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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/neu 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.

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 healthcare, 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 Papanicolaou 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.

Table 1 – Three definitions of personalized medicine.

Definition 1	The use of combined knowledge (genetics, or otherwise) about a person to *predict treatment response* and thereby improve that person's health
Definition 2	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
Definition 3	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

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 Mammaprint, 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 prognosis, 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