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News from Harvard Medical, Dental and Public Health Schools

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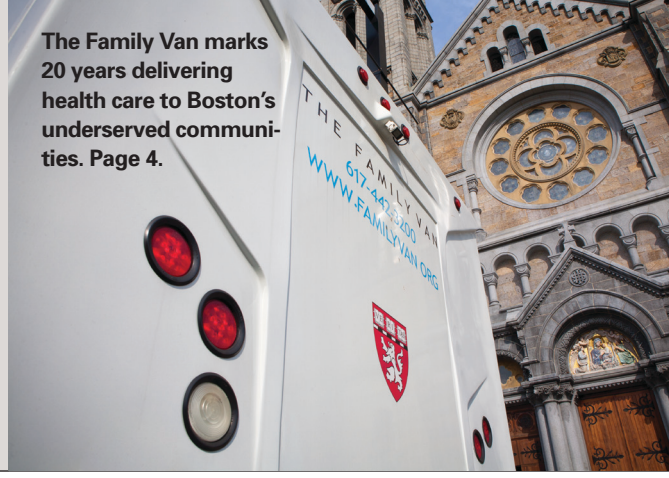


The Family Van marks 20 years delivering health care to Boston's underserved communities. Page 4.

JOHN SOARES

A Hadza man prepares an arrow for the hunt. Social networks enable food sharing and other forms of cooperation vital to survival for hunter gatherers.

COURTESY COREN APICELLA

Dawn of Social Networks

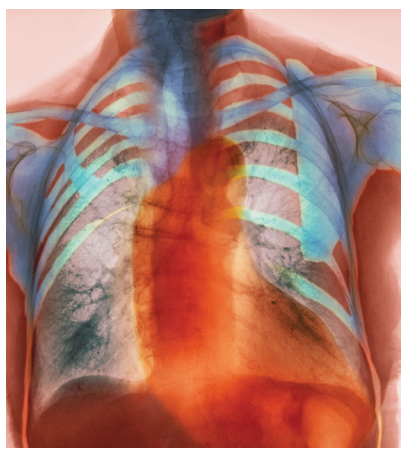
Ancient humans may not have had the luxury of updating their Facebook status, but social networks were nevertheless an essential component of their lives, a new study suggests.

The study's findings describe elements of social network structures that may have been present early in human history, suggesting how our ancestors may have formed ties with both kin and non-kin based on shared attributes, including the tendency to cooperate. According to the paper, social networks likely contributed to the evolution of cooperation.

"The astonishing thing is that ancient human social networks so very much resemble what we see today," said Nicholas Christakis, professor of health care policy (medical sociology) at Harvard Medical School and professor of sociology in the Harvard Faculty of Arts and Sciences, and senior author on the study. "From the time we were around campfires and had words floating through the air, to today when we have digital packets floating through the ether, we've made networks of basically the same kind."

"We found that what modern people are doing with online social networks is what we've always done—not just before Facebook, but before agriculture," said study co-author James Fowler, professor of medical

See Social Networks, page 6



SLP/PHOTO RESEARCHERS, INC.

Genetic Mutation Implicated In 'Broken' Heart

Gene alterations that shorten the body's largest protein could improve diagnosis and treatment of dilated cardiomyopathy, a familial heart disease

For decades, researchers have sought a genetic explanation for idiopathic dilated cardiomyopathy (DCM), a weakening and enlargement of the heart that puts an estimated 1.6 million Americans at risk of heart failure each year. Because idiopathic DCM occurs as a familial disorder, researchers have long searched for genetic causes, but for most patients the

See Heart, page 8

Physician Referrals Doubled Over a Decade

Increase seen to contribute to rising costs of health care, researchers say

Physician referral rates in the United States doubled between 1999 and 2009, a new study finds, an increase that likely contributes to the rising costs of health care.

The increase in referral rates coincides with an increase in chronic conditions such as Type 2 diabetes. The results are staggering: over the same time period, the estimated absolute number of visits resulting in a referral increased 159 percent, from 40.6 million to 105 million.

"If you add that up, it's real money," said Bruce Landon, senior author of the paper and professor of health care policy at Harvard Medical School.

The researchers found a 92 percent increase in referral rates (from 4.83 to 9.29 percent) over the last decade, analyzing a sample of 845,243 ambulatory patient visits from the National Ambulatory Medical Care Surveys, 1993-2009.

"Understanding trends in physician referrals is critical both for improving patient care and for managing costs," said Michael Barnett, lead author on the study and a first-year resident in internal medicine and primary care at Brigham and

See Referrals, page 8

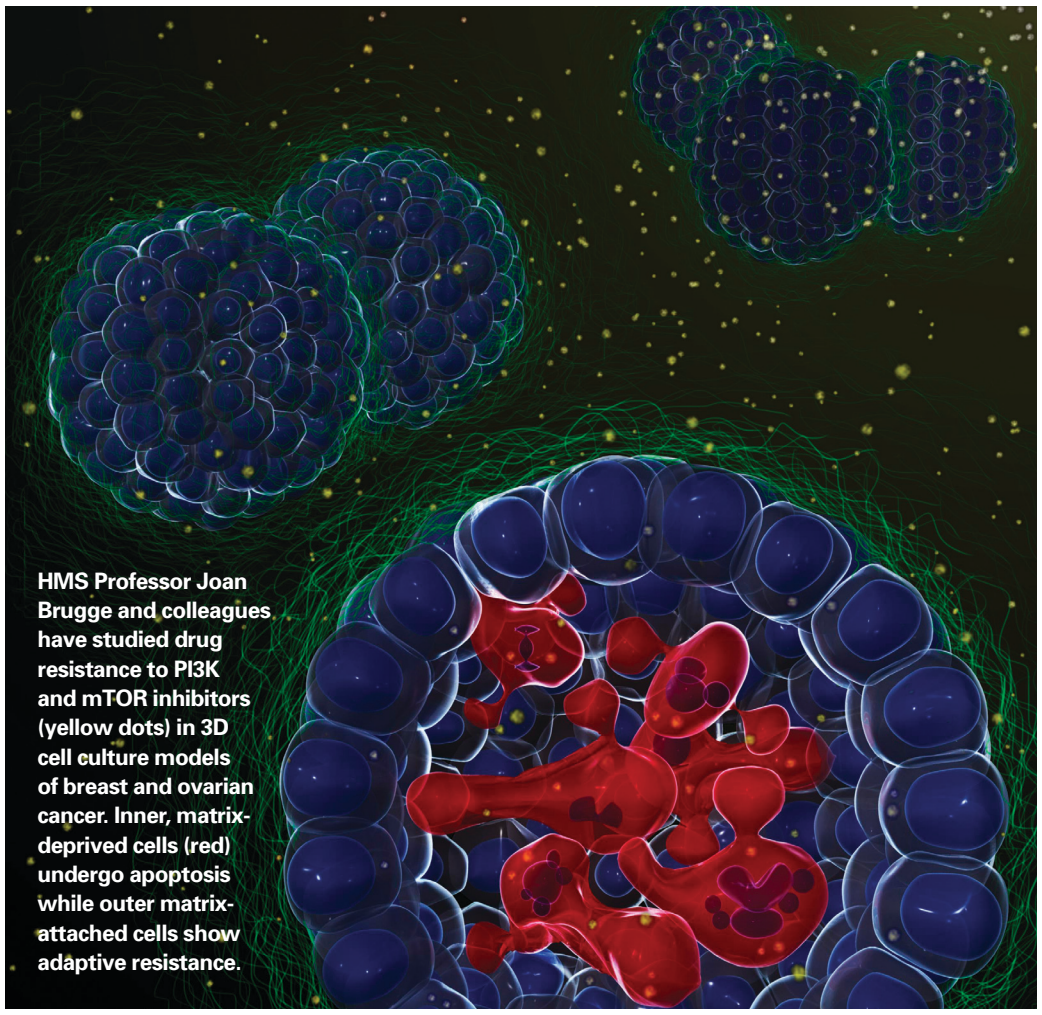
Molecular Secrets Of an Herbal Remedy

Herb used for two millennia regulates autoimmunity and inflammation

For roughly two thousand years, Chinese herbalists have treated Malaria using a root extract, commonly known as Chang Shan, from a type of hydrangea that grows in Tibet and Nepal. More recent studies suggest that halofuginone, a compound derived from this extract's bioactive ingredient, could be used to treat many autoimmune disorders as well. Now, researchers from the Harvard School of Dental Medicine have discovered the

See Chang Shan, page 6

INSIDE



RACHEL DAVIDOWITZ

HMS Professor Joan Brugge and colleagues have studied drug resistance to PI3K and mTOR inhibitors (yellow dots) in 3D cell culture models of breast and ovarian cancer. Inner, matrix-deprived cells (red) undergo apoptosis while outer matrix-attached cells show adaptive resistance.

Targeting Cancer's Power to Adapt

Drug resistance is a bane of cancer treatment. As cancer cells adapt, drugs that worked well at first ultimately lose effectiveness. Patients move to more toxic drugs in an arms race against their own renegade cells. While therapies that target genetic alterations have significantly improved outcomes in several types of cancer, resistance continues to limit the effectiveness of promising therapies.

At Harvard Medical School, researchers in the lab of Joan Brugge, head of the department of Cell Biology, are searching for strategies to overcome drug resistance in order for cancer patients to benefit fully from the potential of targeted therapies. Using a 3-D model of ovarian cancer developed in the Brugge lab, they have identified specific subpopulations of tumor cells that are resistant to drug-induced killing, determined how these tumor cells adapt to a promising drug attack, and identified drug combinations that defy drug resistance—providing insight for the direction of future cancer therapies.

In a study published Feb. 14 in the journal *Cancer Cell*, research fellow Taru Muranen and colleagues from the Brugge laboratory, in collaboration with Gordon Mills at MD Anderson Cancer Center in Houston, show that treatment with drugs targeting signaling pathways commonly altered in human carcinomas induces an adaptive response that confers drug resistance.

Activating mutations in the phosphoinositide 3-kinase (PI3K) pathway are commonly associated with many cancers and these mutations can drive tumorigenesis in cancer models through effects of tumor cell survival, metabolism and proliferation. Therefore, this pathway is a promising therapeutic target and many drug companies are developing drugs that block this pathway.

"Unfortunately, some tumors eventually relapse, often by activating an alternative pathway," said Brugge, Louise Foote Pfeiffer Professor of Cell Biology and senior author on the paper. "Thus, single agent therapies may not be the most potent and effective treatments, since alternative pathways may be activated and lead to drug resistance."

The Brugge lab group, using the 3-D model, observed that a subpopulation of tumor cells attached to extracellular matrix—which provides structural and other support to cells—resisted drugs that targeted PI3K/mTOR. While an anti-cancer drug killed cancer cells inside the model tumors, those on the surface, attached to the extracellular matrix, survived.

"Cells attached to the extracellular matrix would survive drug treatment and contribute to relapse. Thus, it is critical to develop strategies to prevent or inhibit this adaptive response."
— Taru Muranen, first author

"The results suggest that cells attached to the extracellular matrix would survive drug treatment and contribute to relapse," said Muranen, first author on the Cancer Cell paper. "Thus, it is critical to develop strategies to prevent or inhibit this adaptive response."

Importantly, the Brugge group has found that treatment with a second drug that inhibits critical components of the adaptive response interrupted matrix protection and killed the matrix-attached cells. The combined treatment also caused much more effective tumor cell killing in a mouse model of ovarian cancer.

The research was funded in part by the Adelson Medical Research Foundation, which supports multidisciplinary research to prevent or treat life-threatening disease. "There are high hopes for the new generation of PI3K/mTOR-pathway inhibitors, but potential resistance to these drugs in epithelial cancers is a concern," said Kenneth Fasman, vice president and chief scientific officer of the foundation. "Their model reveals that resistance is found only in subpopulations of tumor cells associated with the extracellular matrix, potentially explaining why these drugs are not uniformly effective on all cells in the tumor."

The researchers are collaborating with drugmakers to explore therapies that inhibit this particular adaptive response. In the meantime, adaptive resistance remains a primary obstacle to effective cancer therapies.

—R. Alan Leo

To learn more, students may contact Joan Brugge at Joan_Brugge@hms.harvard.edu.

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Conflict disclosures and funding sources appear online.

Recent books written or edited by members of the HMS, HSPH and HSDM faculty, staff or students may be submitted to *Focus* at the address above. Books received by March 2, 2012, will be considered for the next book section.

We invite letters from our readers, which should be brief and include a signature, address and daytime phone number.

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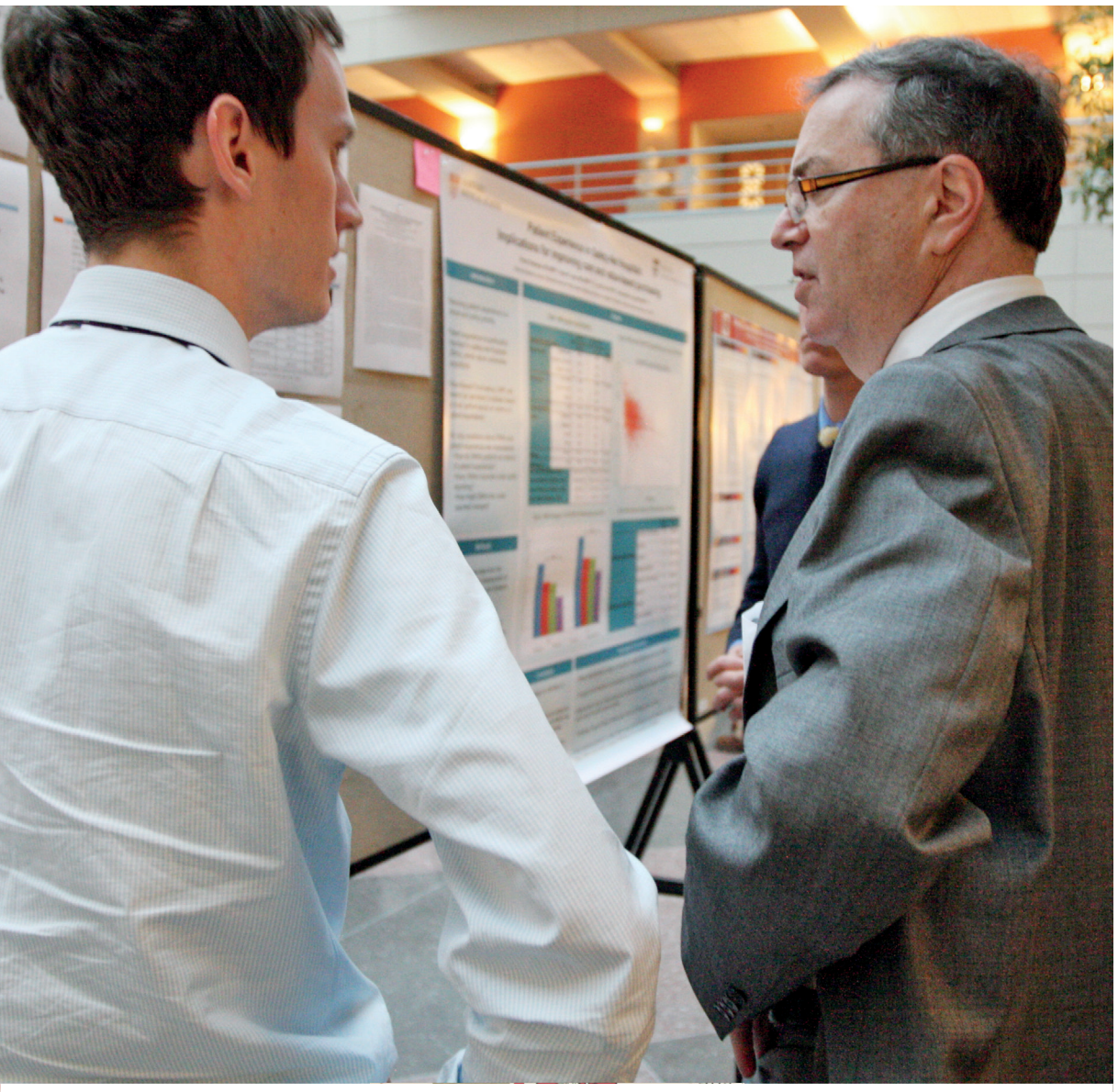
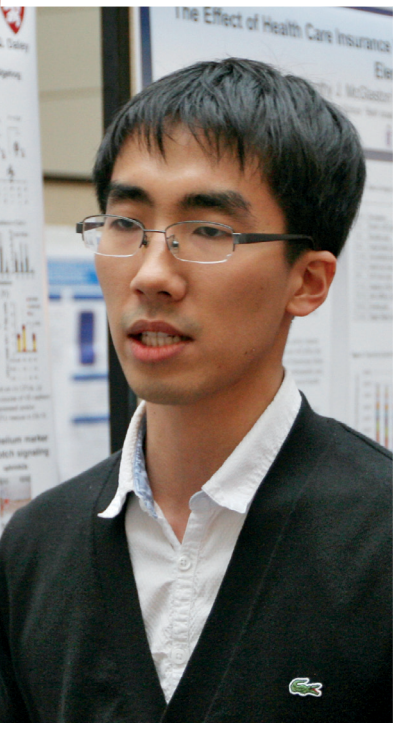


PHOTOS BY JAKE MILLER;



Student Research Takes the Spotlight

Scholars share results at 72nd Soma Weiss Student Research Day

Harvard medical students presented more than 100 research projects Jan. 12 at the 72nd annual Soma Weiss Student Research Day. Founded in 1940, the event is named for Weiss, an inspiring teacher and physician and ardent supporter of student research, who died in 1942.

CLOCKWISE, FROM TOP: Zachary Epstein-Peterson explains his research on the importance of religious and spiritual care provided by oncology physicians and nurses to advanced cancer patients to **Jeffrey S. Flier,** dean of the Faculty of Medicine. **Belinda Wang's** research investigates the possibility that we might be able to manage melanoma, a deadly form of skin cancer with no effective systemic therapies, by transforming melanoma cells into schwannoma cells, which form non-aggressive, treatable tumors; **Steve Xu** investigated the effectiveness of different approaches to promoting medical innovation, including patent protection and technology incubators, using coronary artery stents as a case study. **Peter Geon Kim** explores the fundamentals of hematopoietic stem cell development.

Paper Chase

RECENT PUBLICATIONS
FROM HMS RESEARCHERS

This selection of new studies and review articles by researchers from across the HMS community represents a small sample of research at **focushms.com**.

RISK OF ACUTE MYOCARDIAL INFARCTION AFTER THE DEATH OF A SIGNIFICANT PERSON IN ONE'S LIFE: THE DETERMINANTS OF MYOCARDIAL INFARCTION ONSET STUDY

Mostofsky E, Maclure M, Sherwood JB, Tofler GH, Muller JE, Mittleman MA. Beth Israel Deaconess Medical Center.

Acute psychological stress is associated with an abrupt increase in the risk of cardiovascular events. Intense grief in the days after the death of a significant person may trigger the onset of acute myocardial infarction (MI), but this relationship has not been systematically studied. The authors conducted a case-crossover analysis of 1,985 study participants interviewed during index hospitalization for an acute MI between 1989 and 1994. The incidence rate of acute MI onset was elevated 21.1-fold within 24 hours of the death of a significant person and declined steadily on each subsequent day. *Circulation.* 2012 Jan. 24;125(3):491-6.

DNA BREAKS AND CHROMOSOME PULVERIZATION FROM ERRORS IN MITOSIS

Crasta K, Ganem NJ, Dagher R, Lantermann AB, Ivanova EV, Pan Y, Nezi L, Protopopov A, Chowdhury D, Pellman D. Dana-Farber Cancer Institute.

The involvement of whole-chromosome aneuploidy in tumorigenesis is the subject of debate. The authors identify a mechanism by which errors in mitotic chromosome segregation generate DNA breaks via the formation of structures called micronuclei. The authors tracked the fate of newly generated micronuclei and found that they undergo defective and asynchronous DNA replication. Micronuclei can persist in cells over several generations but the chromosome in the micronucleus can also be distributed to daughter nuclei. Thus, chromosome segregation errors potentially lead to mutations and chromosome rearrangements that can integrate into the genome. *Nature.* 2012 Jan. 18;482(7383):53-8.

ORIGINS OF TUMOR-ASSOCIATED MACROPHAGES AND NEUTROPHILS

Cortez-Retamozo V, Etzrodt M, Newton A, Rauch PJ, Chudnovskiy A, Berger C, Ryan RJ, Iwamoto Y, Marinelli B, Gorbatov R, Forghani R, Novobrantseva TI, Koteliansky V, Figueiredo JL, Chen JW, Anderson DG, Nahrendorf M, Swirski FK, Weissleder R, Pittet MJ. Massachusetts General Hospital and Harvard Medical School.

Tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs) can control cancer growth and exist in almost all solid neoplasms. The cells are known to descend from immature monocytic and granulocytic cells, respectively, produced in the bone marrow. The spleen is also a recently identified reservoir of monocytes. Evaluating the role of the splenic reservoir in a mouse model of lung adenocarcinoma, the authors found that high numbers of TAM and TAN precursors relocated from the spleen to the tumor stroma, and that recruitment of tumor-promoting spleen-derived TAMs required signaling of the chemokine receptor CCR2. Removal of the spleen reduced TAM and TAN responses significantly and delayed tumor growth. *Proceedings of the National Academy of Sciences.* 2012 Jan. 30.

MIM ADKINS

For Family Van, 20 Years Of Wellness on Wheels

Twenty years ago, the Family Van hit the road. Last month, the wellness services center on wheels celebrated two decades of providing free curbside health education, screenings and referrals to more than 40,000 people in Boston neighborhoods.

"It's fascinating to think about what's the same and what's changed over 20 years," said Jennifer Bennet, executive director of The Family Van and Mobile Health Map. "The program was designed by community members and in partnership with them, and to this day, that's very much the way that we run the program."

The Family Van was envisioned by Nancy Oriol, now HMS dean for students, who launched the project with co-founder Cheryl Dorsey, then an MD student and now the president of Echoing Green, a venture philanthropy. The Van hit the streets on Martin Luther King, Jr. Day in 1992, with a mission to increase access to health services in medically underserved neighborhoods. The Van originally served six sites; a seventh site, in East Boston, was added in October 2011.

Today, Van clinicians stay busy, sometimes seeing up to 30 people during a three-hour neighborhood stop. Much of the work involves undiagnosed chronic illnesses such as hypertension and diabetes.

Although Massachusetts has made health insurance more widely available, Van staffers stress that insurance does not translate directly to access to care. Last year, only eight percent of Family Van clients were uninsured. "We primarily are working with people who have coverage, but their lives are too complex, usually because of poverty, to access healthcare," said Benet.

"Dean Oriol came up with a very elegant, user-friendly design," said Caterina Hill, research and evaluation program manager for The Family Van and research associate in the HMS Department of Global Health and Social Medicine, citing drop-in appointments and free services. "Even in Boston with all the amazing hospitals, there's still a need for mobile clinics as a means for providing outreach and between-visit care for health symptoms. The Van's success is built on trust and on meeting people where they are, both geographically and in terms of their health."

In addition to preventative screening and testing, health education and student training, the Van team has expanded efforts in research and analysis. Mobile clinicians now upload data using an online tool called Mobile Health Map. A return-on-investment algorithm developed at HMS analyzes cost savings. "Now we're able to really play a national role," Benet said, "in terms of helping other mobile clinics understand that they really are having an impact."

To date, more than 450 mobile health vans across the United States are using the online service. "Any van across the country can use it," Benet said. "And it has shed light on a community that was previously really unstudied."

One in three Van clients, Hill said, learn for the first time that they have borderline or high blood pressure, total cholesterol or blood glucose. The Van offers referrals and lifestyle coaching. "We're saving the city of Boston more than $1 million annually in avoided emergency room visits because we've been able to identify folks who are at high risk early on, and help them avoid becoming acutely ill," said Hill.

Half of regular clients who presented with a health problem on their first visit to the Van controlled the condition by later visits. And savings aren't just in dollars.

"This is a way to support the goals of primary care doctors, but we do so outside of a primary care setting," Benet said. The Van team is moving in the direction of increased collaboration with care providers. "Doctors have an incredibly important role, and we need to make the best possible use of their time. Is it cost effective for doctors to be doing the education and counseling component of this part of treating people? Does that have to happen in a doctor's office?" asked Benet.

"It was no accident that we were founded on Martin Luther King, Jr. Day," said Hill. "Despite all the changes and growth, we've maintained the social justice aspect of our mission."

—Angela Alberti

FAMILY VAN BY THE NUMBERS

44,148 Miles driven

40,000 People served with 90,000 visits since 1992

36% Percentage of visits that prevented an ER visit in 2010

$6 million Emergency room costs avoided over four years

$2 million Total cost to run the program over the same period

$55 million Savings in downstream health care costs saved through prevention

1 in 2 Regular clients who had high blood pressure at the first visit but not at the most recent visit. (The average change in Diastolic Blood Pressure, -5 mmHg, is associated with 35-40% reduced risk of stroke and 20-25% reduced risk of coronary heart disease if maintained long- term.)

Send an Eco-star Onto Green Carpet

Harvard University's Office for Sustainability is accepting nominations for the 2012 Green Carpet Awards. The awards honor staff, students and faculty across the University for significant contributions to sustainability.

The deadline for nominations is March 9, 2012. Winners will be announced April 12th in Sanders Theatre in Cambridge.

Learn more at **green.harvard.edu.**

KRES SNIBBE

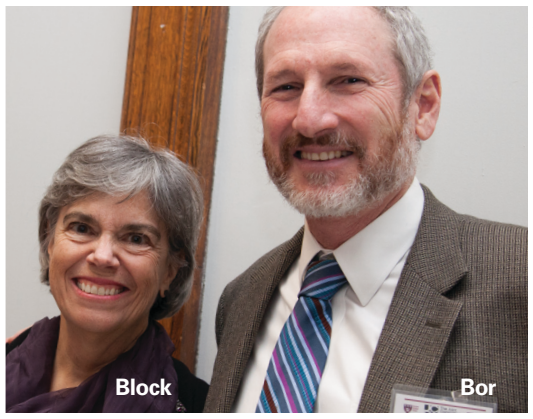
Call for Applications: Marks Fellowships

The Nancy Lurie Marks Family Foundation is seeking applications for two fellowships; application deadlines are Friday, March 16, 2012.

The Junior Faculty MeRIT Fellowship is intended to support junior faculty members developing an autism-related independent research program. Each applicant must hold an MD or MD/PhD, be a faculty member within the first five years of a career at Harvard M edical School or an affiliated institution, have at least two years of postdoctoral research experience and be actively engaged in research related to autism. Fellows will receive $75,000 each year for two years, plus $10,000 each year for supplies.

The Nancy Lurie Marks Postdoctoral Fellowship is intended to provide salary support and limited funds for research supplies to a postdoctoral fellow who holds an MD and/or PhD, is affiliated with HMS or an affiliated hospital, who has at least two years of prior postdoctoral experience and is actively engaged in autism-related research.

For details, visit nlmfoundation.org.



MEGAN HALIGAN

Beyond the 'Mommy Track'

Is the mommy track vanquished? Or is it still a derailer of medical careers? The question loomed large as champions of women's careers at HMS explored the challenges of flexible career paths during a panel discussion convened Feb. 6 by the HMS/HSDM Joint Committee on the Status of Women (JCSW).

The panel, titled "Lessons from Recipients of the Joseph B. Martin Dean's Leadership Award for the Advancement of Women," was moderated by Dean for Faculty Affairs Maureen Connelly and comprised four past honorees: Beth Beighlie, HMS senior client services representative; Susan Block, chair of the Department of Psychosocial Oncology and Palliative Care at Dana–Farber Cancer Institute and Brigham and Women's Hospital; David Bor, chief of medicine at Cambridge Health Alliance; and Tracy Sachs, administrative director for the Center for Health and the Global Environment.

"When I was young, there was one path, and if you stepped off it, you were lost," Block told the audience in Gordon Hall's Waterhouse Room. "And I don't believe that at all. And certainly I stepped off it and I don't think I was lost. But it was scary. I don't want people to have to carry as much fear as I felt about stepping off the traditional path."

Statistics from the American Medical Group Association suggest that an increasing number of physicians are stepping off the traditional full-time path. Since 2005, the part-time medical workforce has grown by 62 percent. A 2010 survey by the group indicated that 13 percent of male and 36 percent of female physicians practiced part-time, up from 7 percent and 29 percent respectively in 2005.

Anxiety about job security for part-timers was on display, with one attendee asking panelists for advice on approaching supervisors to request flexibility during a time of cutbacks.

"This is a major, major challenge for us as a medical society, and I don't think the issue should be borne by the pregnant woman. It needs to be borne by the leaders." Bor said. "Part-time work is absolutely a must, and benefit packages that support that, and policies that support that, and cross-coverage schedules that support it must be part of the culture. And if it isn't, we're not going to succeed as a medical profession."

A recent study reported in the *Journal of the American College of Surgeons* concluded that employing more part-timers may reduce the shortage of surgeons by encouraging them to remain in practice longer and promoting work-life balance, both advantages for a medical workforce in which the two fastest-growing segments are female physicians entering practice and male physicians approaching retirement.

According to the JCSW, although about half of graduates of HMS and HDSM are female and about half of their respective instructors are female, fewer than 1 in 5 professors are female. The JCSW Strategic Plan for 2012-2016 highlights opportunities to job-share or work flexible hours to encourage talented women to stay in the workforce, among both faculty and staff.

Mentorship, peer networking and staff diversity and development were also discussed as key elements of attaining work-life balance and retaining talent.

JCSW co-Chairs Fiona Fennessy and Aun Em concluded the panel discussion by calling for nominations of outstanding faculty and staff for the 2012 Dean's Leadership Award. "Women's issues are community issues at Harvard," Fennessy said.

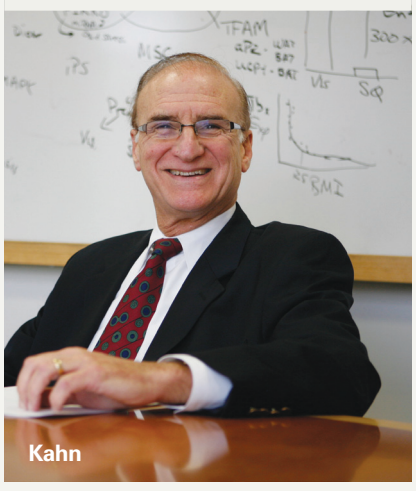
—Angela Alberti

Notable

For details, visit focushms.com.

David Williams is to receive the American Society of Gene & Cell Therapy's highest honor, the Outstanding Achievement Award ■ **Reza Dana** received the Chancellor's Award in Neurosciences and Ophthalmology from Louisiana State University School of Medicine ■ **Mandeep Mehra** was named executive director of the Advanced Heart Disease Center at Brigham and Women's Hospital ■ **C. Ronald Kahn** was named chief academic officer at Joslin Diabetes Center ■ **Patrick Wardell** was named chief executive officer at Cambridge Health Alliance ■ The Association of American Medical Colleges awarded **Massachusetts General Hospital** its 2011 Spencer Foreman Award for Outstanding Community Service.

COURTESY CAMBRIDGE HEALTH ALLIANCE



COURTESY JOSLIN DIABETES CENTER

LEONARD RUBENSTEIN

Metamorphosis of a Medical Student

Third-year experiences in the clinic spur a remarkable transformation

Everything changes during the third year of medical school. Leaving classrooms for the clinic, students begin to apply the skills learned from textbooks, lectures and labs to patients. And for the first time, future MDs begin to feel like doctors.

In a new podcast, *Focus* explores this intense and rewarding year, known at Harvard Medical School as the Principal Clinical Experience, or PCE. Listen as students and faculty members relate how the approach fosters mentoring, communication and empathy.

—Alyssa Kneller

HMS PODCAST

HMS student Kat Wakeham (far right) and her mentor David Hirsh discuss their perspectives on the third year of medical school in a new podcast. Hirsh, an HMS assistant professor of medicine at Cambridge Health Alliance, champions an integrated, longitudinal experience for students.

Social Networks

Continued from page 1

COURTESY COREN APICELLA

genetics and political science at the University of California, San Diego, who, with Christakis, has authored a number of seminal studies of human social networks.

The findings were published Jan. 26 in *Nature*.

ROOTS OF ALTRUISM

The natural world, red in tooth and claw, has a gentle side. While individuals compete fiercely to ensure the proliferation of their progeny, a few animals, including humans, also cooperate and act altruistically. Researchers have wondered if human social networks are a product of modern lifestyles, or if they could have emerged under the kind of conditions that our distant ancestors faced. This question has been challenging for classic evolutionary theory to explain neatly.

For cooperation to arise, an altruistic act, like sharing food with a non-relative, must have a net benefit for the sharers. Otherwise, purely self-serving individuals would outcompete and eventually replace the selfless. All theoretical explanations for the evolution of cooperation—kin selection, reciprocal altruism, group selection—rely on the existence of some system that allows cooperators to group together with other individuals who tend to share.

"If you can get cooperators to cluster together in social space, cooperation can evolve," said Coren Apicella, a post-doctoral research fellow in Health Care Policy at Harvard Medical School and first author on the paper. "Social networks allow this to happen."

While it is not possible to quiz our distant ancestors about their friendships or habits of sharing and collaborating, a team of researchers from Harvard Medical School, the University of California, San Diego, and the University of Cambridge have characterized the structure of social networks among the Hadza, an ethnic group in the Lake Eyasi region of Tanzania, one of the last surviving groups of hunter gathers. (There are fewer than 1,000 Hadza left who live in the traditional way.)

The Hadza lifestyle predates the invention of agriculture. The Hadza eat a wide range of wild foods, foraging for tubers, nuts and fruit and hunting a great variety of animals, including flamingos, shrews and giraffes. Honey is one of their favorite foods, known by half a dozen different names in Hadzane, their primary language.

GETTING CONNECTED

Apicella took the lead in collecting the data for the study, interviewing 205 adult Hadza over the course two months, measuring their tendency to cooperate and mapping their friendships.

Apicella, Fowler and Christakis designed the study and experiments, working with Frank Marlowe, lecturer in the Department of Archaeology and Anthropology of the University of Cambridge, and author of the only book-length ethnography on the Hadza in English.

Collecting the data was not easy. The nomadic Hadza roam over 4,000 rugged square kilometers. Apicella and her research assistants travelled the region by Land Cruiser battling mud-drenched trails—at one point forcing her and her colleagues to pave the ground with felled trees—and, on an earlier trip, even fleeing a horde of marauding elephants.

Using a photo array, subjects chose individuals with whom they would prefer to live in their next encampment.

In order to construct a social network, Apicella and her colleagues took a dual approach. First, they asked Hadza adults to identify individuals they would prefer to live with in their next encampment. Second, they gave each adult three straws of honey and were told they could give these straws as gifts to anyone in their camp. This generated 1,263 campmate ties and 426 gift ties.

In a separate activity, the researchers measured levels of cooperation by giving the Hadza additional honey straws that they could either keep for themselves or donate to the group.

When the networks were mapped and analyzed, the researchers found that cooperators and non-cooperators formed distinct clusters.

The researchers also measured the connectedness of people with similar height, age, handgrip strength, etc., and other characteristics, such as food preference. They also analyzed the transitivity of friendship—the likelihood that one's friends are friends with one another, and other network properties.

The structure and dynamics of the Hadza hunter-gatherer social networks were essentially indistinguishable from existing social network data drawn from modern communities.

"We turned the data over lots of different ways," said Fowler. "We looked at over a dozen measures that social network analysts use to compare networks and pretty much, the Hadza are just like us."

"Human beings are unusual among species in the extent to which we form long-term, non-reproductive unions with other members of our species," said Christakis. "In other words, not only do we have sex, but we also have friends."

Previous work by Christakis and Fowler, who are coauthors of the book *Connected,* has shown that our experience of the world depends on where we find ourselves within social networks. Particular studies have found that networks influence a surprising variety of lifestyle and health factors, such as how prone you are to obesity, smoking cessation, and even happiness.

For the researchers, the Hadza offer strong new evidence that social networks are a truly ancient, perhaps integral part of the human story.

—Jake Miller

Chang Shan

Continued from page 1

molecular secrets behind this herbal extract's power.

It turns out that halofuginone (HF) triggers a stress-response pathway that blocks the development of a harmful class of immune cells, called Th17 cells, which have been implicated in many autoimmune disorders.

"HF prevents the autoimmune response without dampening immunity altogether," said Malcolm Whitman, a professor of developmental biology at Harvard School of Dental Medicine and senior author on the new study. "This compound could inspire novel therapeutic approaches to a variety of autoimmune disorders."

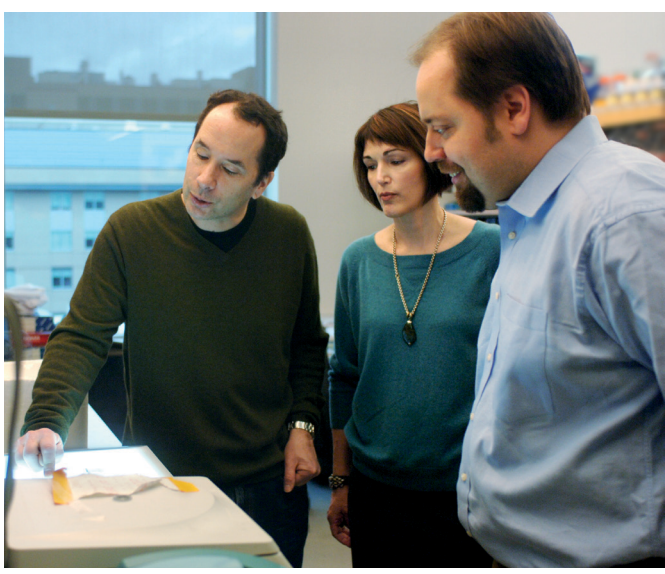
"This study is an exciting example of how solving the molecular mechanism of traditional herbal medicine can lead both to new insights into physiological regulation and to novel approaches to the treatment of disease," said Tracy Keller, an instructor in Whitman's lab and the first author on the paper.

This study, which involved an interdisciplinary team of researchers at Massachusetts General Hospital and elsewhere, was published online Feb. 12 in *Nature Chemical Biology.*

Prior research had shown that HF reduced scarring in tissue, scleroderma (a tightening of the skin), multiple sclerosis, scar formation and even cancer progression. "We thought HF must work on a signaling pathway that had many downstream effects," said Keller.

In 2009, Keller and colleagues reported that HF protects against harmful Th17 immune cells without affecting other beneficial immune cells. Recognized only since 2006, Th17 cells are "bad actors," implicated in many autoimmune diseases such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis and psoriasis. The researchers found that minute doses of HF reduced multiple sclerosis in a mouse model. As such, it was one of a new arsenal of drugs that selectively inhibits autoimmune pathology without suppressing the immune system globally. Further analysis showed that HF was somehow turning on genes involved in a newly discovered pathway called the amino acid response pathway, or AAR.

Scientists have only recently appreciated the role of the nutrient sensing-AAR pathway in immune regulation and metabolic signaling. There is also evidence that it extends lifespan and delays age-related inflammatory diseases in animal studies on caloric restriction. A conservationist of sorts, AAR lets cells know when they need to preserve resources. For example, when a cell senses a



ANGELA ALBERTI

From left: Malcolm Whitman, Tracy Keller and Ralph Mazitschek.

limited supply of amino acids for building proteins, AAR will block signals that promote inflammation because inflamed tissues require lots of protein.

"Think about how during a power outage we conserve what little juice we have left on our devices, foregoing chats in favor of emergency calls," said Whitman. "Cells use similar logic."

For the current study, the researchers investigated how HF activates the AAR pathway, looking at the most basic process that cells use to translate a gene's DNA code into the amino acid chain that makes up a protein.

The researchers were able to home in on a single amino acid, called proline, and discovered that HF targeted and inhibited a particular enzyme (tRNA synthetase EPRS) responsible for incorporating proline into proteins that normally contain it. When this occurred, the AAR response kicked in and produced the therapeutic effects of HF-treatment.

Providing supplemental proline reversed the effects of HF on Th17 cell differentiation, while adding back other amino acids did not, establishing the specificity of HF for proline incorporation. Added proline also reversed other therapeutic effects of HF, inhibiting its effectiveness against the malaria parasite as well as certain cellular processes linked to tissue scarring. Again, supplementation with other amino acids had no such effect. Such mounting evidence clearly demonstrated that HF acts specifically to restrict proline.

The researchers think that HF treatment mimics cellular proline deprivation, which activates the AAR response and subsequently impacts immune regulation. Researchers do not yet fully understand the role that amino acid limitation plays in disease response or why restricting proline inhibits Th17 cell production.

Nevertheless, "AAR pathway is clearly an interesting drug target, and halofuginone, in addition to its potential therapeutic uses, is a powerful tool for studying the AAR pathway," said Whitman.

—Cathryn Delude

To learn more, students may contact Malcolm Whitman at malcolm_whitman@hms.harvard.edu.

Rabkin Fellowship in Medical Education

The Shapiro Institute for Education and Research at Beth Israel Deaconess Medical Center and Harvard Medical School is seeking applications for the academic year 2012-2013 Rabkin Fellowship in Medical Education. The Rabkin Fellowship in Medical Education was established in 1998 to provide faculty the opportunity to develop the expertise and skills needed to launch or advance academic careers in medical education. The Rabkin Fellowship is open to faculty who have a primary appointment at Harvard Medical School and who currently teach at HMS or at a Harvard-affiliated institution.

Participating faculty will develop and enhance their skills as medical educators; conduct education research or undertake a project in an area of importance in medical education; learn the principles of effective leadership and develop the skills needed to create educational change; and join a community of educators dedicated to excellence in teaching across the continuum of medical education.

The deadline is Friday, March 2 at 5 p.m. Fellowship awards will be announced in April 2012.

The request for applications, application instructions and bio-sketches of former Rabkin Fellows can be found at www.bidmc.org/rabkinfellowship.

ROBYN MACKENZIE/ISTOCKPHOTO

The Decision to Test

Chopra

First on the schedule in genetics clinic one afternoon were two sisters, ages 8 and 10, who had an appointment for evaluation of a "possible connective tissue disorder." I remember thinking that they were much younger than the teenagers I had previously seen in clinic for similar reasons, referred by their pediatricians for newly elongated limbs or mild scoliosis. In the elevator up to clinic, my mind conjured vivid images from a seminal textbook on heritable connective tissue disorders. Stark black and white photographs depicted slender children with disproportionately long, spindly limbs and fingers, serpentine spines, sunken chests, and narrow faces with noses wedged between the frames of coke-bottle glasses.

Stepping into the clinic room, I sighed with relief. Seated before me were two well-appearing young girls, gleefully passing the time with their idle chatter. The overweight older sister playfully swung her normally-proportioned legs to and fro beneath her chair. Her younger sibling, both shy and slight in habitus, rested her hands on the front of her knees. I looked at her unremarkable fingers, the petite nails harboring flecks of paint. Even before reaching for the bright red measuring tape dangling from my shirt pocket, my suspicion was low that anything insidious could be afflicting these lovely children.

Their mother described the events that had brought them to Children's Hospital. Several months earlier, the girls' seemingly healthy father had suddenly developed severe chest pain. He was taken by ambulance to his local emergency room where a CT scan revealed a menacing tear in the wall of his aorta. Both fulminant and morbid, an aortic dissection is not uncommonly the presenting feature of an undiagnosed disorder of connective tissue, the biological fabric that binds together the skin, vital organs and blood vessels. His dissection was life-threatening and required immediate operative repair, but he survived the event. Later testing identified a deleterious mutation in the gene *Fibrillin-1*. The test result meant that he had Marfan syndrome.

Marfan syndrome is a genetic disorder of the connective tissue that can affect the body in a variety of ways. While there is no cure, people with Marfan can live a long and healthy life by managing its symptoms. It is a dominant trait, so each girl had a 50/50 chance of inheriting the disease.

After learning everything she could about Marfan syndrome, the girls' mother wondered desperately whether either of her children could have the disorder. I examined the girls and reassured their mother that neither child met the clinical criteria. I explained that because some features of the syndrome may appear as children grow, the plan would be to obtain an echocardiogram to assess for aortic root dilation and then follow the children in genetics clinic on an annual basis. Before I could finish discussing my tentative plan, the mother asked the obvious question: Couldn't we just test the girls to determine whether either had inherited her father's *Fibrillin-1* mutation?

Although I appreciated their mom's desire for a definitive answer, I had mixed feelings. Is it appropriate for physicians to test well-appearing, asymptomatic children for genetic disorders? What were the implications? On one hand, knowing that a child carries a *Fibrillin-1* mutation means that she could receive comprehensive anticipatory guidance for various features of the disorder, as well as take certain precautions to avert a future aortic catastrophe. Perhaps more compelling, medications are being developed to counter the specific cellular perturbations that cause the aorta to weaken in the first place. Certainly, the availability of an effective preventive intervention might warrant assessment of a child's *Fibrillin-1* genotype well in advance of any clinical signs.

On the other hand, I worried about the consequences of identifying a genetic mutation in an asymptomatic young child. Regular doctors' visits and annual echocardiograms would make her a patient. Her mutation status may complicate relationships with family, friends and the opposite sex. She might be discouraged from pursuing certain interests, talents or vocations. Her physical activity would be restricted to limit the stress on her aorta. I also wondered about the psychological impact of knowing that one might die suddenly in the future. Any of these possibilities seemed compelling enough to consider a delay in genetic testing.

Ultimately, the difficult decision to test the girls was not mine to make. Based on the mother's strong wishes, each girl had her blood drawn that day. The results returned several weeks later: Both sisters had inherited their father's *Fibrillin-1* mutation. I imagined mom's anguish upon hearing the news. I was also heavy-hearted for a reason that had little to do with the future health of the sisters. I realized that the lives of these young children would never be the same, forever changed by the results of a single genetic test. Whether they had been altered for better or worse is impossible to know. Only time will tell.

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Heart

Continued from page 1

etiology for their heart disease remained unknown.

Now, new work from the lab of Christine Seidman, a Howard Hughes investigator and the Thomas W. Smith Professor of Medicine and Genetics at Harvard Medical School and Brigham and Women's Hospital, and Jonathan Seidman, the Henrietta B. and Frederick H. Bugher Foundation Professor of Genetics at Harvard Medical School, has found that mutations in the gene TTN account for 18 percent of sporadic and 25 percent of familial DCM.

"Until the development of modern DNA sequencing platforms, the enormous size of the TTN gene prevented a comprehensive analyses – but now we know TTN is a major cause of DCM," said Christine Seidman, who reported the findings Feb. 16 in the *New England Journal of Medicine.*

Idiopathic DCM is one of three different types of cardiomyopathy (the term "idiopathic" indicates that acquired causes for DCM such as atherosclerosis, excess drinking or viral infections have been excluded). It affects only about 4 in 10,000 Americans, but may be under-diagnosed because symptoms often appear late in the course of disease. DCM may cause shortness of breath, chest pain and limited exercise capacity. DCM increases the risk of developing heart failure, for which no cure is available, and the risk of stroke and sudden cardiac death.

SPOTTING THE RISK

These findings will not only help patients understand the cause of their DCM symptoms, but also help to screen family members who might be at risk of developing the condition. Early identification of those at risk allows early intervention with medications that reduce workload on the heart and help prevent the changes in heart muscle, called remodeling, that lead to heart failure.

As DCM progresses, remodeling of the heart tissue makes the heart more prone to disturbances in the normal heart rhythm that can lead to stroke, heart attack and sudden death. "One of the added values to knowing that you are at risk for developing DCM is that we can do prophylactic screening so that silent arrhythmias are picked up before they become harmful," said Christine Seidman. "The discovery is immediately translatable into clinical practice to provide patients with gene-based diagnosis." The Partner's Laboratory for Molecular Medicine, an HMS affiliate, has incorporated TTN analyses.

The Seidmans and others had previously linked other gene mutations to about 20 to 30 percent of idiopathic DCM cases — and, with more success, to a related disease, hypertrophic cardiomyopathy. They had examined almost all of the genes linked to muscle units known as sarcomeres, but saved the biggest for last: TTN, which encodes the protein titin. At approximately 33,000 amino acids, titin is the largest human protein.

"Titin was a missing link," said Christine Seidman. "A very large missing link."

The Seidmans collaborated with researchers from the Imperial College (London) and the University of Washington. Traditional sequencing methods had previously found only a few TTN variants in patients with DCM because complete, accurate sequencing was too expensive.

Using next generation sequencing tools that substantially reduce the cost per base (the TTN sequence contains 100,000 bases) by orders of magnitude over earlier standards, the Seidmans were able to perform comprehensive screening for TTN mutations for the first time. They analyzed TTN in 312 DCM patients, 231 HCM patients and 249 individuals with no disease.

"One of the added values to knowing that you are at risk for developing DCM is that we can do prophylactic screening. The discovery is immediately translatable into clinical practice to provide patients with gene-based diagnosis."

— Christine Seidman, Thomas W. Smith Professor of Medicine and Genetics at Harvard Medical School

Of the many mutations identified, 72 make the titin protein shorter.

Called TTN truncating variants, these specific mutations appeared almost exclusively in patients with DCM. "Our hypothesis is that any variant that shortens titin is going to cause DCM, which will lead to heart failure by the same mechanism," said Jonathan Seidman.

PLANNING AHEAD

To identify the pathological mechanism, the Seidmans plan to model a handful of TTN truncating mutations in mice.

One concern in the search for disease causing genes is that, while there will be many gene variants discovered, only a few will cause disease. This is particularly true for missense mutations that cause singlenucleotide changes — changes that substitute a single amino acid within the protein. "We often don't know if a missense mutation significantly impacts a protein's function, until we model it and study its effects," said Jonathan Seidman.

However, in the case of truncating mutations, "it's the converse," he continued. "We don't have to model all of those different mutations that truncate titin, betcuase they all foreshorten the protein. We can pick a few representative ones and expect that they will reveal a common mechanism." A better understanding of the mechanism may lead to better and more direct therapies for treatment and prevention of DCM.

— Elizabeth Dougherty

To learn more, students may contact Christine Seidman at cseidman@genetics.med.harvard.edu.

HUNTSTOCK/GETTYIMAGES

Referrals

Continued from page 1

Women's Hospital.

The results were published January 23 in the *Archives of Internal Medicine.*

For many years, the rate of referrals stayed flat, until about ten years ago, when they began a steady climb. This paper is the first research to analyze referral data since the trend began. The marked increase in referral rates is likely due to increased specialization in medical care, and increasing responsibilities for primary care physicians during a typical visit. "Sometimes physicians may find it easier to refer a patient to another doctor than to find the necessary time to spend with him or her," said coauthor Zirui Song, an HMS student and PhD student in health policy.

The researchers noted that referrals to specialists are often gateways to a cascade of potentially costly services which may or may not be needed: The cost associated with a referral isn't just the cost of a single visit, it's the potential for an ongoing series of visits, diagnostic tests, procedures and hospitalizations that might result.

In some cases, a more conservative approach can have better results and lower costs. Instead of referring a patient with ankle pain for an MRI and a visit to an orthopedist, a primary care physician might first recommend rest and physical therapy.

"This study is step one, an attempt to start to get our heads around the question by describing the basic epidemiology of physician referrals," said Landon. In order to manage the rising costs of health care and guarantee the best outcomes for patients, he added, researchers need to understand the interactions between networks of referring physicians and the appropriateness of referrals.

—Jake Miller

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