SOUNDING BOARD

Precision Medicine — Personalized, Problematic, and Promising

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The growing recognition of precision medicine by clinicians, health systems, and the pharmaceutical industry, as well as by patients and policymakers,[1] reflects the emergence of a field that is accelerating rapidly and will leave a major imprint on the practice of medicine. In this article, we summarize the forces accelerating precision medicine, the challenges to its implementation, and the implications for clinical practice.

WHAT IS PRECISION MEDICINE?

The terms precision, personalized, and individualized medicine are often used interchangeably. Many physicians contend that they have always practiced individualized and personalized medicine. We agree and, for this reason, prefer the term precision medicine to emphasize the new aspects of this field, which is being driven by new diagnostics and therapeutics. We define precision medicine as treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations. Inherent in this definition is the goal of improving clinical outcomes for individual patients and minimizing unnecessary side effects for those less likely to have a response to a particular treatment.

Arguably, the principles of precision medicine have been a cornerstone of medical practice since the earliest efforts to classify disease and prescribe a specific treatment on the basis of a diagnosis. What is new, however, is the pace of advances in diagnostic and treatment options.

A few examples — some old and some new — illustrate the concepts of precision medicine. For many years, the management of infectious disease has pivoted on the identification of a causative organism and the selection of an effective antimicrobial agent. For bacterial infections, the field is mature, and the choice of antibiotic is based on known or empirically determined drug sensitivities of the causative organism. However, the field of infectious diseases remains ripe for further development. Imagine the prospect of point-of-care identification of bacteria or viruses, ideally with their likely sensitivities. Appropriate treatments could be initiated sooner, sparing patients unnecessary exposure to ineffective or broad-spectrum drugs and ultimately reducing rates of antibiotic resistance. Another familiar example of precision medicine is the use of recombinant biologic agents as replacement therapies. The production of recombinant factors VIII and IX revolutionized the efficacy and safety of treating patients with hemophilia. However, a precise diagnosis of the type of hemophilia is required to inform the specific treatment. Gene therapy is now on the horizon for hemophilia, potentially providing stable, long-term therapeutic levels of the needed clotting factor.[2] More recently, testing for specific genetic abnormalities has been transforming the classification and treatment of cancer. For example, in lung cancer, the traditional classification that is based on anatomic and histologic criteria is being augmented by molecular testing of *EGFR*, *MET*, *RAS*, *ALK*, and other genetic markers. *ALK* fusion genes are relatively rare (<5%) in non–small-cell lung cancer, but clinical responses to targeted inhibitors (e.g., crizotinib) can be dramatic for tumors that harbor the rearrangement.[3] Moreover, the exclusion of patients without these mutations who are unlikely to have a response to such inhibitors can minimize the exposure of patients to costly and potentially toxic therapies that are unlikely to help them. Selected additional examples of precision medicine are shown in Table 1.

TECHNOLOGICAL ADVANCES AS DRIVERS OF PRECISION MEDICINE

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 neoplasia 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 denotes acquired immunodeficiency syndrome, HIV human immunodeficiency virus, and LDL low-density lipoprotein.

cell sorting, epigenetics, proteomics, and metabolomics, is rapidly expanding the scope of precision medicine by refining the classification of disease, often with important prognostic and treatment implications (Fig. 1).[17]

Among these new technologies, genetics and next-generation DNA sequencing methods are having the greatest effect. The prospect of sequencing whole exomes or genomes for less than $1,000 reshapes our thinking about approaches to genetic testing.[18] The clinical implications will be greatest when the results of genetic testing are actionable, thus informing prognosis or treatment.[19] For example, the molecular diagnosis of multiple endocrine neoplasia type 2 allows prophylactic thyroidectomy and regular screening for medullary thyroid cancer, pheochromocytoma, and hyperparathyroidism in affected persons; it also spares unaffected family members from unnecessary screening.[11]

Imaging is not always considered as part of precision medicine, yet it has profoundly changed how we treat patients. Many diagnoses can now be made with reasonable confidence on the basis of imaging, which spares patients from more invasive testing or unnecessary surgery. A generation ago, 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.[20] Positron-emission tomography provides an additional means of detecting metabolically active cancer that is not readily seen with more traditional imaging and is being used to guide management decisions in response-adapted treatment programs for Hodgkin's lymphoma.[21]

Electronic health records contain a rich database of clinical information. In the future, algorithms will be developed to identify patients with disease risk factors (e.g., for 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 on the basis of age and family history) or to apply pharmacogenetic guidelines to assist with drug selection and administration.[22] As the costs of genetic testing fall, electronic health records can be prepopulated with relevant genetic or pharmacogenomic data, providing clinicians with actionable information about which patients are positive for factor V Leiden or

are unable to metabolize the prodrug clopidogrel.[7] With appropriate protections, eligible patients can be identified for clinical trials. None of these approaches will replace physician judgment about individual patients. Among other concerns, medical records contain errors and will not always contain relevant information important for treating a particular patient.

PRECISION MEDICINE AND DISRUPTIVE CHANGE IN THE PRACTICE OF MEDICINE

Patients, physicians, health systems, payers, and the diagnostics and pharmaceutical industries share interests in precision medicine, although such interests are not fully aligned (Fig. 1). Patients seek a clearer understanding of their disease, its prognosis, and the most effective treatment in terms of efficacy and side effects. Physicians and health systems share these interests but also must balance individual patient needs with management of overall health care utilization. Payers are concerned that new diagnostic tests and drugs will drive up health care expenditures and remain skeptical that these costs will be offset by more selective use and fewer side effects. The pharmaceutical industry seeks new drug opportunities, but often such drugs replace existing and profitable therapies. Thus, precision medicine is a classic example of disruptive innovation, defined as a circumstance in which an innovation threatens to revolutionize an existing standard (e.g., when digital photography rapidly replaced film photography).[23] There is a sweet spot where the interests of various stakeholders in the health care sector converge — it is the rigorous evaluation of efficacy, safety, and cost-effectiveness, all performed with an open mind about whether the tools of precision medicine provide value.[24]

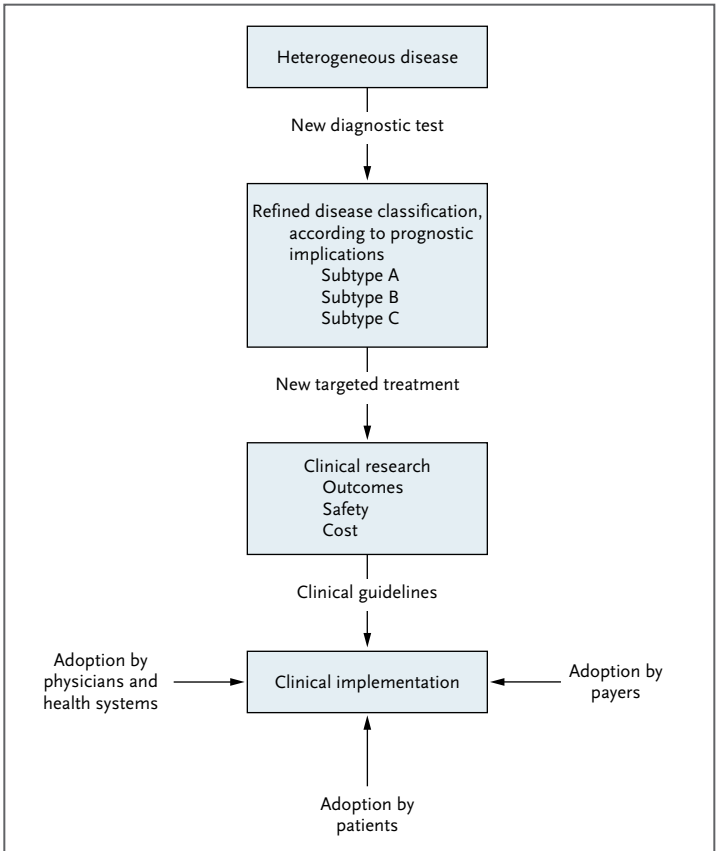

Figure 1. Scope of Precision Medicine.

The need for precision medicine is driven by the heterogeneous nature of many diseases. New diagnostic tests allow for refined classification of disease, which may have important prognostic implications. When targeted therapies are available, clinical studies can assess efficacy, safety, and cost-effectiveness, leading to revised clinical guidelines. Clinical implementation requires adoption by regulatory agencies, payers, physicians, and patients. Each of these groups has a different perspective, role, and incentive when it comes to clinical implementation.

CHALLENGES FOR PRECISION MEDICINE

Perhaps the most daunting challenge for precision medicine is to manage the complexity associated with the progressively refined nosology (classification) of disease. Medicine has a long history of being divided into "lumpers and splitters"; lumpers tend to group related entities together, and splitters tend to apply more precise definitions and thereby define more discrete entities. The advances in genetics and biomarkers will shift this balance in favor of the splitters. Leber's congenital amaurosis can be caused by mutations in at least 14 genes. This phenomenon of locus heterogeneity has historically been the realm of geneticists. However, the gene-replacement strategy for Leber's congenital amaurosis involves viral vector delivery and expression of a specific missing protein, RPE65, encoded by only 1 of these genes. This example foreshadows how more refined disease classification may lead to expanded decision algorithms and treatment options. On the other hand, disorders of particular pathways can be associated with myriad diseases

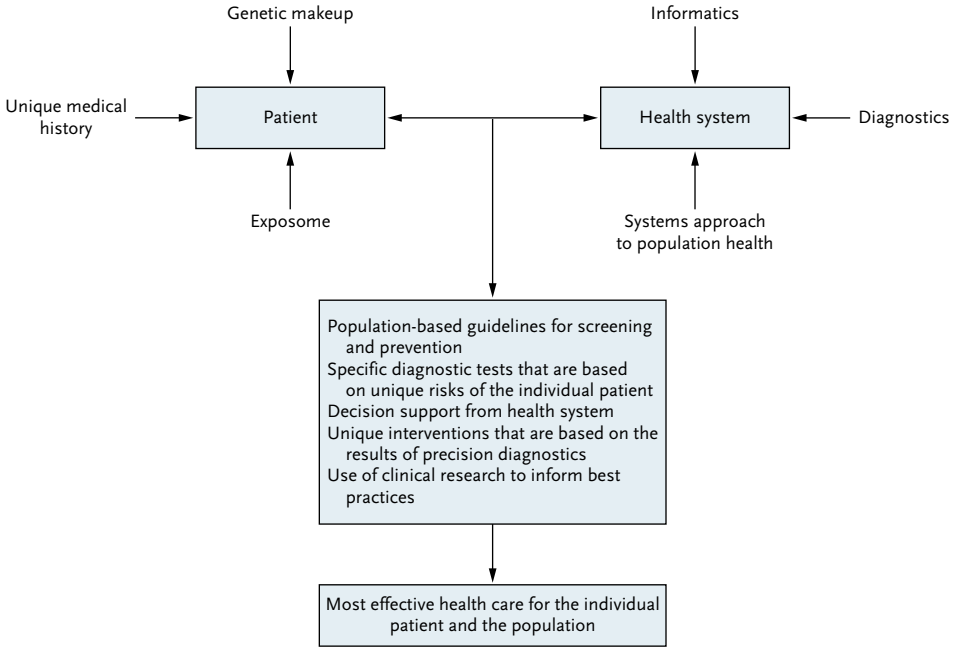

Figure 2. Implementation of Precision Medicine.

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. 1). Mutations in the gene that encodes nuclear lamins (*LMNA*) in patients with so-called laminopathies can cause cardiomyopathy, muscular dystrophy, lipodystrophy, and progeria, among other conditions,[25] which highlights the challenge of predicting how abnormalities in a particular pathway will translate into disease. In addition to the increasing complexity of disease classification, a stunning number of new genetic alterations are being uncovered by next-generation sequencing. Although some of these mutations are clearly associated with disease, it is difficult to evaluate the role, if any, for many of the genetic variants.[19]

How can physicians adapt to this daunting explosion of information and the associated clinical guidelines (Fig. 2)? Memorization no longer serves this function. Increasingly, we must use informatics to assist us — not for replacing judgment but for providing facts. Indeed, primary care providers may have the most challenging role in precision medicine. They stand on the front lines of the clinical care delivery system with a mandate to prevent disease, identify early signs of disease, and navigate referral paths that now have many more branches as a result of precision medicine. Increasingly, referral pathways will be needed to help connect selected patients to an expert with increased access to the emerging data and clinical guidelines.

Better biomarkers are needed to assist with disease detection and to help guide treatment, particularly for common acquired conditions without a strong genetic predisposition. Efforts to identify biomarkers for concussion,[26] imaging tests to detect Alzheimer's disease,[27] and circulating tumor markers[28] exemplify the clinical need for such diagnostic tools. The financial incentives to create new diagnostic tests are not as strong as those to create new drugs, despite the fact that diagnostics and therapeutics are inextricably linked. Controversies about the most

effective use of mammography and testing for prostate-specific antigen serve as a reminder of the challenges associated with establishing clinical guidelines, even when markers are sensitive and specific and have clear utility in selected patients.

FUTURE OPPORTUNITIES FOR PRECISION MEDICINE

In addition to medications that target altered genetic pathways in cancer, such as imatinib for patients with chronic myeloid leukemia who have a *BCR-ABL* mutation[4] or vemurafenib for those with melanoma or thyroid cancer who carry the *BRAF* V600E variant,[29] there is growing interest in targeted immunotherapies for cancer. Such therapies include antibodies against tumor pathways (e.g., trastuzumab against the tyrosine kinase ERBB2 [HER2])[30] or immune checkpoint pathways (e.g., nivolumab against PD-1)[31] and the use of autologous T cells engineered to target specific antigens (e.g., CD19 on B-cell cancers).[32] Of note, these immunotherapy approaches require matching known antigens or pathways with the antibodies or the engineered T cells. Thus, the principle of coupling diagnostics and therapeutics will also be a major feature of immunotherapy.

Advances in DNA sequencing have enabled studies of the microbiome, a surprisingly large ecosystem embedded on the surface of our skin and mucosal tracts. Emerging evidence suggests that the composition of a person's microbiome is a combination of innate immunity, introduction to organisms early in life, diet, and exposure to antibiotics and other environmental factors. Studies examining the microbiome in obesity, cardiovascular disease, cystic fibrosis, inflammatory bowel disease, skin disorders, cancer risk, and autism provide an indication of the level of interest in this emerging field, which may offer opportunities for individualized interventions.[33]

Another provocative opportunity in precision medicine is the use of technology to assist with acute interventions in individual patients. A well-known example is the use of automated defibrillators to detect and interrupt cardiac arrhythmias. One can imagine analogous opportunities in epilepsy or hypoglycemia. Can we develop sensors or biomarkers to better predict premature labor or preeclampsia? As mobile technology is used to assist with health monitoring and becomes more fully integrated with health records, can it be used to detect mood swings or pathologic skin lesions and to serve as a more effective reminder to monitor weight, blood pressure, glucose, international normalized ratio (INR), vaccinations, and medication adherence? Behavioral health may prove to be another dimension of precision medicine, one that is characterized by designing feedback systems or incentives tailored specifically to individual patients.[34]

In this article, we have highlighted the convergence of a variety of technological breakthroughs that are accelerating the field of precision medicine. The extent to which these advances are constructive or disruptive depends on our ability to harness vast amounts of new knowledge and treatment options within the framework of everyday clinical practice (Fig. 2). Changes that occur will require reengineering and adaptations by multiple stakeholders.[35] Medical school curricula will need to focus even more on information management. Physicians will require informatics support and algorithms that work in the background to assist with information management and decision making. Health systems will need to design pathways that facilitate ready access to specialists when appropriate. Regulatory agencies and payers will need to evaluate and support, when appropriate, advances in precision medicine if patients are to receive maximum benefit. When the term precision medicine disappears from our lexicon, we will know that a revised disease classification with more targeted treatment options has become the norm.

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