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Operationalizing Precision Cardiovascular Medicine: Three Innovations

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Abstract

For precision medicine to become a reality, we propose three changes. First, healthcare deliverables must be prioritized, enabling translation of knowledge to the clinic. Second, physicians and patients must be convinced to participate, requiring additional infrastructure in health systems. Third, discovery science must evolve to shift the preclinical landscape for innovation. We propose a change in the fundamental relationship between basic and clinical science: rather than two distinct entities between which concepts must be translated, we envision a natural hybrid of these approaches, wherein discovery science and clinical trials coincide in the same health systems and patient populations.

Keywords

genomics; proteomics; systems biology; big data; precision medicine; healthcare policy

Even the generally progressive physician can be unsure and perhaps even skeptical about how precision medicine will fit into daily practice. In our view, precision medicine is personalized clinical care informed (primarily) by measurements of the genome, epigenome, proteome, transcriptome, metabolome and microbiome. Precision medicine should result in a more healthy life with less disease burden and it should be delivered on an individualized basis.

Many therapies fail when they are tested in large animal models (1, 2) or when transitioning from phase I to phase II clinical trials (3, 4), leading to a decrease in the number of new drugs making it to market (5). Despite improvements based on guideline adherence,

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cardiovascular disease remains the leading killer and a tremendous financial burden on the nation.

Implementation of precision medicine will require collaboration across the spectrum of research and healthcare delivery, including funding agencies, insurers, academic medical centers, private hospitals and consumer ‘omics providers, as well as the potentially underappreciated relationship between patient and physician. Where to begin? How to convince patients and families to enroll? How to persuade clinicians to participate? How to add value to the health system? Who should pay?

In answering these questions, we considered a new model for research and clinical medicine, wherein virtually the entire patient population becomes a perpetual study for personalized medicine (Figure 1). The medical record is continually interrogated to identify new metrics and refine existing ones, transforming our understanding of comorbidities. We propose three key areas of focus: (i) healthcare delivery redesign; (ii) physician and patient engagement; and (iii) changes to discovery science pipeline.

Healthcare Delivery Redesign

Guideline-driven care, while effective on a population scale, fails to account for the individual’s unique susceptibility to disease *and* unique response to therapeutic intervention. Fortunately, ‘omics research in cardiovascular disease has produced a trove of molecular signatures for various conditions. The task now is to convert this information into actionable metrics for the clinician (Figure 1).

Target the right populations

We want to start with the best-phenotyped, most clinically accessible forms of disease, yet these are not always the ones with the simplest means of stratification. The advantage of familial diseases is the relative ease of identifying causal (and modifier) variants, a framework to understand changes leading to disease, and a path to genotype-based therapy (6). Shifting the analytical paradigm to whole genome sequencing and other ‘omics profiling will add value to variants of unknown significance, improve risk prediction and in some cases shed light on disease mechanisms.

An analogy to shoe sizes can be instructive: small, medium and large (current state of medicine) means that most people do not have shoes that fit snugly. In contrast, 320 million shoe sizes, one for every American (the type of precision medicine we *do not* want to pursue), may in theory fit each individual perfectly but in practice would be unworkable. Rather, 10–12 shoe sizes—or *the type of precision medicine we do want*, based first on genetic factors, then building out new modules based on other validated ‘omics markers—would be a practical solution providing outstanding fit for nearly everyone.

The goal is to make actionable the distinct features in ‘omics datasets with high correlation with disease. Expanded electronic medical records is a way to start: genetic data, when available, should be populated into the medical record to aid clinical decision-making, and predictive models that can assign risk should be developed from ‘omics measurements. By

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starting with variants that we already know modify risk and implementing them at the point of care for all patients, the common practice can be changed, facilitating adoption of future ‘omics metrics. This knowledge should also be applied in the clinical trial setting, engineering enrollment based on genotypes likely to respond to a therapy (7).

Building comprehensive datasets

With current technology and sufficient economy of scale, universal genome sequencing could be implemented today if academic medical centers willed it to be. Insurers need to be convinced about the advantages to genome sequencing at birth—the foundation for precision, longitudinal care across a lifetime, which will reduce health care cost in the long term through improved understanding of disease and health. We may not know how to use this information today, but we must have the foresight to accumulate the ‘omics data on our patients while they are still healthy and so that when we do learn the diagnostic value, we have the wherewithal to adapt care. More patients means greater resolution in genetic—and eventually, other ‘omic—architecture of cardiovascular disease, which will in turn result in more accurate prediction, tailored treatments, less waste and better outcomes.

Value may come from knowledgebases of data (8), for example the building of ‘omics-based models from diverse populations. We must build a framework for electronic medical record logic that can integrate risk algorithms and network-based predictors in an actionable manner to aid the physician’s decision making.

Provider and Patient Engagement

For the patient living with a debilitating disease, or the family member who suffers by his side, *the greater good* can ring hollow as motivation to participate in research. Likewise for healthcare professionals: are not their days already trammeled enough with regulations and responsibilities?

A successful precision medicine framework must make enrollment simple. Study coordinators must work across departments, breaking down traditional barriers between specialties. Every patient admitted to the clinic should be approached for participation in clinical studies—universally consented, not just for clinical studies related to population medicine, but also for the measurement of molecular signatures (e.g. from saliva or blood) throughout life.

Make it free (or almost free)

An ECG is performed on nearly every cardiac patient because it has a balance between cost, risk and “number to treat” considerations: cost is low and risk is nil, while the number of people to whom it must be applied to be helpful in a diagnosis is also quite low. A combination of reduced cost due to economies of scale, improved provider education on when to order genetic testing and improved infrastructure to integrate new findings into health system databases will enable ‘omics based measurements to take on a similar place in the diagnostic workflow. Take for example troponin assays, which are now universally ordered in chest pain cases and covered by insurance: this paradigm arose from physicians knowing how to use the test results and insurers appreciating the actuarial wisdom of

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covering them. A near term solution for this challenge is to encourage insurance companies to pay for ‘omics measurements as part of a “test panel”, some of the components of which provide immediately actionable results, whereas others serve research purposes. Lastly, the proliferation of consumer health monitoring devices enables fine tracking of cardiovascular symptoms (e.g. arrhythmias) and presents an opportunity to engage patients in promotion of their own health.

Provide a tangible benefit now—not just in the future

Genetic testing for families with inherited cardiomyopathies is a logical place to start to establish a culture of molecular diagnosis in the clinic. The benefits to patients are immediate: knowing which family members carry various mutations (along with compounded risk) helps with piece of mind as well as practical guidance for changing lifestyle, healthcare decisions and family planning. The best way to motivate a patient and her family to engage in advanced testing is to make it easy and to show the benefit not only to the patient, but also her loved ones. Cardiologists should have the training to judge when genetic and other ‘omic testing is warranted and be able to page an on-call study coordinator to collect the sample and genetic counselor to educate the patient.

A cardiovascular clinician-scientist should be empowered as a health system-wide leader: pioneering new research areas and clinical measurements, directing enrollment, designing patient management protocols for cases in which molecular phenotyping has been performed and staying current on developments from other medical centers.

Patients need to know that the information they provide will not end up in the wrong hands. Notwithstanding valid concerns about cyber security breaches and re-identification of individuals from genetic information, much of the current concerns about information security will, we predict, reside with time. Protocols must establish what types of information is passed back to the patient, ensuring that access to molecular information is accompanied by education. If the clinician initiates this conversation, the patient in turn will become more willing to participate in meaningful research and ‘omics-based health and wellness monitoring, returning benefits throughout life.

Evolving the Discovery Science Pipeline

The saltatory relationship between research and practice means that for precision medicine to usher in a meaningful transformation in clinical care, discovery science too must evolve.

Human models of human disease

Despite the value of mouse studies for superb mapping of cellular signaling pathways (9, 10), more effort needs to be put into studying confounding variables including age, sex and common genetic variation. There is another conceptual paradox between the approach to discovery research in animals versus the treatment of patients in the clinic: modern research interrogates multiple scales of biological complexity, from molecule, to network, to organelle, to cell, to organ, to organism. This progression almost never happens in clinical medicine, wherein patient presentation is complemented usually only by molecular measurements, bypassing the other scales of complexity that fundamental research has

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taught us are critical for normal and diseased physiology. A precision medicine framework that utilizes our current understanding of biological scales could transform care (Figure 1). Achieving this goal will require that more discovery research be performed directly in human populations and in patient derived cells, including induced pluripotent stem cells (11), which can obviate concerns of species specificity and genetic variability earlier in the pipeline from discovery to clinical implementation.

The big data resultant from ‘omics studies necessitates that medical centers develop infrastructure for acquiring, housing, mining and protecting patient information on an unprecedented scale (12). How well institutions extract biological principles from this wealth of information, and the effectiveness with which they make actionable clinical features from the data (revealing phenotypes that are currently masked), will determine the success of precision medicine. Big data science and computing also opens the door to virtual clinical trials based not on single targets, but on sophisticated models that incorporate population level variability. Part of the goal of refined clinical trials goes backwards from validating new drugs to salvaging old ones that may have failed larger randomized clinical trials due to dangerous side effects in an identifiable cohort.

It’s not all genetics

Most molecular diagnostics currently used in clinical cardiology are not genetic endpoints, highlighting that other molecular features harbor prognostic and diagnostic value. Multi-‘omics measurements in a single individual have already been shown to reveal not only new biology but clinically actionable disease insights (13). We are particularly bullish on the clinical value of the epigenome, which integrates the genome, the proteome, in some cases metabolome, and certainly the environment: an objective diagnostic…if we can figure out how to decode it.

Precision medicine is not limited to molecular measurements. Advances in imaging can reveal new physiology and technological innovation is constantly pushing the boundaries of manmade (and cellular) products. The new strategies for molecular phenotyping described in this article can only impact patient care if they are implemented as part of an evolving continuum of clinical care ranging from patient assessment to surgical intervention. Is there a role for symbiotic molecular, imaging and surgical/transcatheter interventions in the care of patients in the uterus, in infancy or even adulthood? Can we develop procedures with predictable anatomic consequences that could be modeled using advanced imaging and 3-D printing techniques tailored to the individual? A better understanding of the relative contributions of anatomic, physiologic, and molecular variables will be key to the successful integration of precision medicine into clinical care.

Concluding Remarks

The provider has the patient before her on a daily basis…the patient and family are burdened with disease…and yet the promise of a cure is always on the horizon. Our purpose for writing this article was to contribute to the discussion on how we as a scientific and medical community can operationalize the vast knowledge from ‘omics technologies. We propose strategies for: (i) precision healthcare delivery redesign; (ii) maximizing provider and patient

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engagement; and (iii) evolving the discovery research paradigm. The time is now to revitalize the effort to transform research and clinical medicine to provide superior care for the individual.

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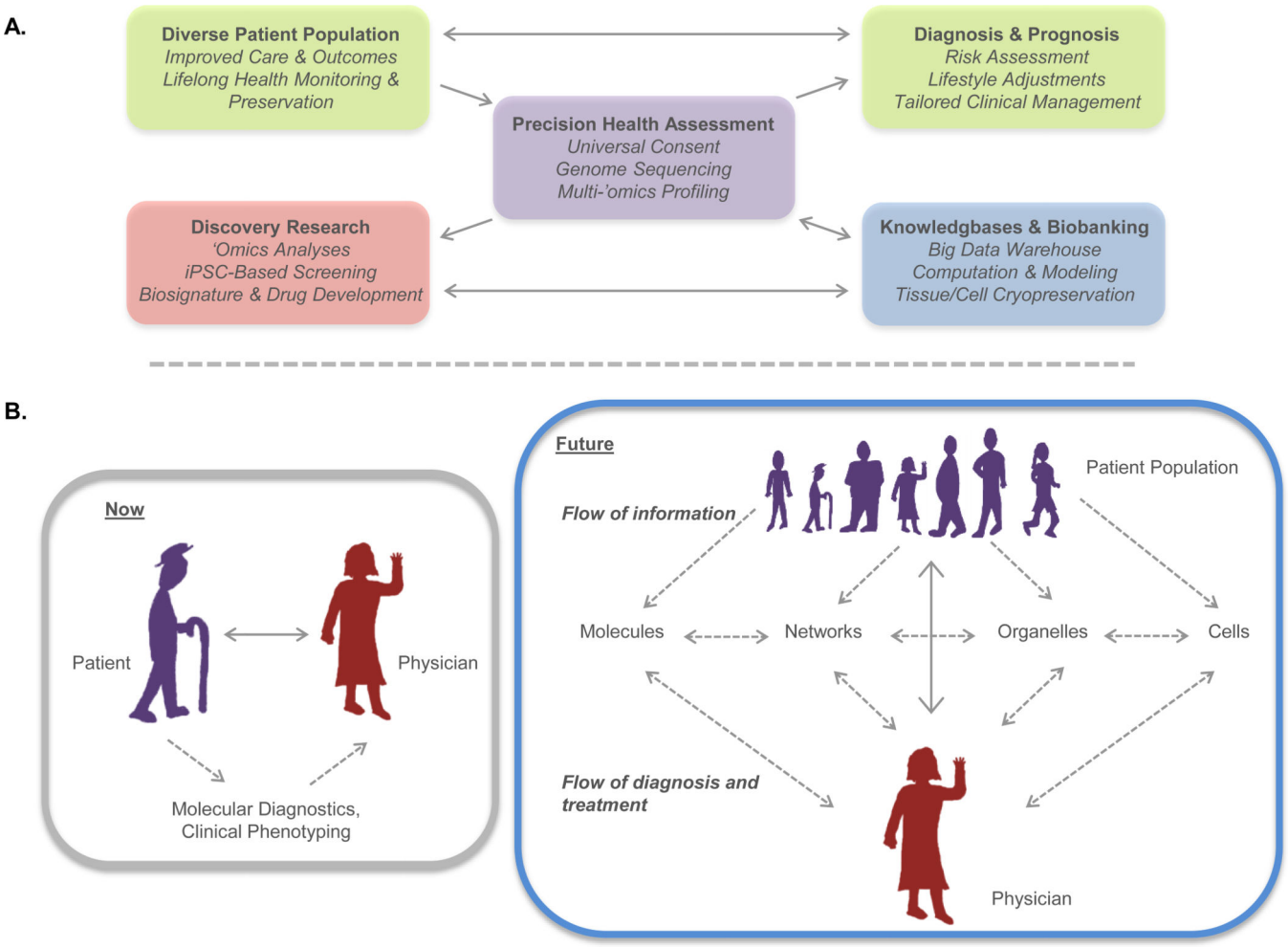

FIGURE 1. Integrating Diagnosis with Discovery and Evolving New Care Models

A, By engaging the patient population as a partner in precision medicine, lifelong health monitoring will facilitate not only improved diagnosis, but a sustained source of human samples for discovery research. This infrastructure also serves as an asset for the health system, due to the increasing burden of cardiovascular disease and the diversification of the American population. ***B***, Once disease manifests, medical treatment often proceeds without heed to factors that may indicate the effectiveness of one therapy over another. In a precision medicine environment, different scales of biological information are measured and become actionable, aiding in the clinician's management of the patient. Medicine will remain the science of treating the individual—the molecular insights from a diverse population will better tailor the treatment process, promoting health.