providing Practical Solutions for Prescribers.

Drug doses may be adjusted based on a marker of response such as glucose/glycosylated hemoglobin, cholesterol, prostate-specific antigen, or blood pressure, responses that can account for pharmacokinetic and some pharmacodynamic variability. When suitable biomarkers are available or can be developed, their use to guide dosing would be expected to reduce response variability more than dose adjustment based on plasma drug concentration.

Trial Designs that Support Investigation of Responders

Exploring the impact of patient and disease covariates is useful for investigating the impact of previously identified known or potential sources of response variability. When a limited number of factors are investigated, trial populations can be stratified for these factors to permit more definitive understanding of their role. However, it is much more challenging to identify which factors in a population of patients might be contributing to response variability when there is little prior information to guide the choice of factors of interest. Failure to understand the impact of response variability can lead to negative trials. Suppose a new drug improves survival by 15% (e.g., from 50% to 65%) in an unknown 20% of the population and has no effect in the rest of the population, whose survival is also 50%. The increase in the overall population is just 3% ($0.15 \times 0.20 + 0.0 \times 0.80$), from 50% to 53%. To detect this improvement reliably (80% power, significance level 5%) would require a trial of >6,000 patients. Thus, a major need exists for trial designs that allow easier identification of subpopulations with beneficial drug effects.

Adaptive designs (74) that allow patient assignments or other design features to change during a trial, while controlling for potential bias, represent one way forward. Such designs require predefined rules for adaptation of the study to emerging data and can be used to explore response variability if potential responder groups can be defined a priori. Although classical designs can also be used, adaptive approaches are generally more efficient. The I-SPY2 trial (75) in neoadjuvant breast cancer allowed adaptive randomization of subjects to one of several possible treatment arms, favoring randomization to the treatments that began to look most effective until such time as the evidence was compelling enough for the selected treatment to graduate to separate confirmatory trials. The adaptation took into account drug and 14 different biomarker fingerprints to identify and enrich recruitment to the drugs that appeared to be effective and also to the patient subgroups in which they were most effective. Veliparib and neratinib have already graduated from the trial in triple-negative and Her 2–positive, hormone receptor–negative breast cancer, respectively (76, 77). Adaptive trials could also include different doses to explore if subpopulations respond better to such doses.

Basket trials—clinical trials that recruit cancer patients based on molecular markers rather than histology—are being used to study the relevance of markers to predict drug response (78–80). Early results show that efficacy can be detected in small numbers of subjects (81). Bayesian-adaptive basket trials offer further design efficiencies (82), including the opportunity to study different doses. However, when researchers have little idea of the likely causes of variability or too many possibilities to test, it is very difficult to design trials that enrich for responder groups. Novel designs and analytic methods are needed that can distinguish and enrich for signals of the responders that begin to emerge from the noise of the nonresponders during a trial.

Concentration-controlled clinical trials have been proposed as a means to reduce pharmacokinetic variability and improve drug response rates (83). The complexity of implementation, the almost inevitable need for TDM-adjusted dosing in eventual clinical use, and the fact that pharmacokinetic variability is often not the major source for response variability have meant these trials have not been adopted into mainstream development (84–86). Effect or biomarker-controlled clinical trials represent an evolution of these study designs that can better explore sources of response variability, whether pharmacokinetic or pharmacodynamic (84, 87). Conceptually, they are similar to the way in which some drugs are used in clinical practice, especially those for which dosing is guided by clinical response or a marker of drug effect. Such approaches remain logistically demanding, but their use should be considered when there is a useful biomarker of drug response.

Managing the Complexity of Multiple Biomarkers

For most diseases, significant heterogeneity is not predicted by a single test. Likewise, rarely can a single test predict the right drug or right dose. Today's right-drug precision medicines, identified by single genomic tests, are effective because the test is for a dominant cause of response variability. Her 2–negative patients do not respond to trastuzumab, and HLA-B*5701-negative patients do not develop Stevens-Johnson syndrome with abacavir. But these will likely be the exceptions in the future. Existing genetic tests to decrease pharmacokinetic variability generally have less overall effect on response variability: They increase the chance of response or of avoiding adverse effects but usually do not reliably predict response or nonresponse in an individual patient. In most diseases, multiple factors contribute to response variability, and many will need to be taken into account to have a big impact on response variability. Algorithms that combine more than one factor will be required. Factors may include the patient's baseline state, drug exposure, and/or biomarkers of response to treatment. With the use of omics approaches, hundreds or thousands of variables might need to be taken into account.

In some cases, initially complex findings will collapse into simple treatment algorithms, such as that available for omalizumab (39), or there may be fixed biomarker fingerprints that will integrate the results from several markers. However, in most cases, more complex models will be required to identify which disease, patient, environment, and response parameters are important to predict response and then to provide a means whereby data for the individual patient can be integrated to yield a treatment recommendation that includes the right drug, dose, and regimen. Anti–programmed death ligand 1 (PD-L1) antibodies are an illustrative example. Patients with tumors that express high levels of PD-L1 respond better on average than those with little or no expression (88, 89). Yet the difference is not reliable enough to assign treatment for an individual because some low expressers have sustained clinical benefit. Consequently, certain anti-PD-L1 treatments are approved for use in some tumors regardless of expression status. To improve the ability to predict response, researchers are studying various approaches of increasing complexity in terms of the type and number of tests and the underlying mathematics. Some seek to identify biomarker fingerprints; others propose that multiple parameters must be considered to optimize treatment in each patient (90–93). To date, this is without consideration of how to optimize dosing, an aspect that will add further complexity.

We will have Precision Medicine 2.0 (**Figure 2**) when several biomarkers can be combined in a fingerprint that explains more of the response variability than any single test. However, what is the right treatment for patients who match the fingerprint only partially? As more parameters are measured and found to contribute to response variability, the fingerprints will likely become more complex and increase the possibility of partial matches. Solving this problem will require more complex modeling techniques, for example, using machine learning and other advances. This will be Precision Medicine 3.0. The models and methods will first be used to reduce the number of available measurements to the minimum set required to adequately explain response variability. For subsequent patients, these measurements would then be incorporated into the refined model to define the best therapy or therapies and dose regimens.

Adaptive Licensing and Conditional Approval

In some cases, the important sources of variability in drug response may be identified early in drug development. The chances of doing so may be increased by studying more heterogeneous populations early in development, but this needs to be balanced against the increased difficulty of identifying small responder groups from amongst larger groups of nonresponders. Realistically, in many cases, important sources of response variability will not be identified until analyses are

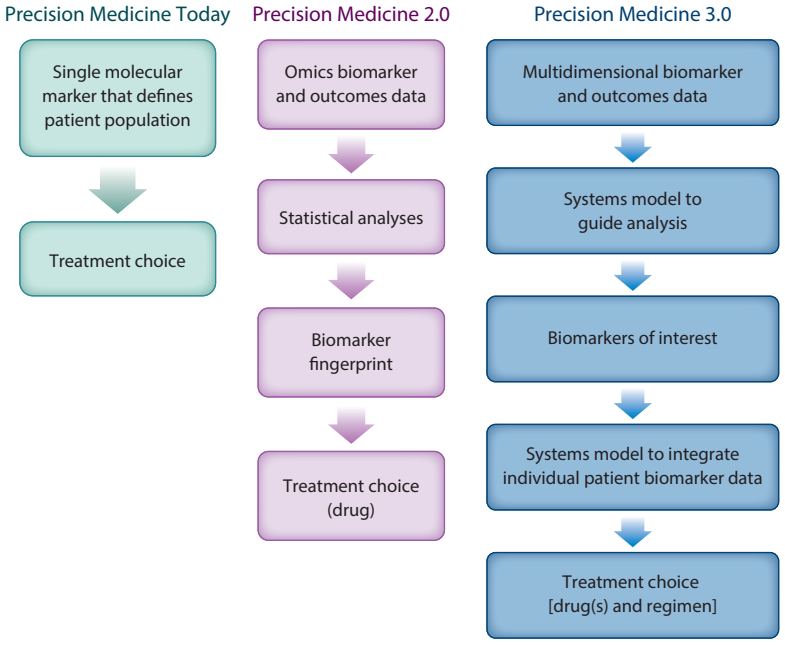

Figure 2

The evolution of precision medicine.

performed during later development, including confirmatory trials. Thus, it will likely not be possible to independently confirm the value of exposure- or biomarker-guided dosing to mitigate response variability during drug development. Adaptive licensing or conditional approval may be used (94, 95). The initial approval may offer limited recommendations to overcome response variability but with the expectation that further investigation will be undertaken to yield recommendations for improved selection of drug or dosing regimens to decrease variability in response and enable more patients to benefit, avoid adverse effects, or both.

Novel Pricing Models

Pricing based on dose offers limited incentive to developers to better understand response variability. For health-care providers and payers, there is incentive to understand when lower doses can be used, but for developers, the incentive might be for higher doses unless the focus is on avoiding adverse effects in a subgroup through lower doses or choosing a different drug. By contrast, outcomes- or value-based pricing models offer greater incentive to understand response and dose variability. Increased use of outcomes-based pricing will be a major incentive for precision medicine. Health-care providers and manufacturers benefit because more patients benefit from the drug. For manufacturers, there is an incentive to ensure patients do not get treated with an ineffective drug or dose and to provide low doses, with lower manufacturing costs, when possible. Higher doses bring greater costs to the manufacturer but are used only in patients who would otherwise not be receiving the drug at all.

Providing Practical Solutions for Prescribers

One dose for all is very easy for prescribers to apply; any recommendations that increase dosing flexibility will add complexity. The increase is small and easy to manage when dosing is by a

clinical endpoint or a simple, cheap, easily measured biomarker, but it is more challenging when more complex or expensive tests are required. One proposal to decrease severe skin reactions by genotyping epilepsy patients for *HLA-B*1502* before prescribing carbamazepine did not decrease adverse effects because rather than perform and pay for additional tests, prescribers switched to using phenytoin, which also caused skin reactions (96). However, when a supporting infrastructure is developed that helps prescribers manage the added complexity, more complex dosing regimens are more likely to be used. Genotype-guided prescribing is conceptually simple, usually requires knowledge of a single genotype per drug, and yet is still a challenge to implement partly because there are many drugs and many genotypes, and the tests and their interpretation are unfamiliar. Nonetheless, several centers of excellence have pioneered genotype-guided dosing to decrease pharmacokinetic variability and have obtained significant use by developing infrastructures that help prescribers undertake the tests, access the results, and understand how to apply them (19, 97–100). It can be expected that similar challenges and infrastructures will be required to implement individualized dosing based on tests besides genotyping. Community pharmacies could be an important means to enable uptake (101), especially when dose individualization expands into primary care.

As discussed above, it is to be expected that in many diseases, multiple parameters will need to be taken into account to make a reliable prediction about the best drug or dose for an individual patient. The use of clinical decision support (CDS) tools (102) embedded in electronic health records or electronic prescribing systems will be important to support the use of more complex choices for individualized dosing regimens. The CDS tool will contain the complex models necessary to ensure the appropriate tests are performed and to integrate the various parameters from each patient to reach an individual dose recommendation.

OVERCOMING THE "ONE DOSE FOR ALL" CULTURE

The current approach to development and use of new drugs generally identifies a single dose that works well for the majority of the population, with simple dose adjustments for a few well-defined patient groups. For many drugs, particularly those that are cheap and have wide therapeutic indices, this has worked well and will continue to do so. However, advancing precision medicine will require a rethink and acknowledgment that greater dose flexibility can be useful to further improve efficacy and reduce adverse effects. Prescribing complexity will inevitably increase. There will be additional complexity for drug developers and prescribers and also for patients, who will undergo additional tests, and payers, who will have to pay for them. This complexity will need to be justified by evidence that the benefit of increased dose individualization is greater than the costs. The initial focus of efforts to improve dose individualization should be for expensive, narrow-therapeutic-index drugs such as cancer immunotherapy and other expensive or widely used drugs for which the significant adverse effects are directly related to the mechanism of action, such as immune modulators or direct-acting anticoagulants (103). Improving drug use in children is also an opportunity for more individualized dosing. Once the methods and benefits of individualized dosing have been established in these cases, the approach can be extended to other drug classes.

SUMMARY POINTS

1. Precision medicine takes into account a patient's genes but must also account for their history, environment, and lifestyle.

2. Variation between patients, including variation in the underlying mechanisms of a disease, means that all patients with a disease do not all benefit from the same drugs, nor do those who benefit from a drug all need the same dose.
3. Some patients respond well at the optimal dose identified from clinical trials in populations of patients. Others do not respond at all, or they develop adverse effects at this population average dose yet respond well to lower doses or have little or no response at the population average dose yet respond well to, and tolerate, higher doses.
4. Achieving more precise medicine requires a better understanding of the reasons for variability in treatment response, including the impact of disease heterogeneity.
5. Pharmacokinetic variability is carefully investigated during development of new drugs and often well understood. However, pharmacodynamic variability, which often contributes most of the variability in treatment response between patients, is usually much less well investigated or understood.
6. Disease heterogeneity is probably a major contributor to response variability.
7. Achieving more precise medicine will require changes in drug development, including better understanding of dose-response, response variability, and its underlying reasons. Such issues will impact the approval process, prescriptions, therapeutic monitoring, and payment for drugs.
8. Treatment individualization, including dose individualization, adds complexity but can be justified by the improved efficacy, cost effectiveness, and reduced adverse events that will result, especially for expensive, narrow-therapeutic-index drugs. Personalized or individualized medicine may thus become the new standard of care, as envisioned by President Obama.

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The author is a full-time employee of, and holds stock in, F. Hoffmann-la Roche Ltd.

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