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Review article

Developing a Cardiac Moonshot 2020 by Leveraging Precision Medicine

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Introduction

Cardiovascular diseases like cancer continues to accounts for millions of death and lost productivity in the USA so finding a moon shot to cure cardiovascular disease and cancer could be the defining moments in medicine as was the discovery of penicillin to fight infection about half a century ago. Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. The article seeks to provide a framework to redefine the treatment of heart diseases by harnessing the power of precision medicine focused technologies whilst leveraging the strength of academia, biotech industry, policy makers and venture capitalist to develop a cardiac moon shot.

Review

Precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. Precision medicine contrasts to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals?

In early 2015, President Obama announced a research effort focusing on bringing precision medicine to many aspects of healthcare. The President's budget for fiscal year 2016 included $216 million in funding for the initiative for the NIH, the National Cancer Institute (NCI the NIH institute focused on cancer research), and the Food and Drug Administration (FDA) [1].The NIH plans to launch a study involving a group (cohort) of at least 1 million volunteers from around the United States. Participants will provide genetic data, biological samples, and other information about their health. These data will be used by researchers to study a large range of diseases, with the goals of better predicting disease risk, understanding how diseases occur, and finding improved diagnosis and treatment strategies [2].

Despite an ever-growing number of studies and editorials herald the promise of 'precision medicine' it is still a young and growing field and many of the technologies that will be needed to meet the goals of the Precision Medicine Initiative are in the early stages of development or have not yet been fully developed. The shift toward a deeper understanding of disease based on molecular biology will also inevitably necessitate reclassification of disease states incorporating this knowledge. To that end, the World Health Organization's century-old International Classification of Diseases must be modernized to take into account the expanding molecular data on health and disease [3].

Precision medicine requires handling of multi-parametric data and some proficiency in interpreting "-omics" data, placing new demands on medical professionals, who may be ill equipped to deal with the anticipated complexity and volume of new information. Addressing these challenges will require effective clinical decision support tools and new educational models. On the diagnostic side, new technologies and analytical tools will allow us to pinpoint patient-specific differences and on the treatment side novel therapies will permit us to exploit those differences for better outcomes. A combination of genomic, epigenomic, transcriptomic, and metabolomics information - a patient's 'panomic' data - may soon be part of an individual medical record. Innovative therapies such as ivacaftor, a cystic fibrosis treatment that targets only a small set of mutations in the CFTR gene, could be weapons in our treatment armamentarium to provide the 'right drug in the right dose at the right time'. Despite the promise of precision medicine researchers will need to find ways to standardize collection of data from more than 1 million volunteers from hospitals and clinics around the country. They will also need to find efficient ways to store large amounts of this patient data in databases [4].

Cardiology and cardiovascular surgery are poised to be a leader in the development of this discipline, based upon more than half a century of contributions. Indeed, the pioneering Framingham Study was instrumental in introducing the concept of disease prediction based upon patient-specific data or 'factors of risk'-serum cholesterol and blood pressure [5].

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One major goal of cardiovascular focused precision medicine initiatives will be to tackle the cornerstones of heart disease, such as hypertension, diabetes or coronary artery disease [6]. Despite their strong inheritability, uncovering a genetic signature for hypertension or coronary artery disease that can lead to meaningful interventions has been challenging because of the underlying genetic complexity. It is a problem of numbers: any single genetic variant contributes only a small amount of information. Further, even in the largest of the recent genetic studies only a few genetic variants meet the strict statistical thresholds for significance, thus leaving us with a limited numbers of variants contributing only a small increase to risk stratification algorithms beyond the traditional coronary artery disease risk factors. To overcome these hurdles new statistical methods and analysis paradigms need to be developed and implemented. One promising approach under investigation is to add orthogonal data, such as information from commonly obtained blood tests, functional data, or some of the new 'panomic' data sets (e.g. metabolomics, transcriptomics, or signatures from our micro biomes).

The U.S. Health Resources and Services Administration is working with several health institutions to figure out how to bring "underrepresented individuals, families and communities to the cohort."Other components of the Precision Medicine Initiative include development of data security principles and framework, development of open standards for electronic health records, an effort by the Veterans Administration and the Department of Defense to develop a research cohort of more than 450,000 veterans called the Million Veteran Program, a guidance from the Office for Civil Rights on individuals' access to their health information under HIPAA, and a precision cloud-based platform under development by the FDA to "encourage genomics researchers to advance quality standards and achieve more consistent and accurate DNA test results"

Genomics

Currently, genetic testing is available for approximately 2000 clinical conditions, and the number of available diagnostic tests is increasing exponentially. Cardiology has also been a trailblazer in applying some of the newer tools of precision medicine. The identification of specific genetic loci associated with congenital long-QT syndrome afforded a platform for genotype–phenotype correlations.

Long-QT patients with mutations in the potassium channel gene KCNQ1 most often experience events during exercise and rarely during sleep while the trigger for long-QT patients with mutations in the sodium-channel gene SCN5A is most often sleep and rarely exercise [6]. Beta-blockade has been the mainstay of therapy for patients with congenital long QT syndrome but 'late' sodium channel current blockers appear to be uniquely efficacious in patients identified with SCN5A mutation8 with such genotype guided therapy is every bit as precise as the developing strategies for mutation guided cancer therapy.

One excellent example is a recent study that analyzed heart failure patients with preserved ejection faction (HFpEF) across 46 different variables. Heart failure patients with preserved ejection faction is a notoriously heterogeneous disease, but this study was able to identify three distinct groups with widely different outcomes. There are bound to be missteps as well as successes, and indeed cardiology has already seen some examples. Since genetic polymorphism at CYP2C19 affects the levels of the active metabolite clopidogrel, determining a patient's genotype promised to help guide anti platelet therapy and led to a US FDA 'Black Box' warning with a suggestion to consider genetic testing. Nevertheless, polymorphism-guided anti platelet therapy has not proved successful. In a similar manner, we are just beginning to develop strategies to respond to incidental genetic findings.

Six percent of asymptomatic and apparently normal individuals harbour a protein-altering missense mutation in KCNQ1, KCHN2, or SCN5A, the three major long QT syndrome loci. Such a high mutation rate invariably leads to diagnostic and therapeutic dilemmas when patients with no syncope and no family history of sudden death are incidentally discovered after whole-exome sequencing for an unrelated condition to have a mutation in one of those genes. Until we develop better means to correlate specific genetic variants with disease risk, we will be challenged to respond appropriately to what promises to be an escalating number of cases. Bayeshain principles would have to be applied to decrease false positives in exercise treadmill testing for coronary artery disease.

Even with these cautions, one can imagine that general approaches such as those advocated for statin therapy in the 2013American College of Cardiology–American Heart Association (ACC-AHA) Task Force on Practice Guidelines will soon transition to more individualized therapeutic approaches decisions informed by precision medicine tools. Understanding disease and identifying the right patients will be crucial for precision medicine efforts to work [7].

Pharmacogenomics and Gene Editing Therapies

Pharmacogenomics is the study of how genes affect a person's response to particular drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to variations in a person's genes. Many drugs that are currently available are "one size fits all" but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. Given the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions.

A notable ongoing pragmatic trial is ADAPTABLE, the first study conducted through the National Patient-Centered Clinical Research Network (PCORnet), which will attempt to determine the optimal dose of aspirin for secondary prevention of CVD. Which is funded by the Patient-Centered Outcomes Research Institute (PCORI). 20,000 patients with prior MI or obstructive CAD plus at least one other risk factor will be randomly assigned aspirin 81 mg/day or 325 mg/day and followed up to 30 months for death, hospitalization for MI or stroke and gastrointestinal bleeding and exiting data sources will be used to collect baseline characteristics. The trial includes an Internet portal for patients and physicians to collect and monitor data. Researchers will collect patient-reported outcomes, use existing data and patient-reported outcomes at follow-up, and perform mechanistic studies, which may include genetic testing and platelet physiology studies.

New targets which include iPSC-derived relevant cells (e.g. vascular smooth muscle, endothelium, macrophages, and platelets) and unbiased whole genome transcriptomics and epigenetic profiling will help identify distinct nodal pathogenic pathways and key regulators of disease-specific phenotypes using genome editing techniques, and drug screening. The expectation is that this interdisciplinary approach using patient cohorts, stem cell technology, and genomics and harnessing the strength of molecular biology, computational biology, bioinformatics and epidemiology to probe these poorly understood regions of the genome to determine the genetic and epigenetic contributions to metabolic status, systemic inflammation, and circulating proteome metabolome, and clinical phenotypes will pave the way for novel therapeutic targets for personalized drugs in cardiovascular diseases.

There are now drugs in the pipeline that have been developed using a precision medicine approach. As one might expect from initial efforts in a new paradigm, they tend to be based on research into a simple relationship; for example, between a single gene and a single phenotype. One example is MYK-461 (Myocardial), a novel therapy for treatment of hypertrophic cardiomyopathy. It was developed to address "a known causal pathway with identified molecular targets in that pathway, "Autosomal-dominant mutations encoding contractile proteins of the heart can cause hypertrophic cardiomyopathy". Specifically, by studying the mechanistic properties of mutations in sarcomere proteins that can cause hypertrophic cardiomyopathy, researchers targeted a specific biomechanical function altered by mutation and identified a small molecule, which they named MYK-461 that specifically modulates that function, correcting for the effects of mutations. They have tested it in mice with several of the specific mutations seen in humans. The researchers found that the molecule counteracted the effect of the mutations and suppressed development of ventricular hypertrophy, cardiomyocyte disarray and myocardial fibrosis. The molecule also reversed the hypertophy in mice that had already developed it with the next step determining which humans could most benefit from it. Currently there is focus on the subgroup with obstructive hypertrophic cardiomyopathy, in those people the abnormal thickening of the heart muscle in the left ventricle impedes the exit of blood from the heart, which can be measured as a pressure difference or gradient between the LV and the aorta. Currently, the only proven treatments are myectomy, an open-heart surgical procedure, or alcohol septal ablation, an invasive procedure that essentially causes a localized MI, so a medication to relieve the obstruction could address an unmet need in a well-profiled, high-risk population. The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma [8].

Remote Monitoring Technologies and Wearable

Through the use of remote monitoring technologies we can continuously monitor those at highest risk for recurrent medical events or re-admissions into the acute care setting. Prior to an anticipated life threatening event, machine learning platforms can alert or send an early warning sign to the individual or the care provider in real time enabling a rapid response intervention. Wearable platforms would be able to collect sensory and physiologic data and using machine learning algorithms curate the data to provide real time actionable data at the point of care .Wearable platforms would be poised to capture and utilize the flood of real-time data from wearable fitness trackers and implanted sensors. Such device data add a temporal dynamic to risk stratification and treatment paradigms. Determining whether a patient continues to have paroxysmal trial fibrillation, and whether to continue anticoagulation therapy, may soon be as simple as checking a Smartphone app. As a new flood of panomic data enters our treatment algorithms.

Internet of Things Health Data Ecosystem

The United States and other countries are investing in multibillion-dollar projects to implement effective electronic health records (EHRs). These systems will store comprehensive, individual-specific data that will be essential as we move toward precision medicine. However, in a U.S.-based survey, physicians reported that EHRs had poor systems for online test ordering and provided only limited decision support in terms of indications for genetic testing, interpretation of test results, and potential impact of results on patients and their families [3]

The quantified self movement is in full swing with 69% of U.S. adults keep track of at least one health indicator such as weight, diet, exercise routine, or symptom according to Pew Internet and American Life Project's report back in January. Of those, half track "in their heads" one-third keep notes on paper, and one in five use technology to keep tabs on their health status. Research by the Center for Medicare and Medicaid Services shows national health care expenditures are nearing $3 trillion dollars per year. By making so many things intelligent with embedded networked sensors, we can add intelligence to almost anything. All of those sensors will continue to create rapidly increasing amounts of data

which so far has not found its way into our electronic health medical records. Decision support tools have the potential to address these limitations and enable precision-medicine approaches to health care by providing clinicians and patients with individualized information and preferences, intelligently filtered at the point of care. They will provide clinicians with options for test ordering indicate the sensitivity, specificity, and positive predictive value of tests; and aid clinical workflow by providing algorithms to facilitate decisions on the basis of test results.

Point of Care Diagnostics & Liquid Biopsies

Point of Care diagnostics seeks to revolutionize laboratory testing by using advanced microfluiditic technologies to detect various biomarkers in urine, blood or sputum with a single drop of blood and validate the technology with standard laboratory testing devices currently used by laboratory services. Companies like Ymir genomics and BBB technologies are leading the front in the area point of care blood testing over several disease specific bio-markers with a single drop of blood for detection of heart failure (BNP) Pulmonary embolism (D-Dimer) ,myocardial infarction (troponin) to name a few Point of care testing would enable disease detection and monitoring in real time beyond hospital care and using cloud health platforms would enable real time monitoring of chronic diseases states like diabetes

3D Printing

Work is being done on bio printing of organs and tissue regeneration one exciting concept is the ability to combine 3D imaging data sets to reconstruct a heart valve and then bio-print valve prosthesis for repairing a damaged heart valve through minimal invasive heart surgery. We can take a patient's 3D ultrasound data of a patient and print a 3D model of a patient's customized prosthetic heart valve ring that could be used to simulate a repair a non functional or damaged heart valve. The basic concepts outlined could be streamlined and scaled using cloud computing software technology to model patient heart valve rings for personalized medicine. The detailed process of generating 3D dataset visible is termed a 3D display and results in either multiple 2D image planes or the creation of a 3D graphic reproduction. Three-dimensional graphic reproduction is the product of graphic rendering, a 2-step computer graphics technique. The first step is segmentation, which separates within the 3D echocardiography dataset the object to be rendered from surrounding structures by specifically differentiating cardiac tissue from blood, pericardial fluid, and air. This step delineates the 3D surfaces of cardiac tissue. After segmentation, the 3D dataset undergoes 1 of the 3 increasingly complex rendering techniques to create a visible 3D object: wireframe rendering, surface rendering, or volume rendering

Advanced Imaging

Advances in imaging have been associated with advances in minimal invasive image guided surgery. Transcatheter valve replacement surgery enables replacement of heart valves without requiring open heart surgery and placement of patients on cardiopulmonary bypass. Recently the FDA has approved transacted aortic valve replacement to be performed on intermediate risk patients thereby increasing the number of patients amenable to such cutting edge technology.

Advances in tablet ultrasound technology would enable smart phone devices to be converted into ultrasound devices enabling the democratization of ultrasound with cloud imaging platforms. It is conceivable that using machine learning algorithms in the near future patients would be able to scan themselves and get real time diagnosis or send the images for real time diagnostics and intervention. Advances on molecular imaging has also enabled better assessment of heart function as well as predicting therapeutic interventions associated with personalized therapeutic regimens.

Robotics and Augmented Reality

Virtual reality techniques allow a pre-operative 3D visualization of the patient that can be manipulated in real time through the use of a patient-specific surgical simulation .In addition, augmented reality techniques superimpose this 3D image on the real image .Thanks to augmented reality it is thus possible to compensate the lack of the sense of touch with visualization of these forces by providing an artificial 3D view included transparency. The combination of visualization software, augmented reality and robotic technology should overcome the current limitations of minimal access surgery and perform extremely safe procedures with no scars. The goal is to develop virtual patient modeling software that uses patient-specific data to enable pre-operative assessment, diagnosis and a personalized plan for surgery. Virtual planning software would enable patient specific navigation and tool positioning within 3D images that can be reconstructed from any multimedia-equipped computer for a virtualized personalized surgery using enhanced robotic techniques.

Hansen Medical an intravascular robotic company which has been applying robotic technology to treat cardiac arrhythmias and peripheral vascular disease. The advantage of intravascular robotics enables remote treatment of patients using advanced robotics and image guided platforms without the risk of radiation which is the archiles heel of interventional procedures done under fluoroscopy.

Summary

New training paradigms will also be necessary for tomorrow's doctors, who will benefit from a deeper, more holistic view of illness integrating traditional pathophysiology-based models with emerging molecular mechanisms. This shift would benefit from international-level attention. Ultimately, cardiovascular focused precision medicine should ensure that patients get the right treatment at the right dose at the right time, with minimum ill consequences and maximum efficacy. But it will change how medicine is practiced and taught and how health care is delivered and financed. It will change the way research and development are financed and regulated. It will deeply affect public trust and the nature of the patient–clinician relationship, and it will require unprecedented collaboration among health care stakeholders.

Undoubtedly, significant challenges lie ahead, though none are insurmountable. The cardiovascular precision medicine initiative also raises ethical, social, and legal issues. With health data on such a large number of people, it will be critical to find ways to protect participants' privacy and the confidentiality of their health information. Participants will need to understand the risks and benefits of participating in research, which means researchers, will have to develop a rigorous process of informed consent [7]. Accomplishments of such an initiative could include measuring risk for a disease based on genetics, environment and the interaction between them identifying why people respond to the same drug differently discovering new biomarkers using mobile health technologies to assess relationships between activity, physiology, environmental exposures and health outcomes reclassifying diseases and putting them into better context and creating a platform by which trials of targeted therapies could be conducted.

Conclusions

For cardiovascular focused precision medicine approaches are to become part of routine healthcare, doctors and other healthcare providers will need to know more about molecular genetics and biochemistry. They will increasingly find themselves needing to interpret the results of genetic tests, understand how that information is relevant to treatment or prevention approaches, and convey this knowledge to patients.

Yet expectations must be realistic: precision medicine will happen neither automatically nor overnight. The transition should be steered by international consortia including leaders from academia, health care, government, and industry that draw up proposals for public consultation [8]. The World Economic Forum Health Council is currently establishing structured dialogue on the key issues outlined here and suggests that multi-stakeholder adaptation. Health Care Stakeholders and Their Roles in Ensuring the Success of Precision Medicine. If all goes as planned, cardiologists and cardiac surgeons will eventually have more treatments in their armamentarium that will be targeted to people who are highly likely to benefit from the therapy and highly unlikely to experience risk from it."To me, the goal is simple" "It's to identify the people who need the treatment the most and who stand to benefit the most, and to avoid ... exposing people to side effects who don't stand to gain" – By Erik Swain.

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