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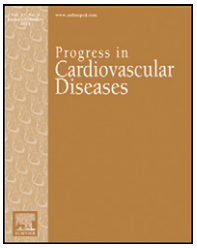

Precision Medicine, Cardiovascular Disease and Hunting Elephants

*Michael J. Joyner**

Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905

ARTICLE INFO

Keywords:
Precision medicine
Genomics
Clinical research

ABSTRACT

Precision medicine postulates improved prediction, prevention, diagnosis and treatment of disease based on patient specific factors especially DNA sequence (i.e., gene) variants. Ideas related to precision medicine stem from the much anticipated "genetic revolution in medicine" arising seamlessly from the human genome project (HGP). In this essay I deconstruct the concept of precision medicine and raise questions about the validity of the paradigm in general and its application to cardiovascular disease. Thus far precision medicine has underperformed based on the vision promulgated by enthusiasts. While niche successes for precision medicine are likely, the promises of broad based transformation should be viewed with skepticism. Open discussion and debate related to precision medicine are urgently needed to avoid misapplication of resources, hype, iatrogenic interventions, and distraction from established approaches with ongoing utility. Failure to engage in such debate will lead to negative unintended consequences from a revolution that might never come.

The purpose of this essay is to raise issues, in an intentionally provocative way, about so-called "precision medicine (PM)" and the limitations of this paradigm as it might be applied to cardiovascular (CV) disease (CVD). The phrase "hunting elephants" is used as a part of this strategy because first, the parable of the blind men and the elephant can be used to think about reductionist approaches to the scientific study, diagnosis and treatment of complex CVD phenotypes.[1] In this story a number of blind men are feeling an elephant and depending on what body part they feel, in the absence of an overall perspective, each one concludes that the elephant is something other than an elephant. For example the leg is thought to be a tree trunk.

The second elephant is the "the elephant in the room", which implies a willful ignoring of or lack of attention to obvious or uncomfortable facts. Together these two elephants are analogies about how the biomedical community is or is not "looking" at issues that can inform a critical evaluation of PM and what our community collectively chooses to "see". As this essay progresses examples germane to PM and CVD will be featured.

What is precision medicine?

There is no clear definition of PM and this term seems to have drifted into use over the last several years and largely replaced its predecessor personalized medicine. From a CVD perspective several prominent authors have focused on the potential for genetic or genomic (DNA sequence variant) information to inform ideas about risk stratification, prevention, drug dosing and choices, therapeutic responses and ultimately outcomes.[2–5] This includes information about both rare and common diseases. It also includes ideas about generating new targets for therapeutic intervention

Statement of Conflict of Interest: see page 657.

* Address reprint requests to Michael J. Joyner, MD, Department of Anesthesiology, Mayo Clinic Rochester, MN 55905.
E-mail address: joyner.michael@mayo.edu.

http://dx.doi.org/10.1016/j.pcad.2016.02.004
0033-0620/

Abbreviations and Acronyms

BP = blood pressure

CT = computed tomography

CV = cardiovascular disease

CVD = cardiovascular disease

GWAS = genome wide association studies

HF = heart failure

HG = human genome

HGP = human genome project

HTN = hypertension

PD-1/PD-2 = programmed cell death protein 1 and 2

PDE5 = phosphodiesterase type 5

PM = precision medicine

VEGF = vascular endothelial growth factor

and the development of new classes of drugs. Notably, the opinion leaders cited above all assert that this version of medicine will have wide and transformational applications and thus is the future. Unfortunately, they offer few specifics about the magnitude of the changes in CVD morbidity, mortality and costs that they anticipate to stem from the approaches they advocate.

The term "precision" has largely replaced personalized because it implies more accuracy across the spectrum of the patient/physician and health care system interaction. This potential for increased accuracy is then on top of the well-established principle that each individual patient should be treated in a personal way that attempts to consider the multi-factorial nature of their individual circumstances and condition. Fig 1 is a schematic published in early 2016 that I adapted from the USA Today newspaper. While it is oversimplified, it largely captures the fundamental appeal of PM as advanced by some of its leading advocates and also reflects concepts common among the general public, supported by political leaders, and pitched to investors.

The Human Genome (HG) Project (HGP) and genetic revolution in medicine

So, where did the concepts that ultimately led to Fig 1 come from? Ideas about the genotype phenotype relationship are at least a century old and preceded by more general philosophical debates about nature versus nurture that date to antiquity.[6] However, by the 1980s it became apparent that it might be possible to sequence the human genome. This possibility led to many bold predictions about the medical advances that would rapidly follow the reading of the so-called "book of life" as the anticipated clear cut genetic causes or contributors to most diseases were identified as a result of the HGP.[7] These predictions tended to ignore epidemiological data showing that disease patterns are largely influenced by environment, behavior and culture. Importantly patterns of disease can shift markedly in homogeneous ethnic groups with migration, and the prevalence of conditions like obesity or stomach cancer can change dramatically in a population far faster than the prevalence of potentially "causal" gene variants.[8–10]

By the late 1990s a few years before the draft sequence of the HG was published, a "genetic revolution in medicine" was envisioned that would rapidly follow the HGP. Fig 2 is redrawn and modified slightly from the Shattuck Lecture given by Francis Collins and published in the *New England Journal of Medicine* in 1999.[11] I have numbered the key nodes of the diagram central to PM 1–6. I have also added a seventh node "reduce costs" based on highly speculative estimates by Dzau and colleagues[12] about the potential cost effectiveness of PM. Cost is also difficult to define and can encompass many factors beyond the just price of a given service. It can also include lower costs of care over time via less waste, fewer complications and side effects, less utilization of services, and things like more economic productivity as a result of better health.

With this framework as a convenient background I will next highlight experimental findings relevant to each node. I view this experimental evidence as pilot work or preliminary data which can inform discussion and debate about the ultimate promise of precision medicine to transform health and health care at lower costs. Many of the examples will be from CVD or related metabolic diseases like type 2 diabetes mellitus (T2DM). Some examples from cancer will also be used because cancer is seen by advocates of PM as a disease where so-called targeted therapies might lead to early "wins" for this approach.[13]

Disease with a genetic component

A key idea underpinning both the HGP, the genetic revolution in medicine and now PM is that for many if not most diseases (including common diseases) a limited number of common gene variants explain most disease risk. This is known as the common disease common variant hypothesis.[14] In this context, gene variants that confer relative disease risks of 5–10× would be highly predictive. These variants could then be identified via screening and then targeted with precision interventions could be tailored to the individual. Additionally, information about the biological effects of the risky variants could be used to develop new drugs.

So, what is the status of the common disease common variant hypothesis? The short answer is that the hypothesis has been rejected. For hypertension (HTN) about 40 genes have been identified that are thought to influence blood pressure (BP) but the biggest effect sizes are on the order of only 1 mm Hg, and experts in this area believe that potentially hundreds of gene variants with subtle effects on BP might ultimately be identified.[15] In a prospective cohort of more than 19,000 initially healthy white women from the Women's Genome Health Study the distribution of gene risk scores based on 101 variants was similar in women who did and did not suffer a CVD event (myocardial infarction, stroke, arterial revascularization, and CVD death) over 12 years of follow-up.[16] As is the case for gene variants and HTN a number have been linked to coronary artery disease but again their effect sizes are small with relative risks barely above 1.0.[17] Similarly a large number of genetic variants with small effect sizes have also been identified for atrial fibrillation.[18]

Taken together the observations highlighted above demonstrate that for most common forms of CVDs any risk associated with gene variants is small and conditional based