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Precision Medicine — Personalized, Problematic, and Promising

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Abstract

Clinicians, health systems, the pharmaceutical industry, patients, and politicians are all beginning to see the potential in precision medicine, indicating the formation of a sector that is gaining momentum and will have a profound effect on the way medicine is practiced. This article provides a concise overview of the factors driving the development of precision medicine, the obstacles in the way of its widespread adoption, and the consequences for clinical practice.

Introduction

Precision medicine, individualized healthcare, and customized healthcare are often used interchangeably. There are many doctors who insist they have always used a person-centered approach to healthcare. We agree, which is why we like using the phrase "precision medicine" to highlight the innovative characteristics of this area, which is being propelled by cutting-edge diagnostics and therapies. Precision medicine is the practice of tailoring medical care to the specific requirements of individual patients based on their genetic, biomarker, phenotypic, or psychological traits that set them apart from others who present with a similar clinical picture. The aim of this definition is to improve clinical results for individual patients while reducing unneeded side effects for individuals who are less likely to respond to a medication.

Since the first attempts to categorize illness and provide a particular therapy based on a diagnosis, the ideas of precision medicine have likely been at the core of medical practice. What's novel, however, is the rapidity with which new diagnostic and therapeutic methods are being developed.

Some classics and some more recent cases

That is, show how the principles of precision medicine work in practice. For a long time, identifying the offending microorganism and then choosing an

Table 1.

appropriate antibiotic has been essential to the treatment of infectious diseases. Antibiotics are wellestablished as a treatment option for bacterial illnesses.

relies on the pathogen's already-established or empirically-established medication sensitivities. Although there has been progress made, the study of infectious illnesses still has room for improvement. Think about how helpful it would be if bacteria and viruses could be identified at the point of care, preferably together with their anticipated sensitivities. More timely administration of appropriate therapies would protect patients from receiving ineffective or overly-broadspectrum medications and eventually lower antibiotic resistance rates. Recombinant biologic agents are another common example of precision medicine. Making recombinant factors VIII and IX has had a profound impact on the quality and security of care for people with hemophilia. However, the particular treatment plan can only be determined when a diagnosis of the specific kind of hemo- philia has been made. Hemophilia sufferers may soon have access to consistent, long-term therapeutic amounts of the necessary clotting factor thanks to advances in gene therapy. 2 Recently, however, testing for particular genetic anomalies has been revolutionizing both the categorization and therapy of cancer. Molecular testing for EGFR, MET, RAS, ALK, and other genetic markers is being used to supplement the conventional lung cancer categorization based on anatomic and histologic criteria. Clinical responses to targeted inhibitors (e.g., crizotinib) may be rather substantial for tumors that possess the ALK fusion gene, despite the fact that these alterations are uncommon (5%) in non-small-cell lung cancer. 3 To add insult to injury, excluding patients who lack these mutations and hence are not expected to respond to such inhibitors might reduce the likelihood that these individuals will be subjected to expensive and perhaps harmful treatments that ultimately won't assist them. The following examples of precision medicine are presented:

The convergence of genetics, informatics, and imaging, along with other technologies such as

Table 1. Examples of Conditions in Which Precision Medicine Has Been Used.*

Medical Field	Disease	Biomarker	Intervention
Cancer	Chronic myeloid leukemia	BCR-ABL	Imatinib[4]
	Lung cancer	EML4-ALK	Crizotinib[3]
Hematology	Thrombosis	Factor V Leiden	Avoid prothrombotic drugs[5]
Infectious disease	HIV/AIDS	CD4+ T cells, HIV viral load	Highly active antiretroviral therapy[6]
Cardiovascular disease	Coronary artery disease	*CYP2C19*	Clopidogrel[7]
Pulmonary disease	Cystic fibrosis	*G551D*	Ivacaftor[8]
Renal disease	Transplant rejection	Urinary gene signature	Antirejection drugs[9]
Hepatology	Hepatitis C	Hepatitis C viral load	Direct-acting antiviral agents[10]
Endocrine disease	Multiple endocrine neo- plasia type 2	*RET*	Prophylactic thyroidectomy[11]
Metabolic disease	Hyperlipidemia	LDL cholesterol	Statins[12]
Neurology	Autoimmune encephalitis	CXCL13	Immunotherapy[13]
Psychiatry	Alcohol-use disorder	*GRIK1*	Topiramate[14]
Pharmacogenomics	Smoking cessation	*CYP2A6*	Varenicline[15]
Ophthalmology	Leber's congenital amaurosis	*RPE65*	Gene therapy[16]

* In the biomarker column, proteins or genes that are probed to find the specific variants of interest are shown. AIDS de- notes acquired immunodeficiency syndrome, HIV human immunodeficiency virus, and LDL low-density lipoprotein.

the fields of cell sorting, epigenetics, proteomics, and metabolomics, among others, are quickly increasing the scope of precision medicine by improving the categorization of illness, frequently with significant prognostic and therapy consequences (Fig. 1).17
However, the field of genetics and the next-generation DNA sequencing techniques it has enabled are having the most significant impact. The potential to sequence whole genomes or exomes for under
The molecular diagnosis of multiple endocrine neoplasia type 2 allows pro- phylactic thyroidectomy and regular screening for medullary thyroid cancer, pheochromocytoma, and hyperparathyroidism in affected persons; it also spares unaffected family members from frank screening for these diseases.19 The clinical implications will be greatest when the results of genetic testing are actionable, thus informing prognosis or treatment.

Despite the significant impact imaging has had on patient care, it is not frequently included in discussions about precision medicine. These days, imaging may be used to make a number of diagnoses with a fair amount of certainty,

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saving patients from invasive procedures they don't need. In this gen-

Positron-emission tomography provides a means of detecting metabolically active cancer that is not readily seen by more traditional imaging and is being used to guide management decisions in response-adaptive medicine.20 In the past, many patients with severe abdominal pain would undergo surgery to rule out appendicitis before rupture. Now, computed tomography and ultrasonography provide greater sensitivity and specificity in the preoperative diagnosis of appendicitis.

There is a wealth of clinical data available in electronic health records. As the price of genetic testing drops, electronic health records can better assist with drug selection and administration, and algorithms are being developed to identify patients with disease risk factors (e.g., patients with diabetes and elevated low-density lipoprotein cholesterol levels who are not taking a statin) or with a need for guideline-based screening (e.g., colonoscopy based on
age and family his- tory).22

gene for nu- clear lamins (LMNA), which are collectively known as laminopathies. The difficulty in foreseeing the pathological effects of a given abnormality is shown by the number 25. Next-generation sequencing is uncovering an astounding amount of novel genetic changes, which is adding to the already substantial challenge of properly categorizing diseases. It is not easy to determine the function, if any, for many of the genetic variations, even if some of these mutations are obviously related with illness. 19

How can doctors make sense of this overwhelming quantity of data and the resulting clinical recommendations (Fig. 2)? We no longer need to rely on memorization for this purpose. More and more, we need to rely on informatics to help us out, not to replace human judgment but to arm us with hard data. It's possible that primary care physicians have the toughest jobs in the medical field.

important part in the field of precision medicine. They are the first line of defense in the clinical care delivery system, tasked with illness prevention, early detection,

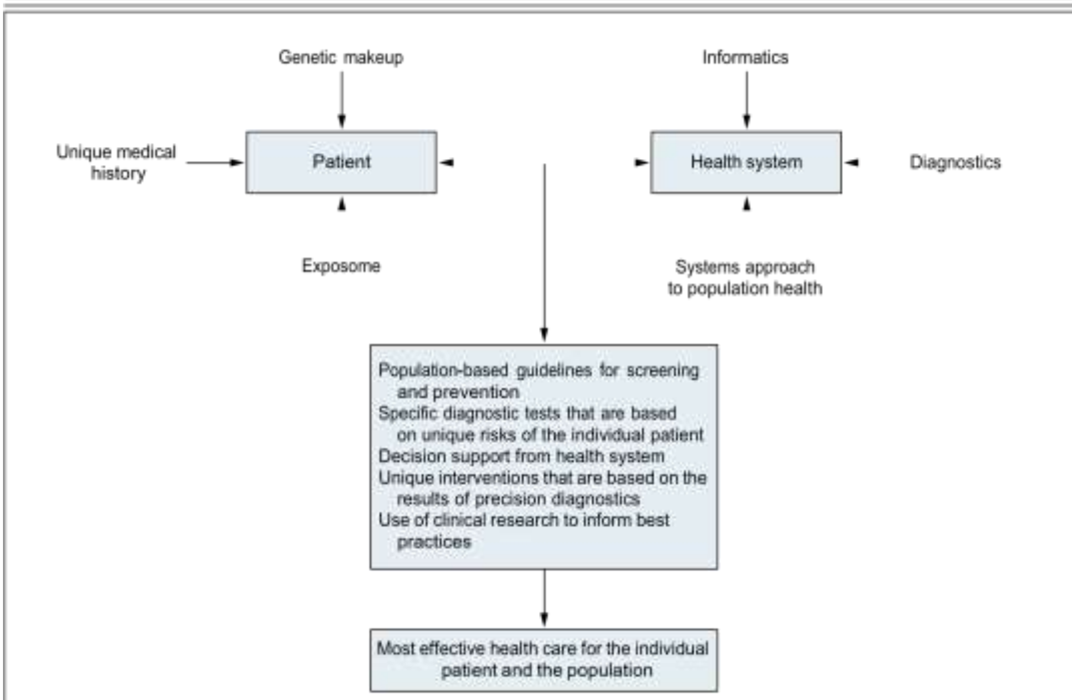

Figure 2. Implementation of Precision Medicine.

The complexity of data supporting precision medicine will require health systems to provide diagnostics, informatics, and decision support to health care providers. Individual patients have specific needs as a result of genetic makeup and exposure to environmental risk factors. The most effective health care for a patient population reflects a combination of generalized screening and prevention measures in combination with the application of individualized diagnostic tests and treatments that are based on a patient's unique genetic predisposition and history. Precision medicine should be viewed as a means of providing the best available health care for a population by identifying the needs and improving the outcomes of individual patients.

(Fig. 1Cardiomyopathy, muscular dystrophy, lipodystrophy, and progeria are only some of the diseases that may affect people with mutations in the

and navigating the increasingly complex referral pathways made possible by precision medicine. It will become more important to have referral pathways in

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place to direct appropriate patients to a specialist who has access to the latest research and clinical standards. For common acquired diseases without a strong genetic predisposition, improved biomarkers are required to aid in disease identification and to help guide therapy. Examples of the clinical need for such diagnostic tools include the search for concussion biomarkers,26 imaging tests for the diagnosis of Alzheimer's disease,27 and circulating tumor markers28. Although diagnostics and therapeutics are inextricably intertwined, the financial incentives to generate new diagnostic tests are not as great as those to create novel medications. Questions of greatest contention

Despite the indicators' sensitivity, specificity, and evident value in a subset of patients, the difficulties in formulating clin- ical recommendations are highlighted by the examples of the successful use of mammography and testing for prostate-specific antigen. Cancer immunotherapies are gaining popularity as an alternative to standard cancer treatments like imatinib (for patients with chronic myeloid leukemia who have a BCR-ABL mutation4) and vemurafenib (for patients with melanoma or thyroid cancer who possess the BRAF V600E variant29). Antibodies against tumor pathways (such as trastuzumab, which targets the tyrosine kinase ERBB2 [HER2])30 or immune checkpoint pathways (such as nivolumab, which targets PD-1)31, as well as the use of autologous T cells modified to target particular antigens, are examples of such medicines (e.g., CD19 on B-cell cancers). 32 Keep in mind that these immunotherapy methods need a match between the antigens being targeted and the antibodies or modified T cells being used to combat them. Immunotherapy will also heavily use the notion of combining diagnosis and treatment.

Recent developments in DNA sequencing have made it possible to investigate the microbiome, a remarkably extensive ecosystem residing on the epidermis and the mucous membranes of human bodies. Emerging data reveals that a person's microbiome is shaped by their innate immune system, their early life experiences with other species, their nutrition, their antibiotic use, and their exposure to other environmental variables. Researchers are paying close attention to this new discipline since it may lead to personalized treatment plans for conditions including obesity, cardiovascular disease, cystic fibrosis, inflammatory bowel disease, skin problems, cancer risk, and autism. 33 Acute therapies in individual patients are another exciting possibility in precision medicine. Automatic defibrillators are a wellknown use of this principle, since they are used to detect and stop cardiac arrhyth- mias. It's easy to picture possibilities in epilepsy or hypoglycemia that are similar. Can we improve the ability to anticipate premature labor and preeclampsia by creating sensors or biomarkers? With the rise of mobile health monitoring and diagnostics, Is it possible that it may be used to monitor weight, blood pressure, glucose, international normalized ratio (INR), vaccinations, and medication adherence if it is better connected with health data, as well as to detect mood swings or pathological skin lesions? Behavioral health has the potential to become yet another component of precision medicine, characterized by the development of feedback systems and incentives that are specific to each individual patient's requirements. 34

We've highlighted some of the newer technological developments that are helping precision medicine move forward quickly. How beneficial or detrimental these innovations are will depend on how successfully we incorporate vast amounts of new information and treatment options into the framework of regular clinical practice (Fig. 2). Numerous stakeholders need retooling and adaptation in light of the forthcoming developments. 35 Less time spent on anatomy and physiology and more time spent on information management are needed in medical school curriculums. Algorithms and informatics tools will be essential for doctors and other medical professionals to manage data and make decisions. Healthcare companies will need to establish protocols to follow in order to provide timely access to specialists when questions arise. Regulatory organizations and payers will need to evaluate improvements in precision medicine and give essential support when merited if patients are to realize the full advantages of these innovations. The term "preci- sion medicine" will become obsolete when a new method of illness classification and therapy recommendation becomes widely used. Full disclosure forms are available with the publication at NEJM.org.

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