The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope

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ABSTRACT

The objective of this article was to provide a framework for understanding the different definitions of the term “personalized medicine.” The term personalized medicine is used regularly but interpreted in different ways. This article approaches the term by starting with a broad view of clinical medicine, where three components can be distinguished: the questions (e.g., what is the diagnosis?), the methods used to answer them (e.g., a test), and the available actions (e.g., to give or not give a particular drug). Existing definitions of personalized medicine disagree about which questions, methods, and actions fall within its domain. Some define the term narrowly, referring to the use of a diagnostic test to predict drug response, thereby clarifying whether or not a patient will benefit from that drug. An example of this combination is the HER2/new test to predict the effectiveness of trastuzumab in breast cancer. Many who adopt this definition associate the concept of personalized medicine with fields such as genetics, genomics, and other types of “omics.” In contrast, others view personalized medicine as a concept that has always existed, because medicine has always considered the needs of the individual. One definition of personalized medicine that accommodates both interpretations is “the use of combined knowledge (genetic or otherwise) about a person to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person’s health.” This predictive ability can increase over time through innovations in various technologies, resulting in further improvements in health outcomes. Moreover, these developments can lead to a better understanding of the underlying causes of disease, which can eventually lead to breakthroughs in the treatment of individual patients. In that sense, a truly personalized form of medicine can also be seen as an ideal, a goal that will be achieved only after multiple advances in science. Although the term personalized medicine was rechristened somewhat recently, our ability to personalize medicine will continue to advance in unimaginable ways as we come to learn more about the heterogeneity that exists among individuals and diseases.

Keywords: companion diagnostic, diagnostic test, individualized medicine, personalized medicine, pharmacogenetics, stratified medicine.

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Introduction

The term “personalized medicine” is used widely in the media and in health care. However, people mean different things when they use the term and do not always realize that others might view the term very differently. The lack of one uniform definition only increases the risk of miscommunication. This article aims to shed some light on the general concept of personalized medicine by teasing out and examining its different components.

Personalized Medicine: What Is It Exactly?

The interest in the term personalized medicine has grown lately, partly because drugs are rarely 100% effective and safe and partly because of developments such as the Human Genome Project [1]. These developments have made it possible to identify subtypes of various diseases on the basis of genetics in addition to other means such as histology, an ability that many believe will lead to an improved capacity to prevent and treat various diseases. For example, knowledge of genetics could help to determine whether patients with certain disease subtypes are more likely than others to be responsive to a particular drug (both old and new). On the face of it, there seems to be agreement about what personalized medicine entails. Further examination of the existing definitions of personalized medicine, however, reveals important disparities among them. For example, personalized medicine has been defined as

1. “a medical model that proposes the customization of health-care, with decisions and practices being tailored to the individual patient by use of genetic or other information.” [2]
2. “the tailoring of medical treatment to the specific characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient. Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment.” [1]
3. “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.” [3]

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While numerous other definitions can be found, these three definitions are sufficient enough to illustrate how much existing definitions of personalized medicine vary. The Wikipedia definition refers to the customization of health care, where the actions taken are tailored to meet the needs of the individual patient. The President’s Council starts with a similar statement, but then explicitly refers to the classification of individuals into subpopulations. Last, the National Cancer Institute definition refers to the type of information as well as three specific goals of personalized medicine (to prevent, diagnose, and treat).

A Bottom-Up Approach to Medical Decision Making

One approach to an article on the definition of a term would be to discuss the merits and shortcomings of existing definitions and argue in favor of one of them. For this article, however, we have opted to take a bottom-up approach by examining what is typically involved in patient care. This involves a brief review of three basic elements in medical decision making: some general questions in patient care that can be answered by using medical tests, the ways in which they can be answered, and the medical decisions that can be taken with these answers.

Frequently Asked Questions That Can Be Answered by Using Medical Tests

The left-hand part of Table 1 shows a list of general types of questions, ranging from the prediseased phase to the later stages of disease. While this list is not exhaustive, it is complete enough to illustrate the points to be made here.

One of the first questions in such a list relates to the risk of a disease in the future. Various types of information can help to estimate the risk of disease (or disease susceptibility), and they can range from relatively easily attainable types such as sex, age, and ethnicity to sophisticated types such as imaging or genetic tests. For example, women with a deleterious BRCA1 or BRCA2 mutation are at increased risk of breast and ovarian cancer than other women.

Most questions in patient care, however, arise after disease has occurred, and the simplest question is whether or not a person actually has that particular disease. Population screening programs (using disease screening tests) focus on detecting disease, especially potentially terminal illnesses, in early stages, often long before there are any symptoms, because early detection can lead to improved prognosis. Screening programs often use low-cost and easily accessible diagnostic tools as a first line of detection before expensive, invasive, and possibly more accurate confirmatory diagnostic testing. Examples of screening tests include the Papnicolaou test for cervical cancer, mammography for breast cancer, and fecal occult blood tests and imaging tests such as sigmoidoscopy and colonoscopy for colon and rectal cancer.

In contrast to screening for asymptomatic disease, other questions about diagnosis arise after symptoms have occurred. In many cases, the differential diagnosis phase is a critical step in determining how best to treat the patient. Consequently, much time and energy has been spent on developing better ways to make a diagnosis and a huge arsenal of diagnostic tests now exists in medicine. While many of us may think of diagnostic tests as ones that require special expertise or equipment (e.g., in vitro diagnostics, imaging), technically speaking, any type of information (including demographic information, parts of the medical history, or results of a physical examination) can be regarded as a potentially valuable diagnostic test [4].

It could be argued that the diagnosis is really only an intermediate step in patient care and not an end goal. That is, while it is useful to establish the diagnosis, attention should really be directed at working out how to solve the problem, which means developing the most effective and appropriate treatment plan for an individual patient. With this focus in mind, other questions arise such as will the patient recover spontaneously, suffer temporary or permanent disability, or die from the disease? Questions such as these can be answered by using prognostic tests, which help in choosing the optimal therapy or the optimal window for therapeutic intervention on the basis of disease severity. Ultimately, the aim of the therapy should be to improve the prognosis. If the prognosis without therapy is considered favorable, the clinician, together with the patient, could opt to forgo therapy. This situation is found with Mammprint, a test based on gene expression profiling that predicts the risk of cancer recurrence within 5 to 10 years after the initial diagnosis of breast cancer [5]. An example of the use of prognostic testing to tailor the intensity of therapy is in acute myeloid leukemia, where gene expression profiling has been used to distinguish patients with a favorable (“low-risk”) prognosis and patients with an unfavorable (“high-risk”) prognosis from patients with an intermediate prognosis [6]. While gene expression profiling can be referred to as a parallel series of diagnostic tests, its main practical value is to improve the accuracy of the diagnosis, thereby helping to improve treatment decision making.

Another question that is closely related to prognosis is whether or not a patient will respond favorably or unfavorably to a particular drug. A companion diagnostic test can help to answer this question before treatment has been initiated. A well-known example of this kind of test is the HER2/neu test, which is used to determine whether the drug trastuzumab (Herceptin) (a monoclonal antibody) is likely to be effective in treating a woman with breast cancer [7]. That is, trastuzumab is effective only on tumors with an overexpression of the HER2/neu-receptor, something seen in approximately 15% to 20% of breast cancer cases. Other companion diagnostic tests focus on predicting and thereby avoiding serious adverse events caused by the therapy, while other tests help to determine the optimal drug dose. Examples of these types of tests are found in a later section. Because of their ability to predict treatment outcomes, companion diagnostics are sometimes referred to as predictive biomarkers [8]. In contrast to prognostic tests, which give information about, predictive tests describe those that give information about outcome regardless of therapy (or at least information that is valid across a wide range of available therapies). Predictive tests generally give information about whether a particular patient’s disease will respond especially well to one treatment (vs. others). Therefore, predictive tests are defined in relation to a particular therapy.

Other questions in patient care arise after treatment has been started. Is the treatment having the desired effect or should the treatment plan be modified? The possible courses of action available during treatment include continuing the therapy as planned, modifying the frequency or dose, switching to another therapy, and discontinuing all therapy.Clinicians can decide which option is best by conducting various types of tests to

<table>
<thead>
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<th>Table 1 – Three definitions of personalized medicine.</th>
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<td>Definition</td>
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determine if the treatment is having the intended effect or causing serious adverse events, or if there are major changes in the patient’s disease or general health status.

Last, after the patient has completed the entire treatment regimen, there is a chance of disease recurrence even if the patient is considered “disease free” or even “cured.” This is the case with many types of cancer such as breast cancer or acute leukemia. Because of this, patients who have had cancer in the past will be followed up for a number of years to check for any evidence of cancer, either locally or elsewhere in the body.

What Kinds of Medical Tests Are Available?

The list of questions discussed above should make it clear that a variety of different clinical questions exists. Fortunately, a multitude of medical tests based on various technologies can be performed to help us answer these questions. The middle part of Figure 1 provides a short (and incomplete) list of the types of technologies that these tests use. This list includes types of tests based on demographics, patient history, and a physical examination, all of which have been used for centuries in the process of differential diagnosis. In this process, even the simplest type of information such as age, sex, and ethnic group can be valuable, because they can be strongly associated with the probability of a particular diagnosis. Besides the tests that have been used for a long time, there are some relative newcomers such as advanced imaging technologies (e.g., magnetic resonance imaging) and so-called -omics technologies such as genomics. Genomics is of particular significance when it comes to personalized medicine [1]. As noted earlier, the emergence of the term personalized medicine coincided with the Human Genome Project and other initiatives in that period, such as the Single nucleotide polymorphism Consortium (a public–private partnership of 10 large pharmaceutical companies and the Wellcome Trust) for a reason, namely, the expectation that greater knowledge of the human genome would enable us to treat diseases much more effectively than ever before. For this reason, most, if not all, definitions of personalized medicine refer to the ability of genetic and genomic technology to “personalize” treatment. Relativists, however, would argue that personalized medicine has existed since time immemorial and that genetic knowledge holds great potential in further improving the quality of personalized medicine.

What Kinds of Medical Decisions Might Be Involved in Personalized Medicine?

No test can make a patient better; something must take place afterwards. For example, a test often informs treatment decisions that ultimately make the patient better. The right-hand part of Figure 1 shows a list of different medical decisions that can be made. To start with, a clinician can use a test to decide whether or not a patient will benefit from a particular drug. As noted earlier, the decision to use trastuzumab can be assisted by the result of the HER2 test. A positive test result can be taken to mean that trastuzumab will be sufficiently effective for that patient, while a negative test result can be taken to mean that the treatment will not be sufficiently effective. When the molecular target of a drug is well defined and specific to the causal pathway of the disease, the combination of test-treatment may be referred to as targeted therapy [9]. Because the action of these drugs is different from that of traditional cytotoxic drugs used in medical oncology, which nondiscriminately impair cell replication, the expectation is that targeted therapies will be more specific for inhibition of tumor growth and will have fewer side effects, for applicable patients.

In other cases, a test can help determine whether the patient will be more likely to have a serious adverse event after being given a drug. An example of such a test can be found in patients with epilepsy and other indications for carbamazepine [10]. Patients with HLA-B*1502 are more likely than other patients to have dangerous skin reactions following carbamazepine therapy. A HLA-B*1502 test before carbamazepine therapy can reduce the frequency of these reactions. This type of test is a pharmacogenomic test, a test that predicts how an individual will respond to a drug on the basis of genetic information about that individual and is usually based on pharmacokinetics or pharmacodynamics [11]. Note that while some people also refer to the HER2 test as a pharmacogenomic test, it is technically not true because that test focuses on the genetic profile of the tumor and not of the patient.

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Type of technology</th>
<th>Medical decision</th>
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<tbody>
<tr>
<td>Disease susceptibility: what is the risk of developing a particular disease in the future?</td>
<td>Demographics, medical history, lifestyle &amp; physical examination</td>
<td>1. Decision about drug use:</td>
</tr>
<tr>
<td>Screening: does a person have the disease?</td>
<td>Histology</td>
<td>a. one particular drug (yes or no)</td>
</tr>
<tr>
<td>Diagnosis: what is the diagnosis?</td>
<td>Clinical chemistry</td>
<td>i. eligibility (effectiveness)</td>
</tr>
<tr>
<td>Prognosis: what is the prognosis of a patient?</td>
<td>Imaging</td>
<td>ii. ineligibility (lack of safety)</td>
</tr>
<tr>
<td>Companion diagnostic: will a particular patient respond favorably/unfavorably to a particular treatment?</td>
<td>genetics and “-omics” technologies (e.g., genomics, proteomics, metabolomics)</td>
<td>b. Decision about drug dosage</td>
</tr>
<tr>
<td>Monitoring: should treatment continue, be changed, or terminated? Are other treatments needed?</td>
<td>Other</td>
<td>c. Decision between drugs</td>
</tr>
<tr>
<td>Disease surveillance: has the disease recurred in one form or another?</td>
<td>Combination of the types listed above</td>
<td>2. Decision amongst different medical treatments (e.g., drugs, surgery, etc.)</td>
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</table>

Fig. 1 – Clinical questions, types of technologies, and medical decisions.
Sometimes the question at hand is not about which drug to use, but rather about which dose to use. One example of a test that helps to determine the optimal drug dosage involves therapy with warfarin and other coumarin derivatives such as acenocoumarol and phenprocoumon [12], which are prescribed for different indications such as primary and secondary prevention of deep vein thrombosis or pulmonary embolism, or the prevention of systemic embolism or stroke in patients with prosthetic heart valves or atrial fibrillation. Treatment using these drugs is challenging because there is large interindividual variation in dose response and a narrow therapeutic window; an excessively low dose increases the risk of thromboembolic events, while an excessively high dose increases the risk of bleeding. Because polymorphisms in CYP2C9 and VKORC1 are associated with lower dose requirements and a higher risk of bleeding, knowledge about the CYP2C9 and VKORC1 genotypes of a patient can help to predict the optimal dosage before treatment is initiated [13]. These kinds of tests can also be referred to as pharmacogenomic tests.

Companion diagnostic tests also can help to predict which of the available drugs will be of greatest benefit to an individual patient. An example of this kind of test can be found in second-line therapy of chronic myeloid leukemia, where the effectiveness of candidate treatments such as dasatinib and nilotinib may be predicted before initiating treatment [14].

Many other treatment decisions, however, involve not only drugs but also other options such as surgery, radiotherapy, and watchful waiting. Consider, for example, the treatment options available to a woman at risk of breast cancer who has the BRCA1 gene. She could opt for a watchful waiting or surveillance strategy, risk modification (e.g., lifestyle modification to reduce her risks), chemoprevention, or even a radical mastectomy.

**What Are Some Possible Definitions of Personalized Medicine?**

All three dimensions discussed above (clinical questions, types of technology, and medical decisions) relate to personalized medicine. A commonly used example of personalized medicine is the use of trastuzumab based on the HER2/neu test result to treat breast cancer. It is therefore safe to say that the domain of personalized medicine certainly includes companion diagnostic tests that are intended to predict the effects of treatment before treatment is initiated. As noted above, one can use these tests to predict the degree of effectiveness, the chance of serious adverse events, the optimal dose (to maximize effectiveness and safety), and the best drug to use with a patient. Companion diagnostic tests are so often used in the literature when people describe examples of personalized medicine that we could even base one definition of personalized medicine on them. A possible formulation for this definition would be as follows: the use of combined knowledge (genetics or otherwise) about a person to predict treatment response and thereby improve that person’s health.

This first definition is shown in Table 1. Others refer to prognostic tests such as Oncotype Dx or Mammaprint when they are asked to provide examples of personalized medicine [11]. Oncotype Dx refers to a set of genomic tests that help to estimate the prognosis of women with breast cancer. If a woman has a relatively low chance of recurrence, adjuvant chemotherapy may not be beneficial. If this type of test, a prognostic test, should be considered as part of personalized medicine, then the definition needs to be expanded (see Table 2). A possible formulation for this definition would be as follows: the use of combined knowledge (genetics or otherwise) about a person to predict disease prognosis or treatment response and thereby improve that person’s health. Finally, others include disease susceptibility tests such as BRCA1 testing when they describe personalized medicine. For example, the definition of personalized medicine provided by the President’s Council explicitly includes disease susceptibility, while the definition used by the US National Cancer Institute refers to disease prevention, which can be achieved only by examining disease susceptibility [1,3]. If this type of test should also be included in the definition of personalized medicine, a possible formulation for this definition would be as follows: the use of combined knowledge (genetics or otherwise) about a person to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person’s health.

**Examples of What Could Be Viewed as Personalized Medicine**

Table 2 provides some examples of how genetic or genomic tests are used in clinical care to improve decision making. It should be clear that the result of a test can be used in different ways. Note the clear biologically based link between the companion diagnostic tests and the decision about the use or dosage of the medicine. Companion diagnostics make it possible to maximize treatment response (by means of targeted therapy) and minimize the risk of adverse events (by means of pharmacogenomic tests). A prognostic test, by predicting the future without chemotherapy, can inform the decision regarding whether to proceed with chemotherapy. A test with high prognostic value not only helps to improve treatment decisions now but may also hold valuable information about how to develop targeted therapy in the future. The same holds true for a disease susceptibility test. One could argue that the prognostic and disease susceptibility tests represent an intermediate form of personalized medicine, because a biologically based direct link between the test and a therapy has not yet been developed.

One other comment to make here is that the treatment response monitoring is not considered as a type of personalized medicine according to any of the three definitions given above. At present, many would not consider treatment response monitoring as part of the domain of personalized medicine, although some have implied otherwise [9]. Regardless of this issue of labeling, it is clear that response monitoring tests (for both effectiveness and safety) can play a valuable role in improving the effectiveness and cost-effectiveness of patient care. A later section examines this in more detail.

**Personalized Medicine Utilizes a Mix of Technologies**

While genetic or genomic information can be extremely valuable in improving medical decisions such as determining whether or not a patient is a good candidate for a particular drug, one should not underestimate how often other information (such as comorbidity, concomitant medication, or even patient preferences) is applied when making treatment decisions. In other words, final treatment decisions are not just based on the results of a genetic or genomics test alone. Moreover, estimates of disease susceptibility or disease prognosis can be improved by combining genomic test results with knowledge about various factors such as age, lifestyle, or tumor size. Indeed, such combinatorial algorithms may be essential when predicting disease susceptibility, disease prognosis, or drug response of an individual patient. A classic example of a prediction tool that combines various types of information is the Framingham risk equation to estimate the risks of various types of cardiovascular outcomes among individuals at risk of cardiovascular disease [15]. The frequent need to combine information to improve predictive ability is the reason why all the definitions for personalized medicine proposed above refer to “the combined knowledge (genetics or otherwise)” to improve health outcomes.
Is Personalized Medicine Truly Personalized?

Many people would assume that personalized medicine is personalized, simply because of the word “personalized.” Is this really the case? While the Wikipedia definition focuses on the individual patient, the President’s Council explicitly refers to subpopulations and not to individual patients. In contrast, the National Cancer Institute definition does not clarify whether or not personalized medicine focuses on the individual or on a subpopulation. What conclusions can we draw if we look at widely used examples of personalized medicine? If we look at the HER2-trastuzumab application, we see that a subgroup of women with early breast cancer have a tumor that is HER2-positive. As a result, this subgroup is eligible for trastuzumab, which is effective for HER2-positive tumors. Because all the women in this subgroup, however, receive trastuzumab in the same way (e.g., same dosage regimen), many view this as an example of subgroup medicine or stratified medicine [16]. The President’s Council acknowledges this and goes one step further by explicitly stating that this form of medicine is still classifiable as personalized medicine. Therefore, the purist may conclude that most current examples of personalized medicine are not truly personalized. Depending on one’s viewpoint, one can claim either that personalized medicine is not really here yet or adopt a more liberal definition of personalized medicine and claim that it is. The definitions provided above accommodate both viewpoints because no explicit distinction is made between personalized and stratified medicine.

Personalized Medicine or Personalized Health Care?

Another term that has emerged in recent years is personalized health care. How can we distinguish personalized medicine from personalized health care? One approach would be to say that personalized health care extends beyond the boundaries of personalized medicine to address questions relating to treatment monitoring and disease surveillance, the last two clinical components. Second, there is disagreement about whether or not personalized medicine always has a genetic or genomic component. Second, there is disagreement about whether personalized medicine focuses only on the optimal use of medicines (see
Fig. 1, right-hand side) or on any medical decisions including surgery. Third, there is the issue about whether personalized medicine really just means stratified medicine. These disagreements make it impossible to provide one precise definition for personalized medicine. The definitions provided in this article, however, have been formulated in such a way that they may be accepted by the majority.

Some would say that the ultimate goal of either personalized medicine or personalized health care is to provide “the right treatment to the right patient at the right time”; a variation of this is “therapy with the right drug at the right dose in the right patient” [20]. It would be folly to say that this goal can be achieved without considering “nonmedical factors” such as patient preferences and psychosocial factors. After all, who truly believes that genetics, genomics, and other -omics technologies should be—or will be—the only basis for treatment decisions? As noted above, genetics will always be combined with other information to determine the disease susceptibility, disease prognosis, and treatment response of an individual. More importantly, the best way to prevent or treat disease in an individual will depend on many factors and not just genetics. Nevertheless, there is much to be gained from innovation in the –omics fields. The Human Genome Project ushered in a new era in the effort to prevent and treat disease [1]. While the term personalized medicine was given new meaning at a time when projects such as the Human Genome Project began, our ability to personalize medicine will continue to advance in unimaginable ways as we come to learn more about the heterogeneity that exists among individuals and current diseases. For this reason, it is possible that the definition of personalized medicine will evolve as new discoveries are made. For now, the most appropriate definition for personalized medicine is perhaps the third and broadest of the three introduced earlier: the use of the combined knowledge (genetic or otherwise) about a person to predict disease susceptibility, disease prognosis, or treatment response and thereby improve that person’s health.

One last footnote to add in closing. As of February 17, 2013, a PubMed search of “personalized medicine” yielded 2841 hits. The oldest of these hits was a reference to an article titled “Can personalized medicine survive?” by C.M. Gibson in the journal Canadian Family Physician in 1971, who lamented the difficulty of a general practitioner in keeping up with all the changes in medicine, including both the health care system and new technologies [21]. In his article, he noted that “we live in times of great change and it would probably be true to say that within the span of a single lifetime, medicine has left medievalism behind it.” While the immediate response would be to say that we did indeed see a great deal of change in the 20th century, the question we must ask ourselves is what kinds of change await us in the next decades? All in all, we can debate about the best definition for terms such as personalized medicine, but every new development will likely force us to reformulate that definition.

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