n 1948, researchers quietly enrolled their first patient in the Framingham Heart Study, launching an observational investigation “that changed forever how society looked at its number-one killer, heart disease,” wrote cardiologist Henry Greenberg in Progress in Cardiovascular Disease. “The validity, robustness and clarity of the Framingham data became a beacon for the world.”

This multidecade epidemiological study of a Massachusetts community identified risk factors and showed that reducing them postpones—and prevents—heart disease. It sparked major community-based preventive programs, the first of which, Finland's North Karelia Project, launched in 1972. Finland had the highest cardiovascular disease (CVD) death rate in Europe, but by improving dietary and exercise habits and reducing smoking, within 30 years they ranked lowest. In 2004, the 52-nation INTERHEART study showed that the nine risk factors linked with 90 percent of heart disease cases are the same for both developed and developing countries.

TAILORING INTERVENTIONS

However, lessons learned from these studies must be applied cautiously. There are vast differences between the regional and cultural settings of middle-class Massachusetts and the mountain villages of Peru or Guatemala, towns in northeastern Spain, cities in India or rural hamlets in China. In order to effectively address cardiovascular and related diseases, interventions must fit the lifestyles and habits of local people.

The importance of this hit home for Cristina Rabadán-Diehl in rural Kenya, where she visited a small village to observe a program that replaced traditional smoky stoves with clean ones. (Indoor pollution from cook fires poses great cardiovascular risk for women in developing countries.) When she arrived, she thought one of the houses was burning. Smoke billowed from the kitchen. Inside, a woman was seated on a low stool, cooking. Next to her was a new, efficient cook stove—unused. “Why aren't you using your new stove?” Rabadán-Diehl asked. “It’s not practical, too small and with only space for one pot,” she said, “and when I cook, I sit. I don’t stand!”

Regardless of health benefits, providing this type of stove had been a huge mistake: It didn't fit within cultural norms.

Tailoring interventions to vastly different societies is a challenge that is often compounded by a lack of data as well as insufficient health care services and personnel. For those suffering from heart disease, diabetes or lung diseases in many regions, living in poverty may take a further toll on health. For example, in sub-Saharan Africa, someone with hypertension may also be fighting tuberculosis, malaria, HIV or other serious illnesses. They may also have a poor diet and live amidst political turmoil or street violence that makes it difficult to get exercise needed for coronary health. Conducting research in such complex settings requires that doctors and other health care workers understand patients, their families, communities, societies and countries in order to draw a complete picture of the social, cultural and political environment.

A New Paradigm for Global Cardiovascular Disease Research

Cristina Rabadán-Diehl, Evan Bennett, Carlos Peyra and Silvia Fuster
NEW RESEARCH MODELS

As Rabadán-Diehl left that smoky Kenyan kitchen, a local researcher remarked, “It’s a shame the manufacturer of these stoves never consulted us. We would have told them the design wouldn’t be accepted.”

Such errors haven’t been uncommon in programs led by well-intentioned researchers from developed nations who knew little about local culture. To avoid these problems going forward, an innovative, 21st-century paradigm is building global research teams. Resident investigators who are intimate with regional customs are at the helm, partnering with universities and research institutes in developed countries.

Eleven Collaborating “Centers of Excellence” in Asia, Africa and Latin America (with partners in the U.S., Europe, Canada and Australia) are building a system capable of monitoring, preventing and controlling chronic diseases, particularly those affecting the heart and lungs. The initiative, launched in June 2009, is co-funded by The U.S. National Heart, Lung and Blood Institute (NHLBI) and the UnitedHealth Group. Eighty researchers from 25 nations are working together across borders and sometimes across continents. Investigators in Kenya and Peru, for example, share data on indoor air pollution. Researchers are also studying high blood pressure reduction in China and Kenya and community health worker training in Mexico, Bangladesh, South Africa and Guatemala. Other centers are testing technological interventions, such as cell phone applications that transmit health data to regional data banks.

Over the past five years, the centers have also provided training in medicine and clinical research for more than 700 researchers. At Kenya’s Eldoret Center of Excellence, for example, training local physicians in clinical cardiology and research has allowed the clinic to triple in size. In-country training counters the “brain drain” of recent decades when local researchers left for opportunities in developed nations, rarely returning home.

In 2009, Centers of Excellence researchers formed a model that was almost entirely new to science. They established subcommittees to compare research on epidemiology, community health and other topics, and agreed to pool their national data and do multinational meta-analysis before publishing results in order to contrast and combine results to identify patterns. It is likely that over the next few years, a flood of articles will appear in peer-reviewed journals, publishing data from joint studies on the use of mobile health technology in China and India, the

“Why aren’t you using your new stove?” Rabadán-Diehl asked. “It’s not practical, too small and with only space for one pot,” she said, “and when I cook, I sit. I don’t stand!”
effectiveness of using community health workers in South Africa, Bangladesh, Mexico and Guatemala, and research that reveals which cardiovascular interventions work in which settings.

**TRACKING TRENDS**

Early data from an epidemiological study at Peru’s Universidad Peruana Cayetano Heredia echoes studies from Argentina and India: Cardiovascular-related disease in developing countries may be higher than previously estimated—and disease patterns may be more complicated. A good example is Argentina, where a new, 30-year study of 8,000 people aged 35 to 74 is finding that up to three quarters of disability and death from cardiovascular diseases are in people under 70—compared with about one third in developed countries.

Based on studies in wealthy countries, researchers in Peru expected urban areas to have the greatest incidence of high blood pressure and diabetes. While hypertension followed this pattern, diabetes was far more prevalent in the small, underdeveloped city of Tumbes (around 12 percent) than in a major metropolis like Lima (8 percent). Both rates are sharply higher than Peru’s 5.4 percent listing in the International Diabetes Federation atlas. “The take-home message,” said principal investigator Jaime Miranda, “is that applying a national average for a geographically diverse country like Peru won’t work. You have to pay attention to what’s happening on the ground.”

These studies are revealing that successful treatment of hypertension and diabetes is far lower in developing countries. Using the Western world’s so-called “rule of halves,” roughly half of all high blood pressure and diabetes cases remain undetected, half of those detected remain untreated—and half of those treated are not controlled. But in Peru, researchers found the situation was far worse. Of 205 people with elevated blood pressure, nearly half knew they had the problem, 40 percent treated it and 30 percent controlled it. Of 33 diabetes sufferers, 71 percent had been diagnosed, 40 percent were under treatment—but just 7.7 percent controlled the disease. “Overall, there are considerable unmet needs in diagnosing, treating and controlling both hypertension and diabetes,” the researchers wrote, posing “major public health challenges” and “significant economic losses” for Peru.

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**UnitedHealth and NHLBI Collaborating Centers of Excellence**

To help combat chronic diseases in developing countries, the UnitedHealth Chronic Disease Initiative and the National Heart, Lung and Blood Institute support a global network of Collaborating Centers of Excellence. Each center includes a research institution in a developing country paired with at least one partner academic institution in a developed country.

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**Map by Jean-François Podevin**
FINDING APPROPRIATE INTERVENTIONS

A fundamental strategy for tackling this global crisis is working on a local level. Toward this end, Centers of Excellence trials in Africa and Latin America are tackling the indoor air pollution problem. Peruvian researchers are studying women’s resistance to new kitchen technology, trying out alternative cookstoves and gathering data on preferences. In Kenya, investigators are studying how smoky stoves cause disease. “We’ve been baffled by the high number of women we see at the Eldoret clinic disabled by right-sided heart failure,” said Gerald Bloomfield, a professor of medicine and global health at Duke University Medical Center. It’s a condition where the heart’s right side loses its ability to pump. The research is possible because of a new portable echocardiogram device that can be used in remote areas to run heart ultrasounds, testing both women who use traditional stoves and those who have replaced them.

Half a world away, China’s International Center for Chronic Disease Prevention is studying sodium intake and hypertension. Unlike the U.S. where 80 percent of salt comes from processed foods, in rural China, Latin America and Africa, most is added during cooking. It’s a taste preference common in nations that once used salt to preserve food. This “China Rural Health Initiative” study involves 120 villages, engaging families, household cooks, shopkeepers and village doctors in an investigation of taste preference, the use of salt substitutes and community-wide education.

This same program trains cardiology specialists to better manage high-risk patients. The specialists then train village doctors to diagnose those patients, conduct follow-up visits, give lifestyle advice, write prescriptions and keep case management records. Then, said initiative Director Lijing Yan, “We digitize the records and do performance feedback for the village doctors.”

In resource-strapped rural areas, partnerships are critical. Bloomfield notes that although their clinical research is an international partnership between the United States and Kenya, it also engages local chiefs, subchiefs, schools and churches, along with “community leaders [who] help introduce projects, give us feedback and good advice.” For example, leaders helped researchers fine-tune house-to-house health surveys. “They told us, ‘This is the rainy season, so it’s not a good time’ or ‘This is harvest time, so… men won’t be represented because they’ll be in the fields,’” Bloomfield said. “I’ve learned: If you want to know, go to the people and ask.”

In another novel program in western Kenya, researchers are using existing HIV infrastructure to diagnose cardiovascular disease. “HIV testers are welcome in many Kenyan communities and homes,” Bloomfield said. “We piggyback on that. We’re testing…not only for HIV, but for hypertension and diabetes—all in one visit, and providing education, too.”

Community involvement takes another form in Argentina. Community health workers are given short, intense training, taught to do lifestyle and dietary counseling, to measure blood pressure and to teach hypertensives and their families to take their own readings. “Task-shifting moves us from a traditional clinic-based setting to a community care–based model,
reaching the most vulnerable people," said Adolfo Rubinstein, who heads the program. "This developing-world approach also has potential for developed nations."

Mobile health (mHealth) technology helps stretch scant resources. Because nearly everyone in Argentina uses a mobile phone, Rubinstein is exploring ways to harness mHealth technology. In a hypertension trial, interactive cell phones send short educational text messages or remind patients to take medications or show up for medical appointments. "We think cell phones can be a powerful ally for changing lifestyles and supporting interventions," he said. Smartphones are also being tested in Tibet, where a cardiovascular health app is used by village doctors.

Another innovative application helps determine cause of death, which in developing countries typically comes from "verbal autopsies"—interviews with families recorded on paper. A Centers of Excellence study is using computer tablets and cell phones loaded with a standardized electronic questionnaire; graphics will eventually be added, giving practitioners a powerful tool for identifying lesions and other signs of disease.

COLLABORATIONS AMONG GLOBAL FUNDERS

The collaborating centers' approach to cardiovascular research is just one example of widening partnerships. Another worldwide research initiative, this one focusing specifically on hypertension, was launched in June 2012 under the umbrella of the Global Alliance for Chronic Diseases (GACD). The alliance includes the world's eight biggest publicly funded research agencies—including the U.S. National Institutes of Health, the European Commission and agencies from Australia, India, China, South Africa, the United Kingdom and Canada. Together, they're funding 15 research teams to address hypertension in the developing world. Each pairs a lead researcher from a developing country with an expert from a high-income country.

About a billion people suffer from high blood pressure, contributing to more deaths worldwide than any other risk factor, according to the World Health Organization (WHO). "We're looking specifically at how we can bring research into rural settings where little research has been done on salt reduction, smartphone support, primary health care worker support, hypertension drug regimens and more," GACD Executive Director Celina Gorre said. "It is still quite early to talk about what works in what settings, but that is exactly the question GACD is seeking to answer."

BUILDING “A CULTURE OF HEALTH”

In the village of Cardona, a town of 5,000 inhabitants in northeastern Spain, the Cardona Integral Project aims to build "a culture of health and fitness." It uses a three-pronged approach, including events, programs and urban design, engaging with the town's social systems, physical environment and the school system to spark healthy behavioral changes. Its Web site will serve as a portal for the area's health-related initiatives.

The goal is to create a model for community-driven health promotion that can be replicated in other communities, both nationally and internationally. Cardona stands as a microcosm of Spain, where 62 percent of all Spaniards are overweight and over half have high cholesterol. Physical inactivity is a significant problem for more than 50 percent of the population. One recent Spanish study found that teenagers from 12 to 16 with sedentary parents were four times more likely to follow suit.

The Cardona Integral Project is using a series of events to raise awareness. Seminars will target young physicians, while a lecture series will educate the public on nutrition and fitness. In addition to selling locally grown food, a monthly farmer's market will promote active living, with bicycle repair clinics, yoga classes, cooking demonstrations and more.

Other programs specifically target health. The S! Program, piloted in Bogotá, Colombia, in 2009 and in Cardona the next year, now teaches healthy habits to 45,000 school children of all ages in those cities using a curriculum developed in conjunction with Sesame Street's Sesame Workshop. Research shows that experiences gained in preadolescence establish lifelong preferences and motivations, so early health education should, in theory, encourage better nutrition and physical fitness.

Another initiative, The Fifty–Fifty Programme, puts small groups of adults together in regular meetings to support healthier eating, weight loss, exercise and efforts to quit smoking. The program, first tested on the Caribbean island
of Grenada and in Cardona, is based on the Alcoholics Anonymous peer-to-peer model. In the first year, one out of every four smokers stopped smoking, half lost weight and nearly three quarters exercised for more than 150 minutes per week.

A mapping study will use GPS devices to map participants’ fitness activities, and Cardona Integral will use this spatial data to improve recreational opportunities. On that list are the town’s soccer field, which is being adapted for other uses, and creation of three “fitness loop” pathways for walking, running and cycling.

Researchers will measure the success of the entire Healthy City “action package” by crunching demographic and public health data alongside information from questionnaires and evaluation of target groups. Oversight comes from collaborating institutions: the SHE Foundation, The Mount Sinai Hospital, the New York Institute of Medicine, the American Heart Association and Spain’s National Center for Cardiovascular Investigation.

The plan is to take the SI! and Fifty–Fifty programs nationwide under the direction of Valentín Fuster—who directs three major cardiovascular centers at New York City’s Mount Sinai Hospital—in conjunction with the Health Ministry.

**A NEW AGE FOR CHRONIC DISEASE RESEARCH WORLDWIDE**

A new age is dawning for cardiovascular research. The lessons learned in Framingham are being applied and adapted by principle investigators in developing nations who are building self-sustaining research institutions that are supported by international partners and funders who have networks connecting them to similar work in other countries. A new cadre of cardiovascular and pulmonary researchers—alongside seasoned investigators—are forging a global research network that will make discoveries benefitting not only their own nations but people around the globe.

With the release of the WHO Global Action Plan for the Prevention and Control of NCDs 2013–2020, it is expected that other innovative platforms will proliferate, sparking new collaborative opportunities for the global health research community and providing data that will help policy makers better respond to the health needs of their people.

Over time, these new research collaborations will likely become comprehensive, extending investigations to other forms of chronic disease. Each participating institution, operating nationally will be part of a greater whole. As we build this national and international research infrastructure, we are creating a global community of investigators without borders, where trust is central, data is shared and benefits are universal.

The value of this new paradigm may best be expressed by Duke University’s Gerald Bloomfield: “I spend about six months out of every year working in Eldoret, Kenya,” he said. “I quickly discovered that some approaches we use in the U.S. just aren’t applicable. As importantly, there are areas where we, in the developed world, can learn a lot from how research is performed and care is administered in developing country settings.” He notes the value of engaging the local community and laypeople in investigations to assure the success of long-term patient therapies and drug regimens. “That’s something we haven’t done much of in developed countries, but perhaps we should,” he said. “Overall, the importance of working with partners internationally, nationally and at the community level cannot be overstated.”

Clearly this is a global partnership from which all nations and all people can benefit.

**ABOUT THE AUTHORS**

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