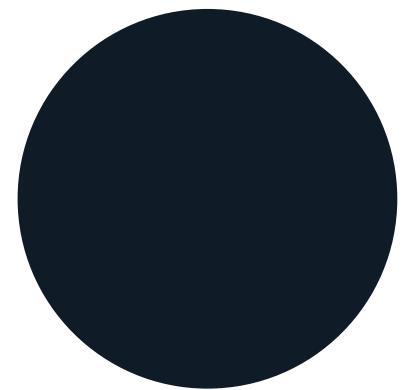


DISRUPTIVE DOZEN



2017 | WORLD MEDICAL INNOVATION FORUM



THE DISRUPTIVE DOZEN
CARDIOVASCULAR

The culture of innovation at Brigham and Women's Hospital and Massachusetts General Hospital—throughout all of Partners HealthCare and collaborating institutions—naturally fosters a good deal of discussion about new “disruptive” technologies and which ones will have the biggest impact in bringing novel complex health care products and services to greater levels of affordability and accessibility. The mission of Partners clinicians and researchers to provide the best care for patients drives a continuous dialogue on what state-of-the-art medical technologies are just over the horizon. The Disruptive Dozen was created to identify and rank the most disruptive technologies that Partners leading faculty feel will break through over the next decade in cardiovascular and cardiometabolic care.

2017 STEERING COMMITTEE CO-CHAIRS



Calum MacRae, MD, PhD
Chief of Cardiovascular Medicine, BWH;
Associate Professor of Medicine,
Harvard Medical School
(World Forum Co-Chair)



Anthony Rosenzweig, MD
Chief, Cardiology Division, MGH;
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Disruptive Dozen | 2017

The Nomination Process

Beginning October 2016 and through December 2016, more than 50 30-minute in-person and telephone interviews were conducted with leading faculty from Brigham and Women's Hospital and Massachusetts General Hospital to elicit their nominations of the technologies they believe will have the greatest impact on cardiac care at any point in the next decade. The interviews resulted in 59 nominated technologies that varied from the broad in scope to quite specific.

Selection Process

Twenty-seven leading Partners faculty gathered in December to form a committee of "selectors" to jointly choose and rank the final 12 technologies. Calum MacRae, MD, PhD and Anthony Rosenzweig, MD served as selection committee moderators and were supported by Partners Innovation staff. To receive consideration for the final Disruptive Dozen, nominated technologies had to meet the following criteria:

Criteria 1

The innovation had to have the strong potential for significant cardio-related clinical impact at some point in the next decade and offer significant patient benefit in comparison to current practices. The innovation may also have had a significant benefit to the delivery/efficiency of cardiovascular-related health care.

Criteria 2

Nominated cardiovascular-related innovations had to have a high probability of successful commercial deployment—e.g., payers will be expected to support it.

Criteria 3

The innovation must be on the market sometime before April 2027. Ideally, the final group selected would involve a blend of disruptive technologies coming to market in the next three to four years as well as ones that will come to market later in the decade.

Final Scores and Announcement at the World Medical Innovation Forum

Selection committee members jointly ranked the innovations from 1 to 12 using the initial scoring and further discussion. The selection committee ranking was final and will be announced May 3, 2017 in a one-hour panel at the World Medical Innovation Forum. The session will be moderated by Calum MacRae, MD, PhD and Anthony Rosenzweig, MD, and feature 12 faculty members selected to briefly comment on each technology.

Aging and Heart Disease: Can We Reverse the Process?

It's not likely that all humans will live to reach their hundredth birthday, but thanks to improvements in public health and medical therapies, the human lifespan is the highest it's ever been. According to a recent report from the National Center for Health Statistics, a woman's life expectancy in the United States is 81 years, while it's 76 for men.

Not surprisingly, the continued expansion of human longevity is resulting in an unprecedented aging of populations worldwide. By 2050, the number of people aged 65 years or older will nearly triple to 1.5 billion. In the United States, adults over 65 years will soon represent more than 20 percent of the population.

Aging continues to be one of the most enigmatic processes in biology, and researchers are determined to unravel its mysteries. Understanding the impact of aging on the cardiovascular system remains at the core of these efforts, as heart disease continues to be the leading cause of death in the elderly. Although advanced age is strongly linked with the incidence of heart disease, it has long been perceived as a non-modifiable risk factor—one that we just accept in the natural evolution of life.

Exciting research into the biology of aging, however, is beginning to suggest otherwise. Today, scientists are not only identifying key molecular mechanisms that drive aging, but are also using innovative approaches to get to the root of some of the most fundamental, yet unanswered, questions in human aging.

For example, how do seemingly "simple" lifestyle interventions, such as exercise and diet, improve health as we age? These groundbreaking discoveries are now pushing the boundaries of aging and leading to the development and testing of novel therapies that will hopefully halt—or perhaps even reverse—the human aging process in the heart and the vasculature.

Boston researchers are studying proteins called Growth Differentiation Factors 8 and 11, or GDF-8 and -11. These proteins circulate in the blood, and GDF-8 levels seem to diminish in older age. The scientists have already reported that GDF-11 has the potential to undo much of the cellular damage triggered by aging, but in mice, not humans.



The results were promising: Daily injections of GDF-11 shrunk the thickened heart muscle in old mice and also contributed to weight loss and improved muscle function. Subsequent studies in humans, however, have yielded mixed results in regards to GDF-8/11's relationship to cardiovascular outcomes—highlighting the many complexities of studying the aging process in humans. The question now remains: Can restoring GDF-8 or GDF-11 to the higher levels of youth reverse the aging process in heart patients?

Researchers from Evanston, Illinois, have recently focused on another target in the aging process, and the results thus far have been encouraging. When cells and tissues reach an advanced age, they enter a state called senescence, in which they lose the ability to regenerate. At this point they begin to secrete certain "old age" proteins that can accelerate aging and the onset of age-related diseases.

The scientists have discovered that one of those circulating proteins, plasminogen activator inhibitor, or PAI-1, not only helps control the body's clot-dissolving system, but also plays a key role in aging. The Evanston group has now created an experimental drug that inhibits the effects of PAI-1, successfully quadrupling the lifespan of certain mice while keeping their organs healthy. Early clinical trials to determine the drug's safety in humans have already begun in Japan. Meanwhile, scientists are also pursuing cellular therapies to potentially combat the diminished regenerative and reparative capacity of the aged heart. Researchers recently conducted an American study of 126 patients with an average age of 65 years—the largest stem cell therapy trial for treating ischemic heart failure to date—and came back with promising results.

The study found that the patients who had been treated with stem cells experienced improved outcomes, with 37 percent fewer cardiac events (including deaths and hospital admissions) related to heart failure. More than 82 percent of patients given a placebo needed hospital treatment, compared with slightly more than half on the stem cell treatment. Eight of the patients given placebo died, as compared to the four who were on cellular therapy during the same period of time.

Although the mechanisms by which this therapy improves heart failure outcomes in older adults remains unclear, the Food and Drug Administration recently granted FastTrack designation to the therapy in the hopes of getting a potentially lifesaving intervention to patients sooner.

While an "anti-aging" drug to treat heart disease may have once seemed like science fiction, examples like these suggest that it may very well be possible in humans in the near future. Groundbreaking discoveries that slow or reverse aging phenotypes in animal models—from improving protein homeostasis to diminishing oxidative stress to killing senescent cells—continue to generate excitement about someday targeting the aging process for therapies for chronic, age-related, medical conditions.

Determining whether these interventions can prevent the development of heart disease in humans and, perhaps more importantly, improve healthspan and function in our growing elderly population, are key questions that remain to be answered. //

Nanotechnologies for Cardiac Diagnosis and Treatment

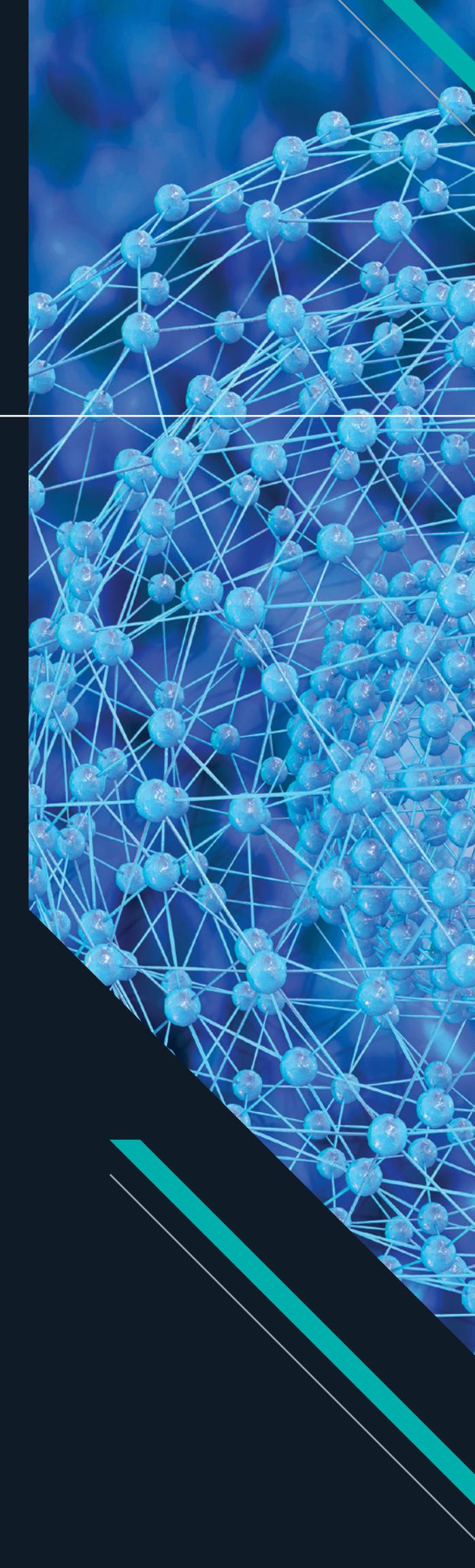
Weighing in at a little less than three-quarters of a pound, the heart has the formidable task of pumping oxygen- and nutrient-rich blood through the 60,000-mile highway of blood vessels to all the tissues of the body. Unfortunately, more than 15 million Americans suffer from coronary artery disease, which occurs when the arteries that carry blood to the heart muscle become narrowed by the buildup of plaque deposits along the arterial walls. This process, known as atherosclerosis, impairs the heart's ability to pump enough blood through the coronary arteries to provide adequate oxygen and nutrients to the body. As a result, a blood clot can form on top of a plaque, leading to a fatal heart attack.

Although current drugs, devices, and lifestyle changes have significantly reduced the number of deaths from atherosclerosis-related disease, there is still no cure. It is critical, therefore, that more effective heart therapies be developed.

Over next decade, nanotechnology—the science of engineering and controlling matter at the molecular scale to create devices with novel chemical, physical and/or biological properties—has the potential to change how atherosclerosis and other heart diseases are treated.

It is difficult to picture a nanoparticle, as a single nanoparticle is 100 times smaller than a red blood cell. To give an idea of how small that is, it would take eight hundred 100-nanometer particles lined up side by side to match the width of a single human hair. Many of the nanomedicines presently in development for heart disease are composed of nanoparticles smaller than 50 nanometers in size.

Researchers are discovering that there is much to be learned from these minuscule nanoparticles. Recently, a group of Boston researchers used targeted nanoparticle technology to reduce atherosclerosis in an animal model in the first study of its kind. By using biodegradable, nano “drones” to deliver a drug specifically designed to promote healing, they were able to successfully restructure atherosclerotic plaques in a mouse, making the plaques more stable. Bearing in mind that mice don't get heart attacks, the scientists hypothesize that by remodeling the original plaque environment for humans, they could block plaque rupture and thrombosis, thereby preventing heart attacks and strokes.



The researchers were able to make the nanoparticles in the study latch onto the arterial plaque, releasing a drug that quells inflammation damage. After five weeks of nanomedicine, the atherosclerosis was significantly repaired, and plaques were stabilized, making it less likely for the plaques to block the blood vessels.

The targeted nanomedicines used were nanoengineered to carry an inflammation-resolving drug payload derived from one of the body's own natural inflammation-resolving proteins, called Annexin A1. About 70 percent of the nanoparticles implanted themselves on the plaques and slowly released their drugs. One thousand times smaller than the tip of a single strand of human hair, the nanomedicines' size was key in facilitating the accumulation and retention within the plaques.

In another recent study, researchers in Ann Arbor, Michigan used nanoparticles on the hearts of sheep to target and destroy cells that cause cardiac arrhythmias. These erratic heartbeats are caused by malfunctions in the myocyte cells of heart muscle, which normally helps regulate heartbeat. The two treatment options for cardiac arrhythmia are drug therapy and cardiac ablation, a procedure which burns away the malfunctioning cells. Ablation, however, can damage the arteries, which is why scientists are trying to develop a safer and efficacious procedure.

The Michigan group used nanomedicine to target and ablate the sheep's malfunctioning cardiac myocyte cells. Since the scientists needed nanoparticles small enough to penetrate the tiny pores inside the heart capillaries, yet large enough to carry the light-sensitivity chemical that causes it to be absorbed by the cardiac myocytes, they created a tiny particle barely six nanometers in size.

Low-level, red light was then delivered to the area, destroying only the cells that had absorbed the nanoparticles, while leaving other heart cells unharmed. By using this red light illumination instead of a high-power laser, they were able to develop a far more precise technique that didn't damage the arteries. The procedure looks much like today's cardiac ablation, and human trials are scheduled.

The multidisciplinary scientific field of nanotechnology has the potential to revolutionize medicine and the treatment of cardiovascular ailments over the next decade, with doctors deploying armies of tiny robots to deliver drugs precisely where needed for the treatment of atherosclerosis and other lethal heart ailments. Challenges remain, but companies are already creating nanotechnologies that are in various stages of development to help treat, repair—and possibly even prevent—heart attacks and other heart-related ailments. //

Breaking the Code: Diagnostic and Therapeutic Potential of RNA

Ribonucleic acid, or RNA, is one of the three major biological macromolecules that are, along with DNA and proteins, essential for all known forms of life. Recently, types of RNA called microRNAs (miRNA) and long-non-coding RNAs (lncRNAs) have been found to play important roles in gene regulation, capturing international scientific attention for their potential as markers of heart health, as well as possible treatments for cardiovascular disease.

A Boston-based research team is now working to identify microRNA molecules that can serve as biomarkers to help predict outcomes in patients with heart disease.

Complications from heart attacks contribute to more than 550,000 cases of heart failure and 300,000 cases of sudden cardiac arrest. Both of these conditions are closely related to a process known as remodeling, in which the structure and function of the heart changes—or remodels—after a heart attack.

By using RNA sequencing technology, the researchers have identified characteristics in extracellular RNAs in plasma that might enable them to better predict patient outcomes following a heart attack. Their ultimate goal is to use miRNA-based tests to predict which patients might be at risk of complications related to heart remodeling. As a result, doctors would be able to more aggressively monitor their patients' conditions and intervene with medications or implantable devices if needed.

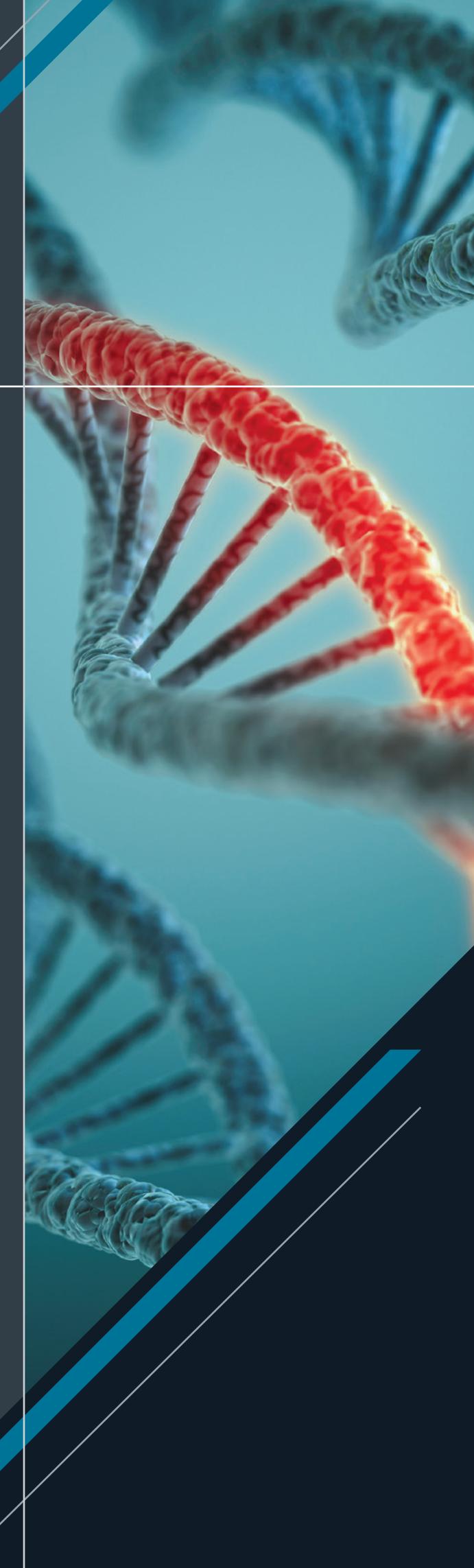
The team has already identified a number of microRNA biomarker candidates. One of these molecules, miRNA-30d, is an important predictor of beneficial cardiac remodeling and outcomes in patients with heart failure. Additionally, miRNA-30d plays a functional role in preventing cell death. The scientists are now incorporating this new discovery into studies in mice to see if miRNA-30d can serve as a new therapy to protect against heart disease.

A 2016 study reported that lncRNA could serve as a drug target for cardiac hypertrophy, a heart disease in which the cardiac muscle thickens, often leading to heart failure and death. German researchers identified CHAST, short for cardiac hypertrophy-associated transcript, and they believe it may contribute to cardiac hypertrophy. They found that CHAST was specifically up-regulated in the heart muscle cells of mice with heart failure. When

CHAST was overexpressed, it triggered hypertrophic growth of the heart muscle cells in culture, whereas when it was silenced it reduced abnormal growth.

Experiments suggest that the lncRNA may drive cardiac hypertrophy by blocking the normal degradation of heart muscle cells. Treating mice with an inhibitor known as an antisense oligonucleotide that targeted CHAST, both prevented and treated cardiac hypertrophy, while simultaneously improving heart function. These findings have set the stage for years to come for developing CHAST inhibitors and other lncRNAs to treat heart failure in patients.

Scientists are also exploring the therapeutic potential of RNA in the treatment of atrial fibrillation, a condition in which the patient's irregular and often rapid heart rate can increase the risk of stroke, heart failure and other heart-related complications. Upwards of six million Americans suffer from this common type of arrhythmia, and doctors typically treat it with a variety of ablation procedures. By interfering with the transmission of the electrical impulses responsible for the arrhythmia, ablation procedures can successfully restore a regular heartbeat. For some, however, multiple ablation procedures are required, leading to scarring and fibrosis outside of the veins, sometimes affecting both of the upper heart chambers. This often results in recurrences of the erratic heartbeats after the ablation.



Now, researchers in Salt Lake City are reporting that certain circulating miRNA molecules can impact the inflammation and fibrosis, and are associating these molecules with the recurrence of atrial fibrillation. The team found low levels of three of the microRNA molecules associated with atrial scarring in a group of patients whose atrial fibrillation came back after ablation. They now believe that in the future these molecules could be used as blood-based screening tools to help determine which patients will benefit from atrial fibrillation therapies.

Over the years, scientists have come to see the important role RNA plays in a myriad of biological and physiological processes, and with extraordinary progress being made in such a short period, novel heart diagnostics and innovative drug therapies will be available within the next decade that can help transform the treatment of cardiac disease. //



Expanding the Pool of Organs for Transplant

Heart transplantation does not adequately address the magnitude and severity of advanced heart failure (HF), a global public health concern that has the potential to reach epidemic proportions. While the gold standard for treating end-stage HF continues to be heart transplantation, there are simply not enough donor hearts available (about 2,000) for the more than 3,000 Americans on the transplant wait list. As such, doctors and scientists are developing alternative means for providing cardiac support, many of which will make an impact in the next decade.

Mechanical circulatory support devices (MCSDs) have the potential to treat many of the patients with end-stage HF, and more than 300,000 American patients each year qualify for some kind of mechanical assist device. These innovative devices replace some of the mechanical functions of the failing heart while improving cardiac output and organ perfusion.

The role of MCSDs in advanced heart replacement therapy is increasing steadily, with some thinking that the improvement in prolonged mechanical circulatory support brought on by their rotary blood pumps could have the potential to overcome heart transplant in the next decade. This would not only provide unrestricted, off-the-shelf solutions in terms of symptomatic relief, but also improve quality of life to those without access to transplantation.

Advances in the technology of MCSDs includes miniaturization, versatility with biventricular support devices, complete internalization, improved hemocompatibility profiles, and responsiveness to cardiac loading conditions. As such, MCSDs could potentially surpass heart transplantation as the primary therapy for advanced heart failure.

Presently, due to the long rehabilitation and potential complications of heart transplant surgery, only about 35 percent of patients with left ventricle assist devices (LVADs) ever get transplanted. Understanding this barrier in moving patients from mechanical support to transplantation, researchers in Chicago recently implanted the first intravascular ventricular assist (iVAC) system to assist and support a patient awaiting a heart transplant. This novel system doesn't require open-heart surgery, and it reduces pain and dramatically shortens rehabilitation. The bulk of the system is in the six-pound external drive that's carried over one shoulder.

An increasing number of people are succumbing to heart disease each year because there are too few hearts available for transplantation. To meet this vital need, a group of Boston-based scientists has successfully grown human heart tissue by using messenger RNA to revert skin cells to stem cells that could then be stimulated to grow into cardiac muscle tissue.

While this is a major step toward bioengineering hearts for people in need of a transplant, creating an entire human heart in the lab from a patient's own genetic material is still some time away. However, this novel research is expected to be used in the coming years to regenerate tissue in hearts damaged by heart attack or heart failure, thereby eliminating their need for a heart transplant in the future.

Another group of Boston researchers is attacking the heart shortage problem by using CRISPR/Cas9 gene editing in an effort to create an endless supply of safe and dependable pig hearts suitable for use in humans. The initial goal of this process, known as xenotransplantation, is to develop implantable porcine hearts that can be used with conventional immunosuppression regimens. Within a year, researchers expect to begin transplanting the organs into primates.



Transporting human hearts to new recipients is fraught with problems. The traditional way the heart is preserved and delivered for transplant is cold storage—flushing the heart with a solution that drops its core temperature, and then putting it in a picnic cooler with ice. This method can have limitations, due to organ decay, time, and distance of retrieval, resulting in the loss of many viable, transplantable organs. Now, seven hospitals are testing a novel device that could prevent this from happening by using a machine that replicates the heart functions as closely as possible while it's in transit.

This “heart in a box” device is a wheeled cart with an oxygen supply, a sterile chamber, and tubing to clamp onto the donor heart and keep it fed with blood and nutrients. Doctors say this technology may extend the time a heart can last outside the body, and can even allow for the recovery of donor hearts that wouldn't have been eligible in the past. Unlike the cold storage in a cooler, the heart in a box simulates the heart's natural environment: It is kept warm; it's beating, and it's fed by a steady stream of oxygenated blood and nutrients. All the while, doctors are able to monitor the organ's vitals.

If and when this device is approved in the U.S., it could expand the number of donated hearts by between 15 and 30 percent, saving the lives of people who would otherwise die from heart failure. //



Finding Cancer Therapies Without Cardiotoxicity

Lasting cardiac damage from cancer therapy can be devastating. Thanks to powerful new therapies, many people are surviving cancers that were once believed to be fatal. We are now seeing, however, that the off-target effects of these cancer therapies can have deadly repercussions, such as heart failure, cardiac arrhythmia, thrombosis, heart attack, severe hypertension, Q-T prolongation, or other serious illnesses.

The primary goal of cancer treatment is to eradicate and prevent the recurrence of cancer, thereby prolonging life. And the modern drug and radiation therapies have done just that: Improvements in the efficacy of modern treatment are demonstrated by the approximately 14 million cancer survivors in the United States alive today who owe their lives, in part, to chemotherapy and radiation treatments.

Nonetheless, cancer survival gains have revealed an unintended consequence of therapy: An increased incidence of cardiovascular injury. Studies have shown that after recurrence and second malignancies, cancer treatment-related cardiotoxicity is the third leading cause of treatment-associated mortality in survivors of pediatric and adolescent cancers. The incidence of treatment-induced heart damage in pediatric survivors of cancer increases over time, and can develop even three decades after therapy.

In adult patients, cardiotoxicity is drug-dependent, and depending on the type of cardiac condition, incidence can be as high as 50 percent. Five- to ten-year male survivors of adult cancer have reported heart problems to be the most common post-treatment issue, while in women survivors it is the third most reported problem, following arthritis and osteoporosis.

The acute effects of cancer treatment primarily impact the vascular system, specifically leading to hypertension, vasospasm, and thrombosis (including venous thromboembolic disease and rupture of arterial plaques). Late effects include long-term toxicities that generally involve structural cardiovascular changes, including atherosclerosis, valvular heart disease, and conduction system disease.



Chemotherapy-induced cardiomyopathy often occurs during active treatment, but it can have a delayed onset, too. With cancer patients living longer (in part because of treatment advances) it has become increasingly important to address these adverse events. Little is known, however, about the pathogenic cardiovascular mechanisms associated with cancer treatment, and even less about how to optimally prevent and manage the short- and long-term cardiovascular complications that could lead to improved patient safety and clinical outcomes.

Biomarkers may represent one of the most cost-effective and minimally invasive means for diagnosing and monitoring cardiac injury following cancer therapy. Ongoing studies are investigating the potential of known cardiac biomarkers to detect asymptomatic, cancer treatment-related, cardiac damage, as well to predict the cumulative effects of initial injury or loss of cardiac muscle cells. High-sensitivity troponin is considered the biomarker of choice for the detection of cardiac injury.

The early and non-invasive detection of cancer therapy-induced cardiac tissue injury will not only help to optimize cancer treatment, but it will also provide much-needed insight into cardio-protective interventions. Researchers are now using ultrasound-based devices, such as 3D echocardiography, strain rate imaging, and tissue Doppler imaging, to assess cardiovascular dysfunction.

Cardiac magnetic resonance imaging (CMRI) methods are also being developed and tested for cardiac toxicity assessment. As research continues, CMRI and the further identification of clinical, genetic, and biomarker risk factors will allow for the stratification of patients at low to high risk for cancer treatment-induced cardiotoxicity. It's expected that this will lead to improved treatment and monitoring options and safer cancer therapy without compromising the patient's survival.

In addition, several clinical trials are exploring various strategies for preventing or reducing the cardiovascular changes induced by cancer therapies. The beta-blocker carvedilol is being investigated as a possible therapy that could prevent—or even reverse—damage to the hearts of young adults who received high-dose anthracyclines,

chemotherapeutic antibiotics that inhibit enzyme topoisomerase II, including doxorubicin, daunorubicin, epirubicin, idarubicin, and valrubicin. Statin drugs are also being tested to see whether they can prevent the cardiotoxic effects seen in lymphoma and breast cancer patients receiving anthracycline treatment.

To assess the potential of novel drugs for heart toxicity in the coming years, drug testing may include lab tests involving animals, or cells from humans engineered to artificially express heart-related genes. Palo Alto-based researchers are now using stem cell-derived heart cells from volunteers to develop a cardiac safety index that may be used to determine how toxic tyrosine kinase inhibitors are to the human heart.

While more than two dozen of these drugs are currently used to treat a variety of cancers, some can cause irregular heartbeats or heart failure. Thus, this new index will not only help the pharmaceutical industry identify drugs that cause heart-related side effects during the drug development process, but it will also help the Food and Drug Administration during the review and approval process. //

Less is More: Minimalist Mitral Valve Repair

In the last decade, there has been a revolution in transcatheter therapies for structural heart disease. The most widely embraced, transcatheter aortic valve replacement (TAVR), was originally intended for patients with aortic stenosis, in whom surgery was considered prohibitive, but it has now been utilized as an excellent alternative to surgical aortic valve replacement in patients at intermediate or high risk and is being trialed for the low risk patients as well.

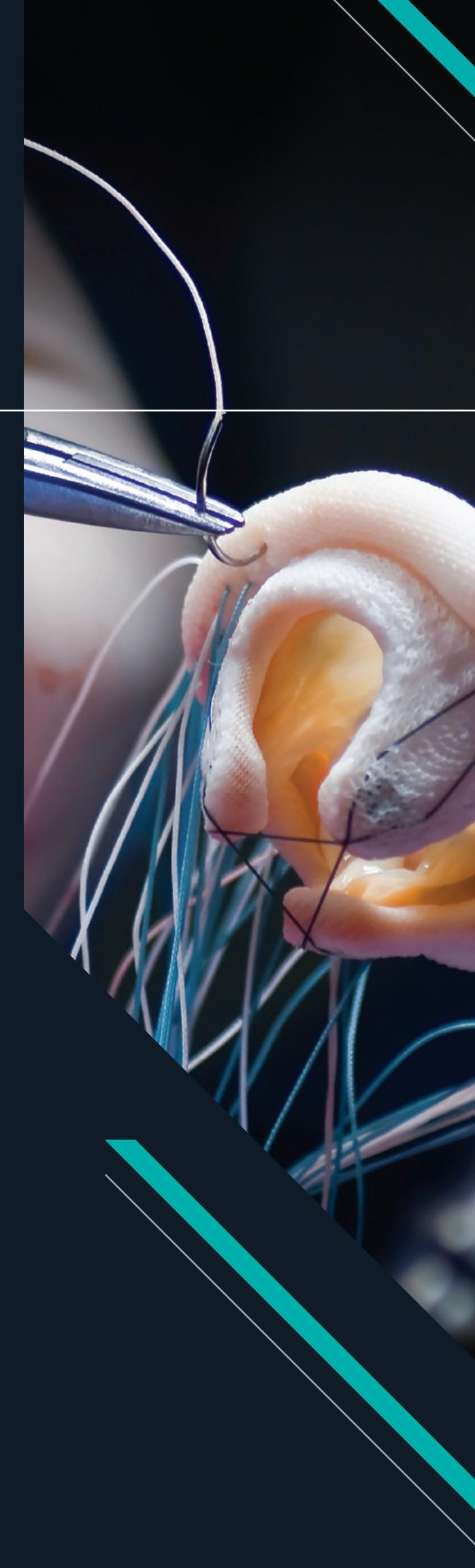
As TAVR has become established with well-designed devices and acceptable safety and efficacy, it has inspired several device manufacturers to push the envelope of innovation to meet the large unmet need for the percutaneous treatment of patients with mitral valve disease, primarily for mitral regurgitation and also for mitral stenosis.

The mitral valve is a one-way valve between the upper (atrium) and lower (ventricle) chambers on the left side of the heart. When open, the mitral valve permits oxygenated blood from the lungs to fill the left ventricle. Once the left ventricle pumps to deliver blood to the body, the mitral valve closes to prevent blood from flowing back toward the lungs.

Mitral valve regurgitation (MR) occurs when imperfect closure of the mitral valve permits blood from the left ventricle to leak back towards the lungs. It is most often caused by myxomatous disease (a kind of degenerative disease). It can also be caused by senile calcific degenerative disease, conditions that cause enlargement of the left ventricle, infections, and trauma. Severe MR affects approximately four million patients in the U.S. alone.

Mitral stenosis, a narrowing of the valve, is mostly caused by rheumatic fever (now rare in the United States) or senile calcific degeneration creates an obstruction to the forward flow of blood and thereby increases the fluid pressure inside the lungs.

Both conditions present with shortness of breath and fatigue, which initially can be managed by medical therapy but will eventually need surgical correction with a repair or a replacement. If left uncorrected on failing medical therapy, it can lead to irregular heart rhythms, increased risk of stroke, heart failure, and death.



Mitral valve surgery is a conventional open heart procedure performed through a standard midline sternotomy incision or through minimally invasive approaches through the front or side of the chest. These procedures necessitate the use of the heart-lung bypass machine and needs the heart to be stopped for the duration of the repair/replacement.

As already seen with TAVR, percutaneous valve procedures are least traumatic. Recovery in the hospital and return to normal lifestyle are quicker than any other operation.

A variety of repair techniques have been and are now being tested for transcatheter mitral valve correction, including replacement valves and repair devices used on the mitral leaflets, the implantation of neochords, and the remodeling of the mitral annulus. While the comparison of TAVR to surgical aortic valve replacement was fairly straightforward, comparing surgical and catheter based mitral valve repairs is going to be a challenge, given the complexity and artistic nature of mitral valve repairs.

The ability to percutaneously repair a mitral valve with the same degree of accuracy and reproducibility will be a challenge. Concurrent development of advanced imaging technologies will play an important role in the success of these procedures.

Anatomically, the mitral valve poses a greater test to percutaneous treatment due to its complex structure and integrated relationship with the left ventricle. Some specific difficulties facing the development of transcatheter mitral technologies are: the mitral is a larger valve; it is difficult to access; it is asymmetrical; it lacks an anatomically well-defined annulus to which to anchor the replacement valve; its geometry changes throughout the cardiac cycle; and placing a replacement valve in it entails the risk of left ventricular outflow tract obstruction.

Despite these challenges, a number of experimental devices are being developed. Initially, the good candidates for transcatheter mitral valve replacements will be patients with a failed mitral valve bioprosthesis, failed mitral valve repairs, and senile calcific degeneration. With ongoing technological advancements in the field of percutaneous valve therapies, within the next decade it is expected that transcatheter mitral valve therapies will become a valuable, minimally invasive alternative to mitral valve surgery for patients with severe mitral valve disease, particularly MR and variable surgical risk. //

Understanding Why Exercise Works for Just About Everything

Centuries ago, the Greek physician Hippocrates noted that when the body is “unused and left idle, it becomes liable to disease, defective in growth, and ages quickly.” These observations—made without the benefit of the exhaustive medical research and detailed studies that we have today—are just as valid now as they were then. Exercise is a natural medicine available to all. Cardiac research has proven that moderate exercise improves the circulation and metabolism, which reduces the chance of heart attack. Regular exercise also lowers both heart rate and blood pressure, improves the cholesterol profile and helps to prevent the development of life-threatening plaque within the heart’s arteries.

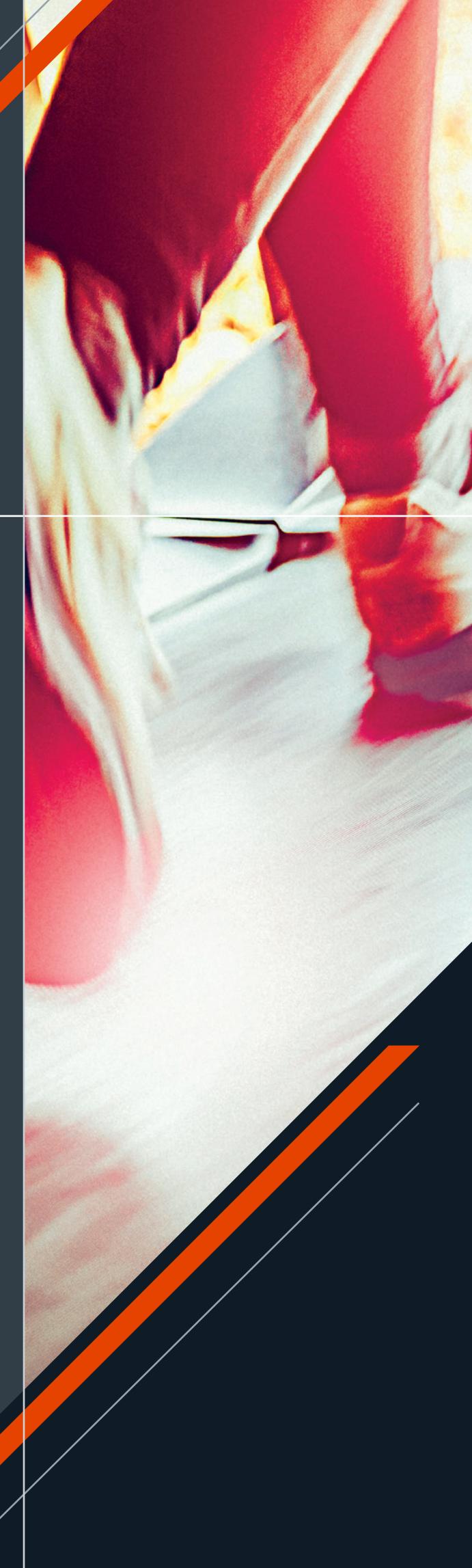
Of course, exercise alone—even if one were to walk more than 100 miles a week—does not grant immunity from life-threatening events such as heart attack and stroke. It can, however, greatly reduce the chances of sudden-death: An exercise study conducted by researchers from the state universities of North Carolina and Washington found that sedentary individuals who devote fewer than 20 minutes a week to vigorous exercise have a 56 times greater risk of dying during their normal activities than do those who exercise for more than 20 minutes daily.

The findings from this study suggest that Americans need to move a lot more: It’s now estimated that 70 percent of Americans are overweight or obese, and approximately 50 percent of adults don’t get enough exercise. Sedentary lifestyle has been directly linked to upwards of 200,000 deaths annually due to coronary artery disease, diabetes, and colon cancer. Some experts now believe that not exercising regularly does as much harm to the body as smoking a pack of cigarettes each day.

Exercising several times a week can be a big step toward improving cardiovascular endurance, muscular strength, muscular endurance, and flexibility—the four basic elements of physical fitness. While each of these elements is essential to overall health, cardiovascular endurance—the ability of the heart, lungs, and circulatory system to do their job—is the most important.

Cardiovascular endurance is built up through exercises or fitness activities that cause the body to deliver increased amounts of oxygen to the exercising muscles. To achieve this, activities must utilize the large muscle groups (such as those in the legs) and, most important, the exercise must be sustained for at least 20 minutes. Importantly, health benefits can be derived from even low-level exercise activities such as walking, hence the “no pain, no gain” paradigm is not the case.

Although fitness has been shown to be among the most potent predictors of future cardiovascular disease, it is one of the only major risk factors that is not routinely assessed by physicians.



Boston researchers are now investigating if specific tests of exercise capacity—and the presence or absence of dozens of molecules in the bloodstream, called metabolites—can be used to identify patients who may benefit from early treatment to prevent cardiovascular disease. The research will also examine how lifestyle, genetic variations, inherited family traits and measurements of heart structure and function match with changes in metabolism during exercise.

This study represents a paradigm shift away from focusing on only resting measurements and a small number of physiologic measurements during exercise in evaluating risk of cardiovascular disease. Instead, the scientists will study breath-by-breath measurements of oxygen uptake as well as a broad array of circulating metabolites during exercise in order to understand metabolic responses to exercise in the population and the ability of exercise response patterns to detect and prevent future cardiovascular disease.

Based on this research, it’s expected within a few years that simple exercise testing equipment will be used in doctors’ offices to assess heart health with a 7-minute test. //



Power Play: The Future of Implantable Cardiac Devices

Electronic device therapy, which includes implantable cardiac pacemakers and cardioverter-defibrillators, is the gold standard in the management of cardiac arrhythmias. Early pacemakers, implanted to treat the abnormally slow heartbeat of bradycardia, can now be programmed to treat a variety of heart problems, including heart failure.

The pulse generator, the electronic control center of a pacemaker, is a unit encased in titanium that usually is placed under the skin below the collarbone. Typically, the unit is small, weighs about an ounce, and has a lithium iodide battery lasting anywhere from five to 12 years. It's estimated that more than 1 million pacemakers and more than 300,000 cardioverter-defibrillators are implanted globally each year. However, complications from limited battery life; infections from compromises in the leads that connect the device to the heart; and pain associated with the high energy needed to terminate tachyarrhythmias are significant drawbacks—impacting patient autonomy, quality of life, and, in many cases, survival.

Researchers are working to eliminate these sources of suffering, poor health, and patient mortality by developing fully implantable heart devices with no external connections and an extra-long energy supply. Experts now believe that advances made in the field of optogenetics will provide a workable light-based antiarrhythmic solution that could be tested in humans within the next ten years.

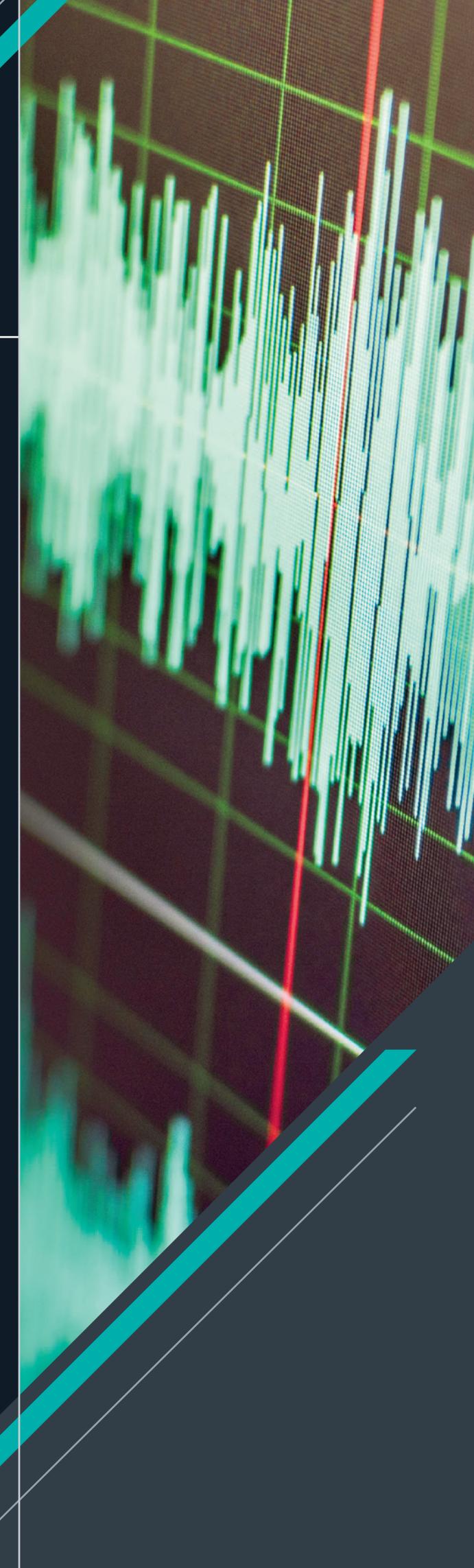
Optogenetics is a technique in which genes for light-sensitive proteins are introduced into specific types of cells in order to monitor and control their activity precisely by using light signals. Scientists anticipate being able to use optogenetics to restore healthy heartbeats painlessly in many patients now requiring implantable devices.

Using high-tech human heart models and mouse experiments, an international team of scientists in Baltimore and Bonn, Germany recently demonstrated that beams of light could replace electric shocks in patients reeling from a deadly heart rhythm disorder. For their 2016 study, the Bonn team conducted tests on beating mouse hearts whose cells had been genetically engineered to express proteins that react to light and alter electrical activity within the organ. When the researchers triggered ventricular fibrillation in the mouse heart, a focused speck of light pulse of one second aimed at the heart was enough to restore normal rhythm.

Opsins, light-responsive proteins, were inserted into individual heart cells in the mice. When exposed to the proper intensity of light, the opsins reacted by opening gateways to the heart's natural electrical impulses, jump-starting the heart's rhythm.

In order to find out if optogenetics might work in human patients, the Baltimore team utilized a detailed computer model of a human heart derived from the MRI scan of a patient who had experienced a heart attack. The researchers used this model to simulate life-threatening arrhythmias that can arise in such patients and to determine whether light would be able to terminate the arrhythmia if opsins had been inserted in human heart. Again, the light pulse effectively stopped the arrhythmia.

The international team is now working towards optical defibrillation of the heart, where the light-sensitive cardiomyocytes responsible for the heart's pacemaker function would be grafted to the hearts of patients at risk for experiencing a cardiac arrest in combination with implantable optical devices that would shine a special light on the patient's chest to restore normal functioning in an effective, gentle, and painless manner.



Scientists are also testing improvements in implantable devices for heart failure. About 155,000 American patients with extreme heart failure are treated annually with cardiac resynchronization therapy (CRT), which consists of a pacemaker that electrically stimulates the heart. Unfortunately, the CRT doesn't work for all patients, due in part to improper lead placement and lead fractures.

A wireless pacemaker recently approved in Europe and now undergoing testing in the United States may offer hope to patients with heart failure who have failed conventional CRT. The experimental device, the first and only cardiac pacing system for heart failure, consists of a tiny electrode the size of a grain of rice that is attached to the inner wall of the left ventricle to provide maximum benefit. With each heartbeat it receives a synchronized ultrasound signal from a small, battery-powered transmitter placed between two ribs. Those sound waves are converted to electrical energy, providing the life-saving cardiac pacing to the two ventricles. And at six months, preliminary study results have indicated achievement of sustained cardiovascular improvement in 85 percent of patients.

The future is looking even brighter for implantable devices. Within the next decade, it's expected that patients will be able to charge LVAD batteries by placing a charger on their skin, or by sitting next to a Wi-Fi power charger. And for some, the battery will be implanted inside where it can be charged, freeing them forever from the battery cables that currently come out of the body. Based on their 2016 research, Swiss scientists envision patients' being able to recharge their pacemakers and other implanted devices with ambient light as the energy source. //

Adopting the Orphans of Heart Disease

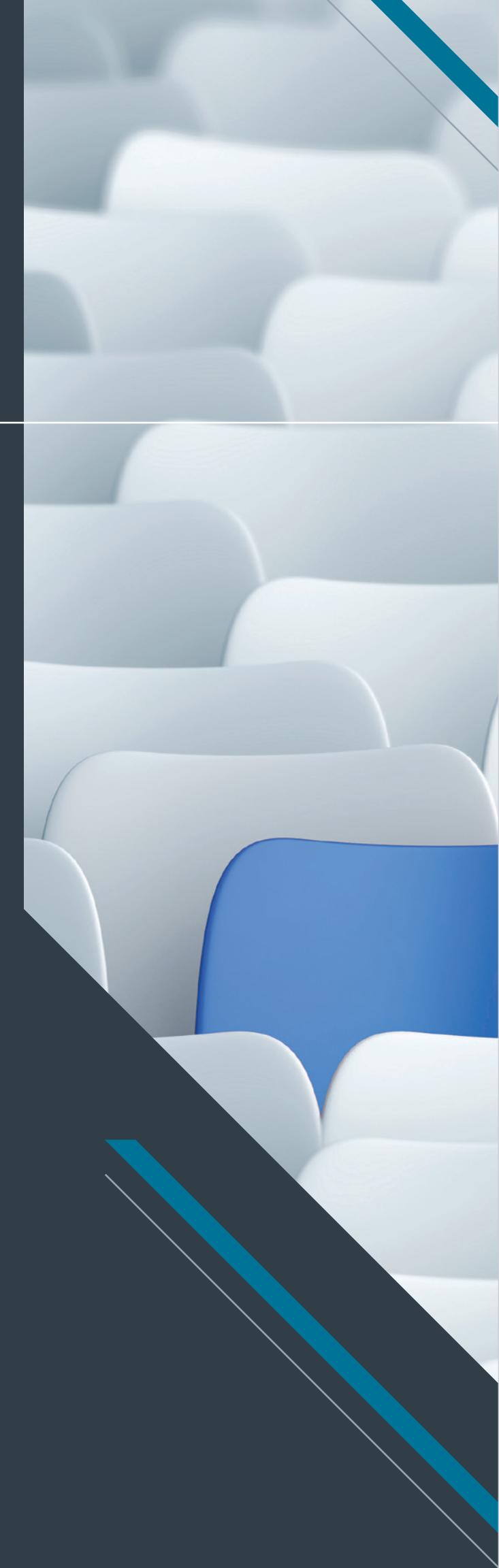
Rare heart diseases, a group of serious but neglected disorders afflicting fewer than 200,000 individuals per disease in the United States, are one of the most scientifically complex health challenges of our time. Most of these rare diseases are genetic and are present throughout a person's entire life, even if symptoms don't immediately appear.

Dozens of these uncommon cardiac ailments, including Brugada syndrome, Marfan syndrome, and arrhythmogenic right ventricular dysplasia, are called "orphans" because they occur so infrequently that it can be nearly impossible to interest researchers in finding effective treatments—let alone cures—for them.

In recent years, however, due to the convergence of regulatory, scientific, and societal forces, there has been a dramatic change in attention to rare diseases, heart ailments in particular. The Orphan Drug Act, signed into law almost 35 years ago, has provided incentives for companies to work on rare ailments, especially those that are genetic in origin and have well-characterized biological mechanisms.

Many people are familiar with orphan diseases like Lou Gehrig's disease because they so visibly impact a person's life over a prolonged period. People are less familiar, though, with other orphan diseases such as congenital long QT syndrome, or LQTS, because the symptoms can go undetected for many years. People can die from this ailment, however, without anyone ever knowing they had it.

LQTS is an inherited heart disease that affects otherwise healthy individuals who, because of a bad roll of the genetic dice, carry an increased risk of sudden death due to uncontrollable arrhythmias. About 1 in 2,500 Americans is affected by LQTS, and 4,000 die annually.



Patients with LQTS are treated with beta-blockers. Nevertheless, 25 percent will still have cardiac events, and in 5 percent that event is sudden death. For those patients who survive, implantable defibrillators (ICDs) are recommended. Since patients are often young, the adverse effects of ICD therapy are compounded, with many ICD battery changes and multiple lead revisions needed over their lifetimes.

Boston-based researchers looking for an effective LQTS therapy have recently discovered a novel class of small molecule compounds that shorten the QT interval in multiple long QT models. The target of the new compounds is a potassium channel which is partially activated when bound by the compounds. In upcoming clinical trials, patients will take this medication to correct the prolonged QT interval and reduce their risk of fainting and sudden death.

Finding a cure for LQTS and other rare heart diseases—such as heritable cardiomyopathy, a lethal genetic disorder in which there is a defect in the proteins that help control cardiac contraction, making the heart muscles either too big or too small—could save the lives of thousands of people, allowing them to experience life to the fullest without the specter of death constantly looming over them.

Over the next decade, finding individual treatments for each of the many orphan heart diseases will be a daunting task, but the increased investment of research efforts and monies can give sufferers of these rare cardiac ailments hope for effective therapies and even cures.

The contribution of public/private partnerships, along with the valuable input of their stakeholders across the medical community, is essential to making sustained progress finding cures for orphan heart diseases. Presently, data on genetics, biological samples, and lifestyle are scattered across many different databases. Combining them into one massive biobank will help speed progress for all orphan heart diseases, as well as increase our knowledge of how to treat them.

Finally, key opinion leaders, patient advocacy groups, and drug companies must join forces with the Food and Drug Administration to help design vitally important clinical trials and recruit patients for them. With these trials underway, there will be renewed hope for the patients desperately waiting for a cure or, at least, the ability to live their lives to the fullest. //

Targeting Inflammation in Cardiovascular Disease

Inflammation is the body's natural way of protecting itself from harm. When fatty, cholesterol-rich plaque accumulates within the arterial walls, the immune system perceives it to be a foreign invader and sends white blood cells to attack, resulting in chronic low-grade arterial inflammation. It's now believed that heart attacks and stroke are linked to this smoldering inflammation: As the plaque continues to accumulate over time, it narrows the coronary arteries and reduces blood flow to the heart muscle, ultimately leading to plaque rupture and heart attack.

Statin medications have been used for decades with great success to prevent cardiovascular disease: In lowering the accumulation of lipid, they significantly reduce cardiovascular risk. For years now, taking statins and adopting a healthier lifestyle have been the keystones in the prevention of cardiac disease. Now, however, scientists are hypothesizing that specifically targeting different inflammatory pathways may also help prevent and treat cardiovascular disease. By zeroing in on various molecular triggers, they are finding ways to effectively close these pathways and reduce arterial inflammation.

A 2016 study identified the mechanism behind the surge in cardiovascular inflammation that takes place following a heart attack. As a result of this discovery, the Massachusetts researchers were able to develop a potential strategy for suppressing inflammation within atherosclerotic plaques—an approach to target the immune cells' contribution to cardiovascular disease.

The researchers found sympathetic nerve fibers are activated within the arterial lining in response to a heart attack, leading to the increased expression of adhesion molecules on the endothelial cells that line atherosclerotic plaques. Those molecules attract inflammatory white blood cells and cause them to stick to the plaques, increasing the risk for another heart attack.



Halting the expression of those adhesion molecules, therefore, could greatly reduce the chances of another heart attack. And the scientists discovered a way to do just that by means of nanoparticle-delivered RNA interference.

In the 2016 study, a series of experiments with a mouse model of atherosclerosis revealed that after a heart attack, the activity of sympathetic nerve fibers within the animals' aortas caused the increased expression of several adhesion molecules. By targeting five of these adhesion molecules with nanoparticles, they not only reduced the recruitment of inflammatory immune cells to aortal plaques in the mice, but they also lowered the expression of inflammatory proteins (called cytokines and enzymes). This was key, as the researchers found that the increased expression of cytokines and enzymes contributed to the rupture of arterial plaque, which then triggered a heart attack.

By applying this treatment before an induced heart attack in the mice, they were able to reduce subsequent inflammatory changes, while applying it after a heart attack cut the recruitment of inflammatory cells in half and improved the recovery of heart function. Once this novel approach is translated, the scientists believe it may help to "cool down" inflammation in patients with vascular disease, which would not only protect them from a second heart attack, but also help the heart to recover.

With inflammation playing a major role in heart attack and stroke, and as patients with elevated inflammatory biomarkers, such as high sensitivity C-reactive protein (hsCRP) are at increased vascular risk, novel drugs directed at specific targets in the inflammatory cascade are now in various testing phases.

An injectable, anti-inflammatory, monoclonal antibody that blocks the body's production of the pro-inflammatory interleukin-1 (IL-1) cytokine is currently being investigated in an international, 10,000-patient, randomized clinical trial. Researchers want to see whether neutralizing the IL-1 cytokine can reduce rates of recurrent heart attack, stroke, and death among heart attack patients who remain at high risk due to a persistent elevation of hsCRP.

While inflammation is an important part of the body's maintenance repair system, too much of it can have devastating effects on the body. Will the careful lowering of chronic inflammation result in fewer cardiac events in the next decade? That answer will be available within the next few years upon the publication of large trial results directly testing the inflammatory hypotheses of atherosclerosis.

And if the answer is yes, it will herald the dawn of a new era in which the treatment of chronic vascular disease moves beyond the reduction of LDL-cholesterol alone, and anti-inflammatory therapies become the cornerstone of lowering vascular event rates. //

Harnessing Big Data and Deep Learning for Clinical Decision Support

A single patient can generate considerable meaningful pieces of data based on information gleaned from the 20,000 to 30,000 genes in the human genome. Multiplying so much data by tens of thousands of patients with heart disease and other ailments results in “big data.” Big data implies large volume and complexity, such that advanced mathematics and high-performance computers are needed to make sense of it.

With all of the reams of electronic health data now available from patients, the thousands of pages of critically important background information from medical journals, and with the doubling of overall medical information every five years, most heart researchers and clinicians can’t keep up with this avalanche of information and derive maximum value from it.

This is where computational biology, which involves the development and use of tools to analyze and model biological data and systems, along with deep learning, which is the ability of computers to learn without being explicitly programmed, can revolutionize personalized medicine and, over the course of the next decade, make heart diagnoses more accurate.

Computational biology offers the promise of finding novel associations in the vast sea of data that underlie important mechanisms of disease and can help uncover potential targets for treatment that would remain hidden to even the most expert investigator.

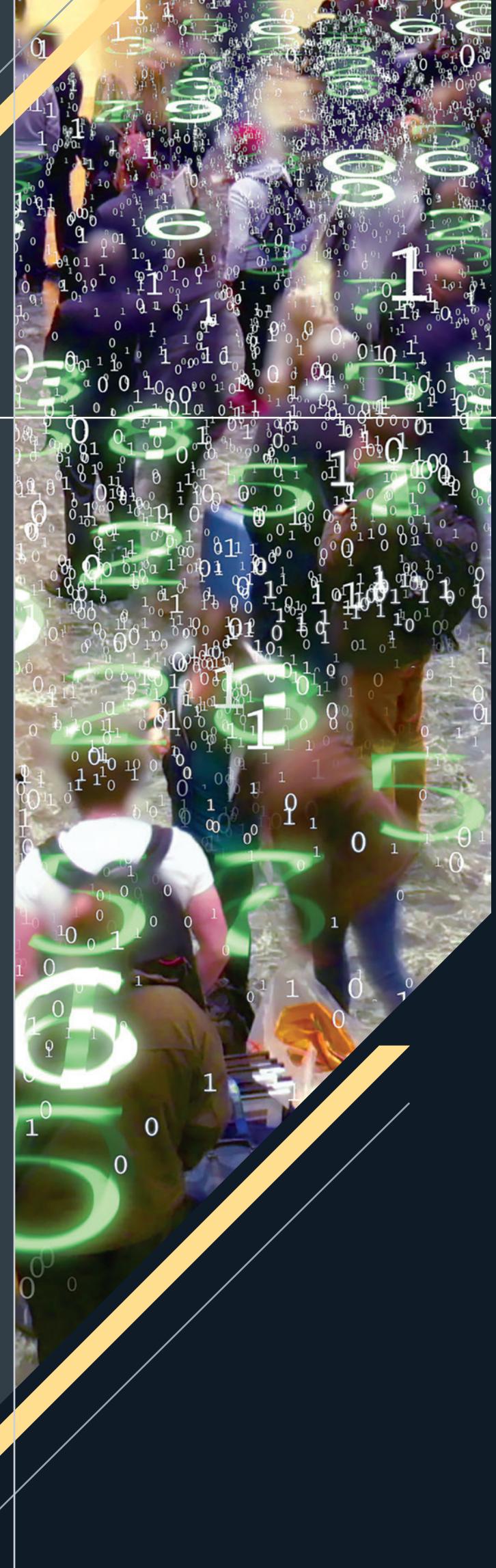
Doctors can’t manage what they can’t measure, which is why to better understand the cause of heart disease and develop more effective methods of prevention, detection, and treatment, clinicians and researchers are being provided access to rich molecular and clinical data sets. The use of electronic information is changing rapidly and over the next few years technology will be revolutionizing the understanding and treatment of diseases, especially heart disease. By gathering the latest information from the patient’s biology, and combining that with trillions of data points from tens of thousands of other heart patients, individualized patient-specific treatment options can then be created in days, and oftentimes in just a matter of minutes.

Over the next decade, the use of big data from the oceans of electronic medical health records that has been sorted, reviewed, analyzed, and stored will help researchers and doctors better understand the root causes of heart disease.

The potential for big data analytics to improve cardiovascular quality of care and patient outcomes is enormous, thanks especially to two ongoing studies. A \$75 million five-year study launched by Boston investigators and a team of international collaborators has begun gathering extensive health information from volunteers whose contributions will potentially provide new insights as to what marks the transition from a healthy heart to one on the road to serious disease.

While much has been learned in the past two decades about coronary disease—lesion formation, inflammation, plaque rupture, thrombosis, and heart attack—very little is known about the initial stages of the disease, where it may initiate in the body, and how it progresses. This novel study promises to provide those answers.

Another heart study, this an ambitious one spearheaded by investigators in San Francisco, is expected to enroll up to one million participants worldwide who will be using smartphones, mobile health apps, and other technology to relay information about their heart health.



After sorting through this big data and analyzing the wealth of information, the Boston and San Francisco researchers hope to be able to reduce deaths due to heart disease by using the accumulated data to create better ways to predict the occurrence and progression of heart disease.

This is where deep learning will turn this vision into reality by using patient data for improved and robust biomarker discovery, enhanced disease diagnosis, prognosis, and prediction of therapy outcomes. This form of artificial intelligence uses computer algorithms to identify patterns in large data sets, and can continuously improve with additional data.

The use of electronic health information is changing rapidly, and over the next decade it’s clear that big data and deep learning will play an ever increasingly important role in the care of the heart, particularly when quality data is available for individual patient. //



Quantitative Molecular Imaging for Cardiovascular Phenotypes

More than 17 million deaths worldwide were attributed to heart disease in 2016, and cardiovascular ailments persistently remain one of the biggest causes of hospital admissions in the United States. Cardiovascular disease also accounts for more healthcare costs than any other chronic illness, and is responsible for one out of every three deaths, on average.

Finally, there is good news on the cardiac care front and it has to do with quantitative molecular imaging. This novel technology that emerged from discoveries made in the field of biology, allows noninvasive imaging of biochemical processes at the molecular and cellular level *in vivo* within the body.

Unlike conventional imaging that relies on visualizing late pathological consequences, the next decade will see quantitative molecular imaging regularly used to interrogate the very molecular events that drive so many heart disease processes.

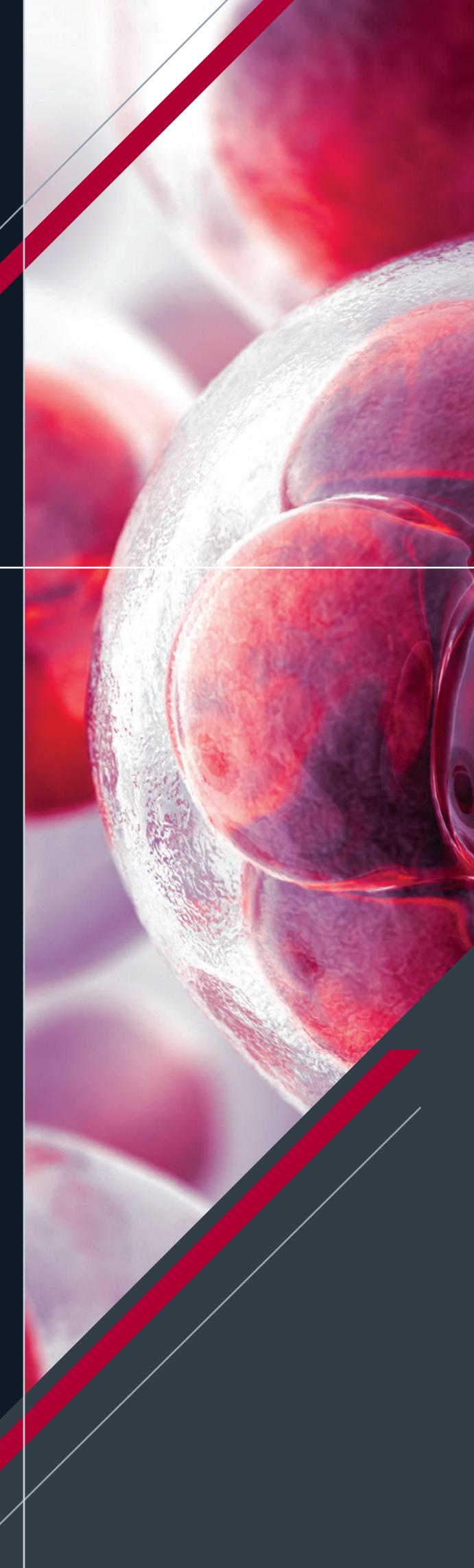
Using biomarkers bioengineered with targeting and signaling components with low risk of toxicity, these sensitive and specific imaging probes will routinely be used to noninvasively pinpoint target molecules of interest within the heart and vasculature when paired with positron emission tomography, magnetic resonance imaging, ultrasound, computed tomography, or optical imaging.

The clinical benefits of quantitative molecular imaging are immense and many critical cardiac questions will be addressed with the targeted probes. The crucial role of imaging in early phenotyping of cardiovascular disease, risk assessment, and management guidance will expand rapidly in ways previously thought unrealistic. For example, by using targeted imaging of vascular inflammation or thrombosis, patients will benefit from improved assessment of atherosclerosis and the uncovering of plaques at high risk of causing accelerated and aggressive disease over the ensuing decades.

Quantitative molecular imaging will also be used for predicting very high risk in younger people in whom risk-lowering therapy is likely to be more beneficial. This matter is going to increase in importance with the introduction of newer, more potent, and very expensive anti-atherosclerotic therapies that may have more adverse effects than traditional statin therapy.

In the coming years, imaging probes will also be used to uncover myocardial apoptosis, metabolic alterations, and injury to the extracellular matrix, providing clinicians with critical information for assessing the risk of arrhythmias and left ventricular remodeling associated with heart failure and progressive cardiac dysfunction.

There's also active research now in trying to determine whether a quantitative molecular imaging approach can help physicians decide which patients with low cardiac function will benefit most from an implantable cardioverter defibrillator therapy. Only about 1 percent of patients currently benefit from defibrillators. Not only are these devices very expensive, but they also pose additional potential morbidity from pre-exposing patients to infection if implanted wires start to fail.



With molecular imaging, however, physicians can improve patient care by accurately identifying those at greater risk of lethal arrhythmias and sudden cardiac death, thereby reducing the need for invasive medical devices and unnecessary surgical techniques for those who will not benefit from a defibrillator.

Since quantitative molecular imaging offers the promise of early disease detection and prediction of treatment response, this may lead to optimal therapies for each patient. In the next decade, this ability opens up new possibilities for realizing the dream of personalized medicine by moving from the one size fits all approach of yesterday to one that can deliver medical care specifically tailored to the needs of each patient based on their individual molecular status. This includes the detection of disease predisposition, earlier disease diagnosis and prognosis assessment, and measurement of drug efficacy.

By understanding the different cellular phenotypes that result from interactions between genes and the environment, precise treatments for cardiac care will be formulated to offer each patient the best therapy and a better chance for a healthy and longer life.

At last, the dream of lowering those 17 million annual deaths to cardiovascular disease may be realized. //

2017 Disruptive Dozen

CARDIOVASCULAR

Below is our Disruptive Dozen for 2017, which was guided through the nomination and selection-ranking process by our committee, each earning scores along the way.

We present these disruptors to you in order of their rank after the final committee voting was completed.

The medical professionals listed below, experts in cardiovascular and cardiometabolic disease, were each paired with a specific disruptive innovation.

At the Forum presentation, each expert explained its potential impact on cardiovascular and cardiometabolic disease in the decade ahead.

1 | Quantitative Molecular Imaging for Cardiovascular Phenotypes

Marcelo DiCarli, MD
Brigham and Women's Hospital

2 | Harnessing Big Data and Deep Learning for Clinical Decision Support

Christian Ruff, MD
Brigham and Women's Hospital

3 | Targeting Inflammation in Cardiovascular Disease

Matthias Nahrendorf, MD, PhD
Massachusetts General Hospital

4 | Adopting the Orphans of Heart Disease

David Milan, MD
Massachusetts General Hospital

5 | Power Play: The Future of Implantable Cardiac Devices

Christine Albert, MD
Brigham and Women's Hospital

6 | Understanding Why Exercise Works for Just About Everything

Gregory Lewis, MD
Massachusetts General Hospital

7 | Less is More: Minimalist Mitral Valve Repair

Prem Shekar, MD
Brigham and Women's Hospital

8 | Finding Cancer Therapies without Cardiotoxicity

Anju Nohria, MD
Brigham and Women's Hospital

9 | Expanding the Pool of Organs for Transplant

Joren Madsen, MD, DPhil
Massachusetts General Hospital

10 | Breaking the Code: Diagnostic and Therapeutic Potential of RNA

Saumya Das, MD, PhD
Massachusetts General Hospital

11 | Nanotechnologies for Cardiac Diagnosis and Treatment

Natalie Artzi, PhD
Brigham and Women's Hospital
Contributor: Jeffrey Karp, PhD,
Brigham and Women's Hospital

12 | Aging and Heart Disease: Can We Reverse the Process?

Jason Roh, MD
Massachusetts General Hospital

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