INSIDE STANFORD MEDICINE

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Stanford Medicine has debuted new, more visually compelling formats for online CME courses.

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Rocket scientists apply engineering know-how to detecting disease through breath analysis

By Kris Newby

In a dimly lit room, next to a supersonic jet engine test rig, three Stanford engineering graduate students sat around a whiskey bottle.

All was quiet on this Friday evening in 2013 except for their lab's visceral hum, a rumbling of fans, flames and gases rushing through jet-propulsion nozzles.

These three rocket-combustion experts — Christopher Strand, Victor Miller and Mitchell Spearrin — were talking about the future. In a few months they would have doctoral degrees, and then what?

As boys, all three grew up away from big city lights, with a clear view of the stars. And they dreamed about rockets and exploring space.

Now that the space shuttle was grounded and its successor scrapped for being over budget, what would they do instead? Work at an aerospace company? Consult on military projects?

It was Strand who initiated a series of brainstorming sessions that challenged them to think beyond outer space.

"Somewhere between ideas on fixing San Francisco's parking problem and inventing a marijuana Breathalyzer, we decided to see if we could use our education and expertise in combustion science to analyze human breath for disease," said Miller.

After all, the human body is essentially a biochemical engine. It consumes fuel and exhales waste gases. Maybe the three of them could engineer a disease Breathalyzer? It would be a gadget straight out of Star Trek — a quick, noninvasive way to detect everything from diabetes to cancers.

Many have tried and failed to create such a device. But these guys are rocket men. They assume risks without fear. They take giant leaps for mankind.

Sure, they didn't know much about medicine, but they figured that with a little luck and a lot of hard work, they might be able to do it. The first step was to find medical experts to help, so they contacted a group of pediatricians at Stanford's medical school.

Saving Ethan

Five years ago, professor of pediatrics Gregory Enns, MD, was called into the neonatal intensive care unit at Lucile Packard Children's Hospital Stanford to help a newborn in trouble.

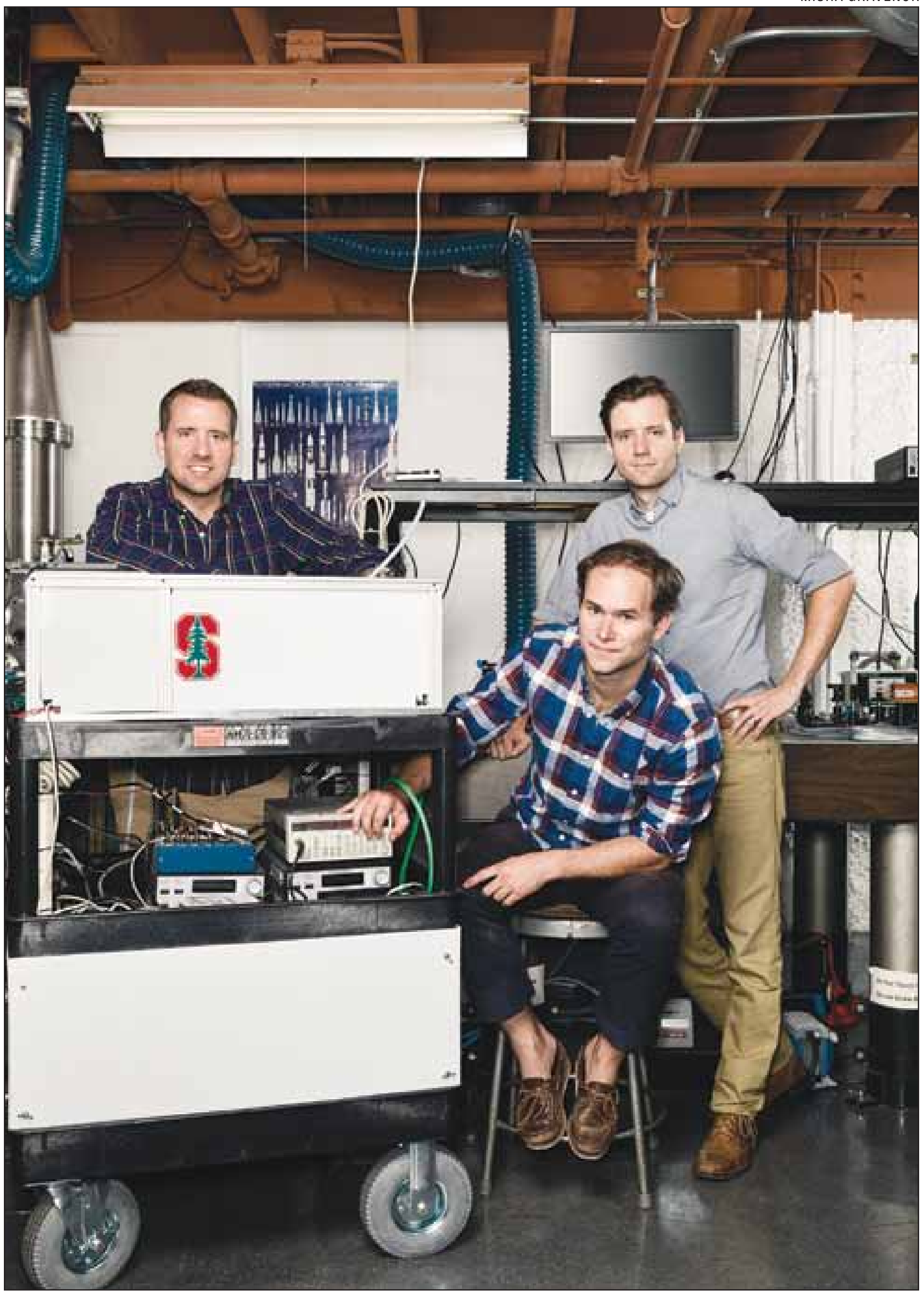
The child's mother, Tiffany Nguyen, was a software consultant and his father, Luan Pham, was a systems engineer. They were immigrants from South Vietnam, excited about starting a family in the United States. After 18 hours of labor, their baby boy was born. They called him Ethan, a biblical name that means "enduring strength" in Hebrew.

But the morning after his birth, Ethan cried continually. His blood sugar and temperature dropped. His body became limp. The attending pediatrician couldn't figure out what was wrong, so two days after Ethan's birth, he was moved from a San Jose community hospital to Lucile Packard Children's Hospital Stanford. That was when Enns, a biochemical geneticist who diagnoses and treats metabolic diseases, was contacted.

When Enns first examined Ethan, the baby's tiny heart was beating erratically and his blood sugar level was dangerously low. Enns didn't think he would survive the night. But he put this possibility out of his mind and did his best. Enns, with his reassuring smile, quirky cartoon ties and clear blue eyes, is also a professional optimist.

First, the cardiac team was called in to help stabilize See ROCKET, page 6

MISHA GRAVENOR



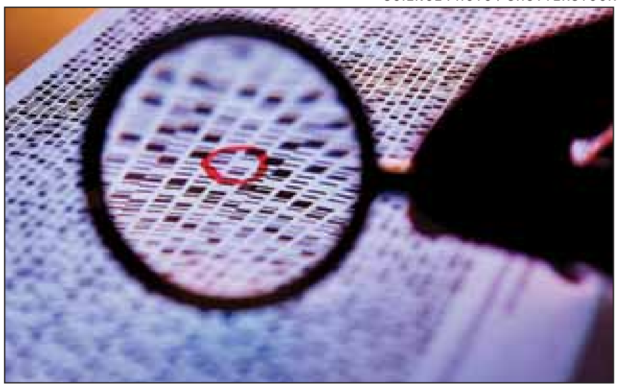
Mitchell Spearrin, Victor Miller (seated) and Christopher Strand developed a prototype of a noninvasive device for measuring ammonia levels in the body.

Researchers identify potential for compromising security in network used to share genomic data

By Jennie Dusheck

Sharing genomic information among researchers is critical to the advance of biomedical research. Yet genomic data contains identifiable information and, in the wrong hands, poses a risk to individual privacy. If someone had access to your genome sequence — either directly from your saliva or other tissues, or from a popular genomic information service — they could check to see if you appear in a database of people with certain medical conditions, such as heart disease, lung cancer or autism.

SCIENCE PHOTO / SHUTTERSTOCK



Work by a pair of researchers at the School of Medicine makes that genomic data more secure. Suyash Shringarpure, PhD, a postdoctoral scholar in genetics, and Carlos Bustamante, PhD, a professor of genetics, have demonstrated a technique for hacking a network of global genomic databases and how to prevent it. They are working with investigators from the Global Alliance for Genomics and Health to implement preventive measures.

The work, published Oct. 29 in *The American Journal of Human Genetics,* also bears importantly on the larger question of how to analyze mixtures of genomes, such as those from different people at a crime scene.

A network of genomic data sets on servers, or beacons, organized by the National Institutes of Health-funded Global Alliance for Genomics and Health, allows researchers to look for a particular genetic variant in a multitude of genomic See SECURITY, page 4

Experts debate public health consequences of e-cigarettes at forum

By Lindzi Wessel

How do we reduce health risk in the face of harm that can't be eradicated completely? That's the question Lloyd Minor, MD, dean of the School of Medicine, presented to the audience at the recent Health Policy Forum on e-cigarettes — a topic about which he said "intelligent and reasonable people can disagree."

E-cigarettes are a controversial subject in the public-health community. Panelists at the event debated whether the recently developed devices hold promise to help long-time smokers move away from combustible cigarettes, or whether they could abet a renormalization of smoking.

All panelists agreed that those under the age of 21 shouldn't be using any nicotine delivery devices, and they shared a goal of minimizing general use of harmful health products. They disagreed, however, on what the advent of e-cigarettes means in accomplishing those goals.

Clinical psychologist David Abrams, PhD, executive director of the Schroeder Institute for Tobacco Research and Policy Studies at Johns See E-CIGARETTES, page 5

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Dietitian on report labeling some meats carcinogens

In late October, the World Health Organization's International Agency for Research on Cancer released a report concluding that red meat and processed meat should join the list of foods that can, under certain circumstances, raise our risk of cancer. The group analyzed more than 800 studies on cancer in humans to reach its conclusions. The reaction was noisy: Prosciutto makers in Parma, Italy, protested; vegetarians and vegans saw it as an affirmation; and the rest of us wondered what it all meant. Must we swear off these kinds of meats completely, or is it safe to consume a little every now and then?

Raymond Palko, MS, RD, is a clinical dietitian who provides nutritional counseling to cancer patients at Stanford Health Care. In an interview with writer Sara Wykes, Palko shared his thoughts on the WHO report and offered some suggestions on what we might want to change about our food choices.

1 What did you notice first about the WHO report?

PALKO: Many of its numbers and guidance on red meat and processed meat is what we've been using at Stanford Health Care for years. Cautions on processed meats have been around since 2007. What I like is seeing how much fanfare it's caused. It's important to be having these conversations about meat consumption. The report itself will become another tool that dietitians can use when we talk to people about what they eat. No longer will this idea of lowering how much red and processed meat you eat be an idea we just made up. It does build a framework for what a cancer-prevention diet looks like. There's been a lot of conversation about it in the oncology dietitian community because it confirms the recommendations we've been making with our patients. It's good to see that expanded to a broader stage.

2 What should people know about the relationship between cancer and the consumption of red meat and processed meat?

PALKO: I do have an issue with any conclusion that says if you eat red or processed meat, you will get cancer. No matter what numbers you choose to accept about the increased risk related to eating these kinds of meats, it's important to remember that cancer is a multifactorial disease. It's not just diet alone. It's diet, weight related to that diet, inherited risk and environmental exposures. Your cancer risk can also be raised by other illnesses you may have had and treatments for those illnesses. Diet is just one part of cancer risk, albeit an important one.

Raymond Palko

3 If you decide not to eat red meat, how can you get enough protein and iron?

PALKO: Chicken, fish, turkey, eggs, dairy, beans, nuts and seeds are very good sources of protein. Plant foods like dark-green vegetables contain the iron we need and do not have the risk of the form of iron found in red meat — a form called heme iron. Ample evidence suggests heme iron contributes to chronic disease risk, such as heart disease and digestive tract cancers. Heme iron, a strong pro-oxidant, is also found in other meats like fish and poultry, but in much smaller quantities that are not associated with cancer risk.

When we talk with people about their diet, we like to start first by talking about fruits and vegetables — not about protein. Fruits and vegetables should be the first building block of a diet. There are other benefits, too. When people stop eating red meat, we often see weight loss and an improvement in their daily digestive health. We know this sometimes happens because people have been eating fast-food burgers or burritos, washing them down with unhealthy beverages and just overconsuming calories.

4 If you want to eat some red meat, how much is safe?

PALKO: Our guidance on red meat is a maximum of 18 ounces a week. We tell our patients that 3 ounces of meat is about the size of a deck of playing cards. We do recommend that you don't eat red meat every day. Have a fish or vegetable protein meal instead.

5 Is there such a thing as a cancer-prevention diet that's trustworthy?

PALKO: A cancer-prevention diet looks very similar to a heart-disease or diabetes-prevention diet: lots of vegetables and fruits; more plant foods like beans, legumes, nuts and seeds; high-fiber, lower-fat, limited-fried, processed or salted foods; and alcohol in moderation. If you had to summarize what that is, you could look to food writer Michael Pollan's shorthand version: "Eat food. Not too much. Mostly plants." ISM

In letter, scientists urge removal of NIH funding restrictions on chimeric research

By Krista Conger

Citing the "tremendous potential" of research on human stem cells in nonhuman embryos, scientists and a bioethicist from the School of Medicine have co-authored a letter urging the removal of funding restrictions imposed on such research in September by the National Institutes of Health.

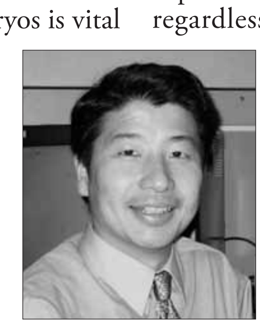
The researchers believe that work on what are called chimeric embryos is vital to advance our understanding of early human development, further our ability to accurately model devastating diseases and facilitate drug testing to ensure that potential therapies are safe and effective.

"Currently, it is impossible to accurately recapitulate human development in vitro, and there is no ethical method to obtain post-implantation stage human fetal tissue for isolating tissue and organ stem cells for regenerative medicine," they wrote.

The seven Stanford authors of the letter include Irving Weissman, MD, who directs Stanford's Institute for Stem Cell Biology and Regenerative Medicine, and David Magnus, PhD, director of Stanford's Center for Biomedical Ethics. The letter also was co-authored by four prominent scientists from other research institutions across the country.

It was published in *Science* Nov. 6 — the same day a workshop was held at the NIH to discuss the restrictions and deliver new research guidelines.

"By eliminating federal funding for all aspects of this research, the NIH casts a shadow of negativity toward all experiments involving chimera studies regardless of whether human cells are involved," said assistant professor of medicine Sean Wu, PhD, MD, one of the senior authors of the letter. "The current NIH restriction serves as a significant impediment to major scientific progress in the fields of stem cell and developmental biology and regenerative medicine and should be lifted as soon as possible."



Sean Wu

Weissman is the other co-senior author.

Studying human cells in animals

At issue is the growing field of research that seeks to understand how human pluripotent stem cells, which can become any cell type, may integrate and contribute to the development of a nonhuman animal, such as a laboratory mouse. Pluripotent stem cells can be isolated from human embryos or created in a lab from adult human cells, in which case they're known as induced pluripotent stem cells. Once obtained, these versatile cells can be injected into an early-stage animal embryo and studied as the embryo develops into an adult animal.

Tracking where these cells go and how they function in the growing embryo and the adult animal can help researchers understand early stages of human development that can't be studied any other way. (Although researchers can and do study the development of fertilized human eggs, the study period is restricted to only a few days after fertilization for ethical reasons.)

Furthermore, if cells from a person with a heritable disease, like sickle-cell disease, are used, it may be possible to generate an animal with the same disease for further experimentation or for testing to ensure drug safety before use in humans. Finally, if an animal is engineered to lack the ability to create a specific organ, such as a pancreas or liver, it may be possible for the human pluripotent stem cells to step up and develop an entirely human organ in that animal for study — or even for transplantation.

However, such studies have prompted ethical concerns, and on Sept. 23 the NIH abruptly suspended its funding of "research in which human pluripotent cells are introduced into nonhuman vertebrate animal pre-gastrulation stage embryos while the agency considers a possible policy revision in this area." The agency hosted the Nov. 6 workshop of researchers and bioethicists from around the country to consider issuing new guidelines about the research.

Authors: Concerns lack support

The authors of the letter believe that concerns about the research are not supported by previous studies, and argue that an ongoing dialogue among scientists and bioethicists is sufficient to ensure the research is conducted in an ethically responsible manner.

"Much of the bioethical concern in regard to human/non-human chimerism arises from the possibility of chimeric animals harboring human neurons and germ cells. Can human neural cells coexist with those from animals and establish 'humanized' cerebral anatomy and circuitries? Furthermore, would such chimeras be elevated to a higher metaphysical state and 'think' more like us? Current scientific data have not supported such possibilities, despite hundreds of xenotransplant studies introducing human neurons into the mouse brain," they wrote.

The researchers also cited current restrictions by the National Academy of Medicine and the National Research Council against breeding animals in which human pluripotent stem cells were implanted during development. These rules aim to prevent any possible transmission of human genes via the sperm or egg of the animal.

They also pointed to the stricture against using nonhuman primates, which are considered too similar to humans, for such studies as reasonable boundaries for chimeric research.

"Ultimately, we believe that human/nonhuman chimerism studies in pregastrulation embryos hold tremendous potential to improve our understanding of early development, enhance disease modeling, and promote therapeutic discovery," they wrote.

In addition to Weissman, Magnus and Wu, other Stanford-affiliated co-authors of the letter are Joseph Wu, MD, PhD, professor of medicine and director of the Stanford Cardiovascular Institute; Hiromitsu Nakauchi, MD, PhD, professor of genetics; Christopher Scott, PhD, director of Stanford's Program on Stem Cells and Society; and Vittorio Sebastiano, PhD, assistant professor of obstetrics and gynecology and director of Stanford's Human Pluripotent Stem Cells Core Facility.

Nakauchi and Stanford bioethicist and law professor Hank Greeley, PhD, attended the Nov. 6 workshop at the NIH. ISM

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STANFORD MEDICINE

New bioengineering major is off to its first academic year

By Tom Abate

Ever since the schools of Engineering and of Medicine jointly created the Department of Bioengineering in 2002, the plan was to eventually offer a bachelor's degree program alongside its master's degree and PhD programs.

The Faculty Senate brought this plan to fruition during the last academic year by approving an undergraduate bioengineering major in perpetuity. Senate Chair Russell Berman, PhD, described the new major as a milestone in Stanford's academic life.

"Not only does it address an exciting and growing field of knowledge at the interface of the life sciences and engineering," said Berman, professor of comparative literature and of German. "It also is the first time that the School of Medicine, working together with the School of Engineering, has offered an undergraduate degree."

Norbert Pelc, ScD, professor and chair of bioengineering, said approval of the major culminated years of effort by faculty, graduate students and pioneering undergraduates.

"We grew this department gradually around a core faculty and graduate program, and began testing our undergraduate curriculum in the 2009-10 academic year," said Pelc, who is also a professor of radiology. "One of our challenges has been that bioengineering is such a broad field that we had to distill it down to the essential foundations."

'An excellent start'

Brad Osgood, PhD, a professor of electrical engineering, was senior associate dean for student affairs at the School of Engineering during the lead-up to senate approval. Osgood likened bioengineering to computer science: an important but rapidly evolving field in which it took some time for a foundational curriculum to come into focus.

"How we present new fields to undergraduates boiling over with energy, enthusiasm and intelligence is the question," Osgood said. "I don't think anyone would say that we have the one answer, but we've made an excellent start."

Leading this effort has been Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences, in his capacity as the department's associate chair for undergraduate education.

"Joining the Bioengineering Department at Stanford shaped my whole career in a very positive way," said Deisseroth, a noted researcher who pioneered optogenetics, which involves using laser light to activate or inhibit nerve-cell signals in animals.

"The opportunities created at the interface of biology and engineering are immense and only beginning to be capitalized on," Deisseroth said. "I want to help create the same opportunities for undergraduates at Stanford that I enjoyed."

From its outset, Stanford sought to imbue the Bioengineering Department with the different but essential traditions of the School of Engineering and School of Medicine.

"Engineering brings problem-solvers and the medical school brings problem definition and some of the underlying science on which to build solutions," said Jim Plummer, PhD, professor of electrical engineering.

Plummer was dean of the engineering school when the department was formed. He worked with Philip Pizzo, MD, former dean of the medical school, to bring about this faculty-inspired vision of a department anchored in both schools and grounded on a quantitative and systematic approach to solving problems not just in human health, but in the environment, industry and other areas.

"We had undergraduate education as a high priority from the outset but purposefully delayed it until we had achieved a critical mass of faculty, graduate and postdoctoral programs," said Pizzo, professor of pediatrics and of microbiology and immunology. "With the initiation of an undergraduate major, bioengineering now moves from adolescence to adulthood."

Teri Hankes, student services director for bioengineering, is eager to answer questions from prospective majors. "We've been working on this so long and now it's a reality," she said.

Approval of the major coincided with the department's move to the Shriram Center for Bioengineering and Chemical Engineering, a recently constructed building on the Science and Engineering Quad. "All of this came together to enable us to grow our educational program," Pelc said, adding that undergraduates enrich the department with their ideas and enthusiasms.

'They are fearless'

"The more mature we get, the more we get encumbered by our preconceived ideas of what is doable and not doable," Pelc said. "Undergraduates are free from that. They don't know what they cannot do and therefore they are fearless."

Maya Anjur-Dietrich, who graduated with the Class of 2015, voiced that same sentiment.

"Anything you want to do is probably part of bioengineering if you look hard enough," she said. "I don't think you should let yourself be limited by what other people have done because maybe they haven't thought of what you wanted to do."

VIGNESH RAMACHADRAN

Karl Deisseroth, who played a leading role in creating the bioengineering major, teaches undergraduates.

Anjur-Dietrich was among the Stanford undergraduates who helped pioneer the major by pursuing a general degree in engineering with a concentration in bioengineering.

"These students were our guinea pigs," Pelc quipped. "They helped us refine and prove the curriculum."

Another of these undergraduate pioneers, Evan Masutani, said bioengineers delve into chemistry, physics, biology, math, and computer science, giving them a profound respect for the experts in each field.

"To be a bioengineer is to be a jack-of-all-trades," said Masutani, Class of 2014, who is now doing post-baccalaureate research with the National Institute of Allergy and Infectious Diseases.

"Many of society's biggest problems require interdisciplinary solutions," he said, adding, "The realization that one is not an expert fosters a strong drive for collaboration."

The breadth of the major, coupled with the need for depth, made for a strenuous program of study, but Rashmi Sharma, Class of 2014, said the department evolved a coping mechanism.

"We had a really tight community of students and teachers, and that helped us all get through," said Sharma, now an associate engineer at Genentech.

Her classmate, John Pluvinage, also recalled those study sessions as high points of his undergraduate experience. Immersed now in the MD/PhD program at Stanford, Pluvinage predicted that future undergraduates will be reassured by the fact that the university has given the curriculum its official blessing.

"It will also be nice to have bioengineering on the diploma," he said. ISM

Tom Abate is the associate director of communications for the Stanford School of Engineering.

It's bad for the bone: The toll of childhood chronic disease

By Kathy Zonana

Mary Leonard, MD, is pointing at a spine MRI scan of a young adult who had a bone marrow transplant in childhood. "That vertebra is compressed," said Leonard, a professor of pediatrics and of medicine who serves as an associate dean for maternal and child health research. "These patients who are in their teens or early 20s have little-old-lady kinds of fractures."

SEBASTIAN KAULITZKI / SHUTTERSTOCK

An illustration of osteoporotic bone structure. Osteoporosis afflicts some children who have suffered chronic diseases.

Preventing early osteoporotic fractures in those who have withstood childhood chronic diseases is a central aim of Leonard's research program. She and her colleagues have documented abnormal bone structure, muscle mass and muscle strength in children and teens with conditions ranging from cancer to Crohn's disease to organ transplantation. Immobility, inflammation, malabsorption of nutrients and treatment with radiation or steroids can all pose threats to developing bones.

"We believe that once you go through puberty, you're not getting that bone back," Leonard said. "I feel like we've described and described the problem, and now we need to do clinical trials to see what we can do to improve bone health in these patients. We just want to make sure they go into adulthood with the best, strongest skeleton possible — with bones to last a lifetime."

Clinical trials could assess the efficacy of exercise programs, compare kidney-transplant patients on a steroid-free protocol with those who are given steroids and, eventually, test pharmaceutical interventions. In a new Stanford research center on Arastradero Road in Palo Alto, both kids with chronic diseases and healthy control subjects will undergo three assessments: a muscle-strength exam; a full-body DXA scan to quantify bone, muscle and fat; and ankle and wrist scans in the latest-generation XtremeCT machine. The total radiation dose from the three tests, Leonard said, is less than a week of background radiation exposure from living on Earth.

The XtremeCT is one of 10 in the United States, and one of only two being used to assess children with chronic diseases. "Its name is the HR-pQCT, but we call it the hokey-pokey machine, because you put your right arm in; you put your right arm out," said Leonard. As long as you don't actually shake it all about — children under 5, it seems, are too wiggly to be scanned — the high-resolution CT yields a fine-grained look at bone structure in those arms and legs.

"DXA bone density scans tell you how much bone is there, but don't tell you enough about bone quality — its thickness, porosity and micro-architecture," she said. By comparing before-and-after scans from the HR-pQCT machine, "we can really look at what the treatment is doing to bone structure and strength."

Leonard sees two implications of her work. First, some children with chronic diseases may need to be treated more aggressively before and during puberty, to improve their overall health and enable them to build more bone. "If you wait to treat the Crohn's until their bones are done developing, or if they don't get their kidney transplant until their bones are done developing, that window of opportunity may be lost," she said. Second, as life expectancy improves for children with rare and once-fatal conditions, physicians need to anticipate the lasting effects of their illness and treatment.

"As patients with complex congenital heart disease or cancer are surviving well into adulthood, the focus of research has to shift from improving survival to understanding some of the long-term complications," Leonard said. "And osteoporosis and fractures are part of it." ISM

Division of Plastic and Reconstructive Surgery celebrates 50 years

By Sara Wykes

Robert Chase, MD, founder of the Division of Plastic and Reconstructive Surgery, kicked off a recent celebration of the division's 50th anniversary by recounting the history of an innovation with far-reaching consequences.

The celebration brought together past and present residents, fellows and faculty of the division. Chase, the Emile Homan Professor of Surgery, Emeritus, said that shortly after he arrived at Stanford in 1963, he proposed upending how plastic surgeons learned their craft. The traditional sequence — seven years of training in general surgery, followed by two years focused on plastic surgery — just didn't make sense to him.

"General surgery was mostly about repairing intra-abdominal organs, and plastic surgery involves many tissues types: bones, nerves and tendons," said James Chang, MD, current division chief and professor of plastic surgery, who co-chaired the celebration, which included a conference. "You would train for seven years to sew tissues you would never touch again in practice."

Chase recalled that, in the 1960s, the tools and techniques for craniofacial surgery, microsurgery and hand surgery were advancing at breakneck speed. "Learning all that in two years was not good for the doctor and not good for the patient," said Chang, the Johnson & Johnson Distinguished Professor in Surgery

Chase's plan was to train surgeons in plastic surgery techniques from the very start, for five years of direct training in the specialty. It also included another innovation: a sixth year for residents to conduct research or concentrate on a particular kind of surgery — even outside the Stanford medical school.

For example, Chase encouraged one resident, Vincent Hentz, MD, to spend a year working at a hospital in New York City with hand surgeon William Littler, MD. Littler was Chase's teacher and one of plastic surgery's legendary innovators. Hentz also spent six months learning about surgical techniques for head and neck cancer. "It was a very nonstandard residency," Hentz said. In 1975, he joined the Stanford division as faculty member No. 6 and, later, became its chief. Hentz, who co-chaired the celebration, is now a professor emeritus of surgery.

An idea that caught on

Fifty years on, Chase's approach to plastic surgery residencies dominates the field nationwide. Stanford Medicine's plastic and reconstructive surgery residency program, recently lengthened to seven years, is now directed by Gordon Lee, MD, associate professor of surgery. The program attracts more than 300 applicants each year for three spots.

Andrew Zhang, MD, a recent alumnus of the program, was first drawn to the field by an anatomy lecture Chase gave to Stanford medical students and further in by Chang, who invited Zhang to join him in a tendon-tissue-engineering project. After earning a medical degree, Zhang stayed on at Stanford as a resident and then as a fellow in hand surgery. Now, he is an assistant professor of surgery at the University of Texas Medical Branch at Galveston.

The celebration also provided a good opportunity for the division to gauge the accomplishments of its alumni: Twenty-six of them, including former residents and fellows, direct programs in plastic and reconstructive surgery. Thirty-nine have been hospital chiefs. Seventy-eight hold academic titles. More than 5,000 journal articles have come from the research and clinical work of the division's former trainees, who have also authored or co-authored 396 books and book chapters. Nearly 170 serve on the boards of professional journals.

Two of its alumni have served as president of the American Society for Surgery of the Hand, and Chang, another alumnus of the residency program, will become the president in 2018. In addition, alumnus Robert Pearl, MD, is executive director and CEO of the Permanente Medical Group, which operates 21 medical centers in California. And alumnus Ronald Iverson, MD, is a past president of the American Society of Plastic Surgeons, the profession's top national organization. Alumna Debra Johnson, MD, is the society's next president. "We have a presence," Hentz said.

LIBBY ROBERTS

Robert Chase, James Chang and Vincent Hentz at the Division of Plastic and Reconstructive Surgery's 50th anniversary celebration.

Donald Laub, MD, one of the program's first graduates and, eventually, one of the division's first six chiefs, founded Interplast, now Resurge International, the first organization to send American surgeons, many of them trained at Stanford, to developing countries to repair cleft palates, disabling wounds, burns and other injuries.

The division has also grown in numbers, too. When Chang became chief in 2006, there were just six full-time faculty. Now, there are 16, and there are plans to add four more by 2020. "We have some huge names here," Chang said, "who could all be chiefs and chairs in their own right, but we keep them here by fostering an environment they can thrive in. We give them support and acknowledgement and room to do their own thing."

The division's current faculty have been awarded more than $38 million in research grants. Two of them, Michael Longaker, MD, and Geoff Gurtner, MD, have large laboratory enterprises. The division's clinical volumes have quadrupled in the last decade. Its clinical expertise draws patients from all over the world for complex hand, craniofacial, reconstructive and microsurgical treatments.

The most recent change to the residency program has been the addition of a seventh year — a new year of professional development for its residents. The year can be used for research, additional clinical training or work in biodesign, public health or government.

The division's strong network of alumni maintains close ties to each other, said Ronald Iverson, MD, who founded the alumni group. The anniversary celebration was "a great way for all of us to see what we've been doing, to share our memories" — and to find out about the next generation of Stanford-trained plastic and reconstructive surgeons, he said. ISM

Sara Wykes is a writer for Stanford Health Care's communications office.

Security

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databases. The networking of genomic databases is part of a larger movement among researchers to share data. Identifying a gene of interest in a beacon tells researchers where to apply for more complete access to the data. A central assumption, though, is that the identities of those who donate their genomic data are sufficiently concealed.

"The beacon system is an elegant solution that allows investigators to 'ping' collections of genomes," said Bustamante. Investigators on the outside of a data set can ping and ask which data set has a particular mutation. "This allows people studying the same rare disease to find one another to collaborate."

Beacons' vulnerability

But many genomic data sets are specific to a condition or disease. A nefarious user who can find the match for an individual's genome in a heart disease beacon, for example, can infer that the individual — or a relative of that person — likely has heart disease. By "pinging" enough beacons in the network of beacons, the hacker could construct a limited profile of the individual. "Working with the Global Alliance for Genomics and Health, we've been able to demonstrate that vulnerability and, more importantly, how to put policy changes in place to minimize the risk," said Bustamante.

To protect donors' identities, the organizers of the network, which is called the Beacon Project, have taken steps, such as encouraging beacon operators to "de-identify" individual genomes, so that names or other identifying information are not connected to the genome.

Despite such efforts, Shringarpure and Bustamante calculated that someone in possession of an individual's genome could locate that individual within the beacon network. For example, in a beacon containing the genomes of 1,000 individuals, the Stanford pair's approach could identify that individual or their relatives with just 5,000 queries.

Genomic information isn't completely covered by the federal law that protects health information, and the consequences for a person whose information is disclosed can be significant. For example, although the national Genetic Information Nondiscrimination Act prevents health insurers from denying someone coverage or raising someone's premiums because they have a particular genetic variant, the act does not apply to other forms of insurance, such as long-term care, disability or life insurance.

Carlos Bustamante

Approaches for better security

The Beacon Project has the potential to be enormously valuable to future genetic research. So plugging this security hole is as important to Shringarpure and Bustamante as to the Global Alliance for Genomics and Health. In their paper, the Stanford researchers suggest various approaches for making the information more secure, including banning anonymous researchers from querying the beacons; merging data sets to make it harder to identify the exact source of the data; requiring that users be approved; and limiting access in a beacon to a smaller region of the genome.

Peter Goodhand, executive director of the Global Alliance for Genomics and Health, said, "We welcome the paper and look forward to ongoing interactions with the authors and others to ensure beacons provide maximum value while respecting privacy."

Goodhand also said that the organization's mitigation efforts, which adhere to the best practices outlined in its privacy and security policy, include aggregating data among multiple beacons to increase database size and obscure the database of origin; creating an information-budgeting system to track the rate at which information is revealed and to restrict access when the information disclosed exceeds a certain threshold; and introducing multiple tiers of secured access, including requiring users to be authorized for data access and to agree not to attempt specific risky scenarios.

Shringarpure and Bustamante are also interested in applying the technique described in their study to the area of DNA mixture interpretation, in which investigators seek to identify one DNA sequence in a mixture of many similar ones. The DNA mixing problem is relevant to forensics, studies of the microbiome and ecological studies. For example, Bustamante said, if a weapon used in a crime had DNA from several people on it, DNA mixture interpretation can help investigators pick out the DNA of a particular person, such as the suspect or the victim, revealing whether they touched the weapon. In fact, investigators could potentially use the same type of analysis used on the beacon network to look for individuals who may have touched a railing in a subway station or other public space.

This research was partially supported by the NIH. Stanford's Department of Genetics also supported the work.

Bustamante is on the scientific advisory boards for Ancestry.com, Personalis, Liberty Biosecurity and Etalon DX. He is also a founder and chair of the advisory board for IdentifyGenomics. None of these entities played a role in the design, interpretation or presentation of the study. Stanford University's Office of Technology Licensing has evaluated the work presented in the paper for potential intellectual property and commercial rights. ISM

Stanford Medicine debuts new, more visually compelling formats for online continuing medical education courses

By Sara Wykes

STANFORD CENTER FOR CONTINUING MEDICAL EDUCATION

Stanford Center for Continuing Medical Education has debuted new online courses that show how information freed from words-only presentation can be an effective medical education tool. Above, a still from a course on managing shoulder pain in the clinic.

Online courses that doctors take to learn and maintain their skills have a reputation for being tedious: They are often just videotaped lectures or PowerPoint presentations with voiceovers and not much in the way of graphic design, animation or video.

The Stanford Center for Continuing Medical Education, in the School of Medicine, aims to help upend that legacy: It has debuted new online continuing medical education courses that show how information freed from words-only presentation can be an effective medical education tool. It's show, not tell, with animation and video, and a minimum of talking heads.

Based on the knowledge that more than half of us are visual learners whose attention may drift during a video of a podium-bound lecture, online-course designers in all fields increasingly incorporate animation, infographics and videos to illustrate information. The medical school's new CME courses reflect this trend.

The new courses also include teaching topics that have become more important in recent years, such as antibiotic and opioid overuse — two national health issues now near the top of the priority list of the Centers for Disease Control and Prevention. Other courses are meant to engage primary care physicians as partners in prevention health care for conditions with serious consequences.

"These new courses are designed to be more engaging for learners," said Griff Harsh, MD, associate dean for postgraduate medical education. "We believe they are also unique in quality and content. Their development also reflects the innovation possible at Stanford when faculty, medical educators and our IT experts collaborate."

Using actors

The new courses don't resemble video games, as do Septris and Sicko — two CME offerings recently developed at Stanford. They do, however, share the use of a teaching environment that is more image-driven than word-dependent, including some dramatic recreations based on what doctors have experienced in practice. "We wanted to break free of the passive culture of lecture and find ways to visualize what's being taught," said Kimberly Walker, PhD, the instructional designer with Stanford Medicine Information Resource and Technology, who worked with Stanford Health Care doctors to design the courses.

The new CME course on prescription drug misuse is a good example of what Walker means. The course uses actors to portray patients in a series of videos that dramatize what actually happens in doctors' offices. Anna Lembke, MD, assistant professor of psychiatry and behavioral sciences, wrote the scripts based on her knowledge of the kinds of conversations doctors experience when patients are pressing for medications.

"The video, far more interesting than a deck of slides, really pulls you into the situation," Walker said.

That's the kind of reaction Lembke wants for a topic she has usually seen addressed only with depictions of cases with perfect endings. Lembke wanted those cases to reflect the imperfections of typical conversations between doctors and patients. She designed the course's videos "to show exactly what a doctor shouldn't do," she said. "I've found that in medicine we learn the most from our mistakes."

Another new course, one that will feature an introduction by Arjun Srinivasan, MD, the CDC's associate director for health-care-associated prevention programs, was developed because of the worldwide value of its content: the antibiotic timeout. "Studies show that up to half of all antibiotic use in the hospital is inappropriate, and we know that antibiotic overuse leads to medication-resistant superbugs and can harm patients," said course co-creator Marisa Holubar, MD, clinical assistant professor of infectious diseases. "We also know that clinicians don't necessarily have the right training to make these decisions. That's why we developed the course."

Antibiotic timeout

The antibiotic timeout, a term promoted by the CDC, asks doctors to take some time 48-72 hours after a patient has started a first course of antibiotics to re-evaluate the prescription, using clinical information and laboratory data. The timeout allows doctors to think about the value of that medication, its dosage, delivery method and duration, Holubar said. It's a question of teaching the kind of approach that will become second nature to physicians in all fields.

There's no lecture in this online course, either. Holubar and her collaborators created five case studies, supported with illustrations that include the molecular structure of certain medications, photographic images of organisms and, instead of a talking head, a narrator's voice. Each case study presents a clinical condition — sepsis is included — followed by clinical treatment options that could be applied in that case. "We wanted to make it case-based and real-world and appropriate for learners with some experience," Holubar said.

The antibiotic timeout is a priority for the CDC, and this course will be featured on its website and that of the California Department of Public Health.

An online course designed by Laura Bachrach, MD, professor of pediatric endocrinology and diabetes, aims to teach pediatricians about the testing and treatment of congenital hypothyroidism. It's a common disorder but can be easily detected with a blood test in newborns, Bachrach said. Without screening and proper treatment within the two to three months of life, followed by continuing appropriate care, infants with the condition will suffer intellectual disabilities. By the time clinical symptoms appear, Bachrach said, it can be too late to reverse the damage. That's why the mandatory screening of all infants is so important.

How to counsel patients

"We have many more babies with congenital hypothyroidism than we have pediatric endocrinologists, so we need the help of pediatricians to care for them," Bachrach said. Those doctors may also need help teaching parents about the condition, so the course includes a special video in which Bachrach plays a primary care doctor working with parents upset by the news of their newborn's condition. "Teaching pediatricians and family physicians through this online resource allows us to reach many more providers on the frontline," she said.

"I am so grateful to Stanford," Bachrach added. "This is the first time I've ever done anything like this." She's also happy that Stanford will offer the course for free and that the American Academy of Pediatrics will link to it from its website.

Linda Baer, director of the Center for Continuing Medical Education, said a second round of new courses will become available next year.

"The online learning space is evolving," said Mark Rosenberg, the online program manager for Stanford's CME center. "Each context has its own set of best practices: There are differences between online academic learning and professional development training. CME falls somewhere in the middle. What we're doing now is very different from what's typically out there. We think of ourselves as innovators, and we'll continue to explore and experiment." ISM

Sara Wykes is a writer for Stanford Health Care's communications office.

E-cigarettes

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Hopkins University, described himself as a harm reductionist. At the event, held Oct. 26, he argued that, as an alternative mode of nicotine delivery, e-cigarettes pave the way for saving lives by helping addicted smokers avoid traditional cigarettes.

"I do think the evidence is very solid that they are dramatically less harmful than cigarettes ... because they absolutely have very low, almost undetectable levels or trace amounts of the top eight carcinogens that are found in cigarettes, and they have no carbon monoxide," he said.

ANDREY_POPOV / SHUTTERSTOCK

But a lack of extensive research makes Stanford's Robert Jackler, MD, professor and chair of otolaryngology, and Bonnie Halpern-Felsher, PhD, professor of adolescent medicine, question whether vaping is actually safe. And a prevalence of candy-flavored e-liquids leaves them concerned about the potential for harm to youth.

"Let me point out that you can smoke [combustible cigarettes] for many years before you get chronic destructive lung disease," said Jackler, the Edward C. and Amy H. Sewall Professor in Otorhinolaryngology, who leads a Stanford research team studying the impact of tobacco advertising, marketing and promotion. "So while I agree ... that they are safer, the presumption that they are safe for teenagers to adopt as opposed to combustible tobacco, we won't know that for decades."

In the meantime, he worries that "we're experimenting with the lungs of teens."

Jackler and Halpern-Felsher also expressed concern about the perception of e-cigarettes in the eyes of young people. They worry that touting e-cigarettes as cessation devices has led to a misconception that e-cigarettes carry no health risks.

"We are now seeing early evidence that those ... who never would have used or intended on using a tobacco product, when you ask them about e-cigarettes they do have an intention. They are more susceptible to it," said Halpern-Felsher. She explained that when teens see claims about the cessation benefits associated with e-cigarette use, they assume that it's safe to start using them.

"Kids are seeing tons of advertisements about the benefits, but not about the risks," she said.

Abrams acknowledged these concerns but countered with an analogy to safe sex: "What we say to kids is that we'd rather you don't have sex at all, but if you do please use a condom. We don't go on and on [about the fact] that 2 percent of condoms fail and therefore you shouldn't use them."

In the end, the three all agreed that marketing plays a huge role in the popularity and social acceptability of smoking.

"Brilliant marketing of a lethal product that nobody needed made half the population buy it," Abrams said, referring to traditional cigarettes.

"And now we're seeing it again with e-cigarettes," Halpern-Felsher added. ISM

Lindzi Wessel is a science-writing intern for the medical school's Office of Communication & Public Affairs.

Rocket

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Ethan's heart. Then Enns tried to figure out why Ethan's blood sugar was so low. He suspected that Ethan had a genetic defect of the metabolic system. This could result in a buildup in the bloodstream of ammonia, a chemical that is normally detoxified by the liver. The blood test for this condition, called hyperammonemia, is slow and unreliable. Its analysis takes about an hour. By the time Ethan's blood test came back, the level of toxic ammonia was almost 10 times higher than normal. Even if Ethan survived, he would always be at risk of another ammonia surge that could cause serious brain damage if not treated promptly.

Ammonia is a chemical byproduct released when the human body turns digested protein molecules into energy. The body eliminates this toxic waste by converting it in the liver to nontoxic urea, then sending it through the kidneys so it can be eliminated in urine. If anything goes wrong in this chain, ammonia builds up.

At this point there wasn't time to do an in-depth genetic analysis to figure out what was wrong, so Enns expedited a biochemical blood test that revealed Ethan's body was unable to digest long-chain fatty acids, a major component of breast milk and its precursor, colostrum. Because of this, Ethan's body lacked enough energy to fuel his vital organs.

So Enns fed Ethan intravenously with a solution of high-calorie sugar and medium-chain fats. Then he administered a drug to remove the excess ammonia circulating in his bloodstream. Against the odds, this strategy saved Ethan's life.

"Ethan was the sickest child in the intensive care unit I've ever seen turn around," Enns said.

Once Ethan was out of danger, Enns sat down with the parents to talk about the vigilance required to care for a child with a metabolic disorder. They have to protect Ethan's metabolism from stress, especially viruses. And they have to be alert to signs of lethargy and confusion — indications of high ammonia levels. If they suspect an excess of ammonia, a life-or-death drill will be initiated. Rush to the hospital. Watch a phlebotomist poke the child with needles. Wait an hour for blood-test results. If the result is high, hospital staff will administer ammonia-grabbing drugs and intravenous fluids, retest the blood and repeat as needed. Delayed treatment could lead to permanent brain damage or even death.

Enns has a superhuman ability to connect with patients and families in these difficult situations. Most of the children he works with have extremely rare diseases, for which research is limited and treatment plans are based on comfort care, guesswork or some combination. He is able to talk with a 10-year-old with severe developmental disabilities at exactly the right level, then turn to offer advice to parents on health insurance issues, never lapsing into technical doctor-speak.

When asked how he protects himself from the emotional stress associated with these conversations, Enns pointed to his prematurely silver hair and said, "I don't."

This was the dilemma for Enns: He could save these newborns, but then what?

Hope came out of the blue two years later, when he received a call from David Stevenson, MD, senior associate dean for maternal and child health at Stanford. Stevenson told him he knew of three Stanford rocket engineers with a novel idea for analyzing human breath, and they were looking for a medical condition to try it on. Would Enns collaborate with them? Enns immediately thought about patients like Ethan, and he jumped at the chance.

"Maybe these engineers could succeed where many others had failed," said Enns. "I thought, after all, they're *rocket scientists*."

> "Ethan was the sickest child in the intensive care unit I've ever seen turn around."

Mission control

The idea for the disease breath analyzer was born in Stanford's High Temperature Gas Dynamics Laboratory. This lab, tucked into an unobtrusive, sandstone-and-tile building behind Stanford's Main Quad, has served as the launch pad for almost 100 combustion engineers, all of whom earned their doctorates under the mentorship of mechanical engineering professor Ronald Hanson, PhD.

In 2013, two of Hanson's students — Christopher Strand and Victor Miller — sat at adjacent desks near a wall with a "Rockets of the World" poster on it. They were both finishing dissertations on supersonic combustion ramjets, or scramjets. Strand was working on better ways to measure engine gas mixtures using lasers. Miller was developing gas-flow visualization techniques using lasers and high-speed cameras.

Scramjet technology, conceptualized in the 1950s, still presents researchers with extreme technical challenges. These engines use atmospheric oxygen to burn their fuel rather than having to carry liquid oxygen along for the ride. This allows scramjet-equipped craft to fly at speeds of more than five times the speed of sound. Theoretically, scramjet space planes could carry greater payloads and operate more efficiently.

Strand, now 30, tall and lean with British-schoolboy wavy brown hair, has always wanted to be an astronaut. He was raised on a small farm in rural Alberta, Canada, the son of a single mother who worked as a bookkeeper. Strand didn't apply to college during high school. But when he accompanied his girlfriend (now wife) to her first day of classes at the University of Alberta, he realized he'd made a horrible mistake.

"All of a sudden I knew that I belonged at a university," Strand said. So that week, through a fortuitous connection, he met with the dean of engineering and talked his way into the school's engineering-physics program.

Miller, 28, with mischievous eyes and the energy level of someone who just downed a triple espresso, is a fix-anything guy with a penchant for testing boundaries. He grew up in Watertown, Wisconsin, an hour east of Madison. His father was an ex-Marine-turned-engineer and his mother was a travel agent. As a boy, he was obsessed with airplanes. He graduated from Cornell University, summa cum laude, in mechanical and aerospace engineering.

MISHA GRAVENOR

Born with a metabolic disorder, Ethan Pham spent about half of his kindergarten year in the hospital.

Miller's worldview had been influenced by a year in Stanford's Accel Innovation Scholars program, which gives 12 PhD students access to entrepreneurial leaders in Silicon Valley. This program encourages engineering scholars to explore ways to apply their knowledge to some of society's biggest challenges. In other words, Miller had absorbed the culture of Stanford entrepreneurship.

Strand also felt the allure of inventing a Silicon Valley "new new thing," he said. "I think Vic and I empowered each other to pursue breath sensing. There is a certain confidence that comes with having a partner."

When the team first began looking into the breath analyzer idea, a search of scientific literature revealed that breath testing with the human nose has been used in medicine since ancient times. The rotten-apple smell of acetone is a sign of diabetes. The smell of putrid socks is associated with kidney problems. A fishy smell is indicative of liver disease. Though these nose-based diagnostic skills are still used by some clinicians today, many researchers have recognized the opportunity to develop a medical device that could transform this art into a science.

The late Nobel laureate and Stanford chemistry professor Linus Pauling was one of the pioneers of modern breath testing. In the 1970s, he used a gas chromatograph to detect several hundred volatile organic compounds in breath, providing the first evidence that it is a more complex mixture of gases than anyone had imagined. Since then, more than 3,000 compounds have been detected. And though the signatures of ingested chemicals, like alcohol, may be easy to measure, it's much more difficult to detect disease biomarkers, unique combinations of small molecules that may be present only in trace quantities.

The engineers figured that the technology they used in rocket testing, laser absorption spectroscopy, would be sensitive enough to make measurements of trace compounds in the breath. For detecting gases in combustion flows, the technology works like this: A laser beam at a specific frequency is fired across a stream of burning gases, and a sensor on the other side of the beam measures the quantity of light that is transmitted through the gases. From this information, gas properties like temperature, velocity and chemical composition can be identified almost instantaneously. Just as engineers can use these data to tell if an engine is operating efficiently, they could tell if a human "engine" is operating in a healthy range.

To analyze the gases in human breath, Miller and Strand realized they'd need a laser that emits light in the mid-infrared frequency range. They also needed someone experienced in this range, and luckily, there was just such an expert on the other side of the rocket lab: Mitchell Spearrin.

All systems go

Spearrin's life trajectory was set when he watched a rocket from Cape Canaveral soar over his home near Bryceville, Florida, population 3,000.

"I wanted to be an astronaut," said Spearrin, 31, who is married with two daughters and looks like someone who might be cast as a square-jawed hero in a Hollywood blockbuster.

Although the U.S. space program was nearby, this career goal seemed light years away from his small, rural town. As a kid, he focused on sports and became captain of his high school football and baseball teams. He also was good at math and graduated as the straight-A valedictorian of his senior class.

Encouraged by his parents, an elevator mechanic and a stay-at-home mom, Spearrin was determined to be the first in his family to attend college. He also hoped to play sports at the collegiate level, and it was through football that he found himself recruited by Harvard late in his senior year. In a matter of weeks he went from never having considered an Ivy League school to committing to Harvard's football program and, in turn, an education he could not have fathomed. It eventually led him to Stanford's mechanical engineering doctoral program.

During his time at Harvard, Stanford and a stint at aerospace manufacturer Pratt & Whitney, Spearrin fell in love with rocketry. "These machines represent a certain pinnacle of engineering: Rockets control a convolution of physical extremes with a precision driven by intolerance for human error," he said.

Spearrin, who at one point was voted by his Harvard football teammates as "most likely to start a business," liked the idea of the breath analyzer, so he joined the effort. At that point, they had a team in place. Strand knew about lasers. Miller knew about gas handling and photonics hardware. Spearrin knew about rapid analysis of gases using mid-infrared lasers. And Enns agreed to be their medical research mentor.

They started off the project with two roundtable discussions that included Enns, Stevenson and several other pediatricians. (Stevenson had worked on breath analysis of bilirubin, a chemical that can signal jaundice, early in his career.) They discussed the most urgent clinical needs for newborns, and ammonia screening rose to the top. A second priority would be to detect acetone, a diabetes marker.

The graduate students then wrote a three-page proposal for their breath ammonia analyzer and submitted it for a pilot grant from Spectrum, a Stanford program that funds researchers with bold ideas for addressing important health-care problems. (Primary funding for these grants comes from the Spectrum Clinical and Translational Science Award from the National Institutes of Health.) They were awarded $49,000 to launch the project and teamed up with an industry mentor, Darlene Solomon, PhD, senior vice president and chief technology officer of Agilent Technologies. Then the countdown began. They had a year to get a prototype working.

"I thought it was a simple, elegant solution — though at the time, it seemed as if it was too simple to actually work, given the small quantities of ammonia they were trying to measure within the complexity of human breath" said Solomon.

They began with a schematic. A person blows into a tube and breath gases are collected in a pressure-regulated cylinder that directs a controlled gas stream across a mid-infrared laser beam. When the beam hits ammonia, the molecules absorb specific wavelengths of light. A photodetector measures the amount of light that passes through the ammonia, then custom software calculates quantities of ammonia and plots it on an easy-to-read graph on a laptop computer. The device also measures carbon dioxide as a way of telling the software that one breath cycle is complete and another one is beginning.

The first prototype, built on an 8-foot by 4-foot table, used a clear quartz tube for the gas cylinder, which Miller purchased for $50 on eBay. The breathing tube was attached to one end of the cylinder. Flow meters, pumps and valves were attached to the other end, all scavenged from the rocket lab. These would direct the gas stream across the laser beam. Optical mirrors directed the laser beam onto the photodetector. During the first trial runs, the team realized why no one had ever successfully developed an ammonia breath analyzer.

"Ammonia is a nightmare to work with," said Spearrin.

Because the molecules are highly soluble in water and have an unstable electrical charge, they tend to stick to everything, including the inside of the human mouth and the walls of plastic tubing. So they switched to non-stick Teflon tubing. Temperature fluctuations distorted ammonia measurements, so they added an on-board heater and insulation.

Finally, after six months of tweaking, the team brought its second-generation prototype into a quarterly grant-review meeting. The prototype was packed inside a custom box, which was placed on a wheeled cart. Beneath were a data acquisition system and various measurement instruments, all of which would be miniaturized into a more compact format in a commercial product.

A volunteer from the meeting blew into the tube, and a graph of the levels of ammonia and carbon dioxide in that given breath appeared on the computer screen.

Enns' first impression of the rapid, easy-to-use device was "jaw-dropping amazement."

We have liftoff

With the help of Enns, the engineers received Institutional Review Board permission to test their ammonia breath analyzer on human subjects, specifically two 16-year-old boys admitted to the hospital for hyperammonemia. These teens were representative of their target patient population — they were cognitively and physically impaired from ammonia surges. One used a wheelchair. Both spoke slowly, in broken sentences.

It brought home the importance of why the team was working on the breath analyzer project.

Their plan was to have the teens blow into the device's breathing tube after each of their blood draws over the two or three days it would take to normalize their ammonia levels. But they soon realized it was difficult to explain to the teens how hard to blow.

Finally, Strand figured out a strategy that worked. He gave one boy the tube and said, "Pretend that this is your elephant nose and make a sound like an elephant."

This insight prompted the team to redesign the software to provide visual feedback that showed patients when they were blowing hard enough. They also started designing a passive, under-nose breathing tube that could be used without active blowing, which will be necessary for some patients but requires more sensitive detection.

Patient testing also refined their thinking on the technological advantage their device brings to the field. The major weakness of the ammonia blood test is that by the time the results are received by a treating physician, it is hour-old information that may not represent the true ammonia levels of a patient. The breath analyzer enables super-fast, repeatable testing so ammonia levels can be verified and treatment can begin immediately.

In just a year, the team had gone from a rough idea on paper to a working prototype, patient-tested. This is warp speed in the medical device world. They are also preparing articles for publication describing the underlying spectroscopy, the device and, ultimately, their clinical studies.

Spearrin didn't realize how hard this project was supposed to be until he called a respected expert on hyperammonemia for advice. Before Spearrin could ask his questions, the expert said, "You've chosen a horribly challenging project because ammonia is the most difficult molecule to measure, and newborns are the most difficult patient population to work with."

Spearrin replied, "But we've already built a working prototype and we've tested it on two patients."

The team is planning a second, larger patient trial that will involve younger children. There's a good chance Ethan will be in that trial. Since they finished their first prototype, they've received grants from the NIH's Small Business Technology Transfer program and the Wallace H. Coulter Foundation. The Stanford Office of Technology and Licensing has filed a provisional patent, and the team has formed a company, Lumina Labs. The company, funded by the NIH small business grant, has established a research consortium with Enns and Stanford.

"What impressed me about this development team is that they really listened to all the advisers' technical concerns, methodically addressing each one. And they did so while still getting a prototype into testing amazingly quickly," said Solomon.

Waiting to exhale

Five years after his birth, Ethan Pham, with chubby cheeks and bear-cub ears, looks and acts like a typical kindergartener. His mother plays with him as he sits in his hospital bed, happily singing with cartoon farm animals on TV. On the bed tray is a sheet of paper where he has practiced writing his name with crayons.

"Maybe these engineers could succeed where many others had failed."

Ethan is recovering from a surgical procedure to insert a tube through his chest into an artery of his heart. This permanent IV port will make it easier for the care team to quickly administer ammonia-grabbing drugs when needed. He's also under observation for high, unexplained fluctuations of ammonia.

It takes a dedicated team to keep Ethan alive. His family, schoolteachers and medical practitioners are continually on the lookout for signs of high ammonia levels. Episodes can happen at any time. Each incident means a 30-minute drive to the critical care unit, where staff members stand ready to draw blood. Ethan's medical team — his pediatrician, Rebecca Fazilat, MD, at Sutter Health San Jose; Enns; and the hospital staff at Stanford Children's Health — is on call 24/7.

MISHA GRAVENOR

Gregory Enns, professor of pediatrics, served as the engineers' medical research mentor.

Many times the ammonia blood tests, which can be done only at the hospital, are wrong or ambiguous. If the test is positive, it typically takes a day or two in the hospital to normalize the ammonia levels, with repeated blood tests every few hours. Sometimes the family is halfway home when a nurse calls them back to redo a test. Ethan has spent about half of his kindergarten year in the hospital.

Ethan's teachers have been trained to accommodate his condition. His work areas must be extra clean and sick kids need to be kept away. His diet is carefully monitored — no birthday cake, since he can't digest it. Ethan doesn't have the muscle strength to climb on the playground equipment, so he often sits on the side, playing with his plastic farm animals or trying to kiss Catherine, a girl in his class he really likes.

Nguyen and Pham, like most parents who have children with metabolic defects, are perpetually fatigued. When Ethan is in the hospital, Nguyen stays by his side and Pham joins her after work. They often eat dinner at the hospital cafeteria. Nguyen's parents and sister live close by, and they help out when they can. For Nguyen, it's a full-time job keeping Ethan from slipping into an ammonia-induced coma.

What keeps them going is their faith (Nguyen is a Catholic and Pham is a Buddhist) and the hope that someone, maybe even the rocket men, will find a better way to test ammonia levels in children with metabolic diseases at the hospital and at home. This would allow Ethan, with his enduring strength, to live a more normal life.

Blue-sky thinking

It's worth looking at the breath analyzer project and asking, what can fuel more of these big ideas in medicine?

Spearrin recently summed up what motivated his team: "For us, it's not that ammonia sensing is the perfect challenge. It's that the breath analysis field is underdeveloped. We're leaders in this particular gas-analysis technology, and there are clinical researchers here at Stanford really open to collaborating with us. It gives us a chance to make a significant contribution through cross-disciplinary efforts."

What worked was to empower an ambitious team of young engineers to look at an old medical problem with fresh eyes. They were given starter funds to try out their big ideas without fear of failure. There was institutional buy-in, making it acceptable for people outside of the medical system to observe, ask questions and change the way things have been done in the past. And they were given access to mentors who could inspire them, help remove bureaucratic roadblocks and keep them from making big mistakes.

Strand added, "Being in a clinic and working with kids gave me a unique sense of purpose that I haven't felt in my research before. I've had the good fortune of getting to be part of a lot of exciting and challenging research, but never where the need is so tangible, urgent and, most certainly, so personal. It makes a difference if this problem is solved today instead of tomorrow."

Of course, anyone familiar with medical device development would be quick to add that there's a tremendous amount of work to be done before the ammonia breath analyzer is widely available. There needs to be more prototypes. Clinical trials. Independent validations. But one thing we all can probably agree on is this: Medicine needs more rocket scientists. ISM

Kris Newby is the communications manager for Spectrum, the Stanford Center for Clinical and Translational Research and Education.

Mariann Byerwalter to serve as interim president, CEO of Stanford Health Care

Mariann Byerwalter will serve as interim president and CEO of Stanford Health Care beginning Jan. 2. To ensure a smooth changeover, she will transition into her new role over the final two months of current president and CEO Amir Dan Rubin's tenure.

Byerwalter, who earned a bachelor's degree from Stanford and an MBA from Harvard, has served on the SHC board of directors for more than 15 years, including eight as chair. She has a long history of service and commitment to the Stanford community.

Mariann Byerwalter

She serves on the Lucile Packard Children's Hospital Stanford board of directors and chairs the Stanford Medicine Advisory Council. From 1992 through 2012, she served three terms on the Stanford University board of trustees, chairing the Trustee Committee on the Medical Center. In recognition of her dedication, Byerwalter received the 2015 Gold Spike Award, which recognizes exceptional volunteer service and leadership for the university. In addition, she was awarded a 2015 School of Medicine Dean's Medal in recognition of her contributions to advancing Stanford Medicine.

Byerwalter also served as chief financial officer and vice president for business affairs at Stanford.

Currently, she is chair of the board of directors of SRI International, a nonprofit independent research center that was originally founded as a Stanford research institute. She also sits on the boards of Pacific Life Insurance Co., Franklin Resources Inc., WageWorks Inc., Redwood Trust Inc. and the Burlington Capital Group.

"Given her years of leadership experience, deep understanding of Stanford's culture, and exemplary dedication and commitment to the mission of Stanford Health Care, Mariann is uniquely equipped to serve in this interim capacity," Lloyd Minor, MD, dean of the School of Medicine, and John Levin, chair of the SHC board of directors, said in a statement.

A committee co-chaired by Levin and Minor is conducting a nationwide search for a new president and CEO. Rubin will step down from his post in January to take a position as executive vice president of UnitedHealth Group and its Optum Organization. He served as the hospital's president and CEO for five years, overseeing a period of expansion and innovation in patient-centered care. ISM

PEOPLE

Story of family's tumor donation inspires others, helps launch research

By Erin Digitale

On her son's first day as a brain tumor patient at Lucile Packard Children's Hospital Stanford, Danah Jewett asked one of his doctors if her family could donate 5-year-old Dylan's organs to other children when he died.

Most organs from cancer patients can't be transplanted, the pediatric neuro-oncologist, Michelle Monje, MD, PhD, explained. But the Jewetts could make an even bigger difference by giving Dylan's tumor to Stanford for research, a donation with the potential to fill a gaping hole in the science of childhood cancer.

Surprised, Dylan's parents said yes.

After Dylan's death on Jan. 8, 2009, Monje and her colleagues transformed his tumor into the first cell culture of its type anywhere in the world. A few months later, a story in *Stanford Medicine* magazine about the Jewetts' gift inspired more families to make similar donations, further boosting the research.

Dylan had diffuse intrinsic pontine glioma, which grows in the brain stem region that controls breathing and heartbeat, tangling its cancerous cells with healthy cells "like a sweater knitted of multicolored yarn," said Monje. It's rare, striking a few hundred school-aged children in the United States each year, but not rare enough: Of every 100 patients, 99 die within five years of diagnosis. And DIPG's dismal prognosis has not improved in 40 years.

Monje, now an assistant professor of neurology, was motivated to study the disease by the plight of a young patient she cared for while still a medical student. But when she began her work, she hit a roadblock: Because of its location, the tumor isn't usually biopsied. There were no DIPG cells to examine in the lab.

In 2008, when Monje received approval for a protocol to collect tumor tissue from recently deceased DIPG patients for research, she worried about how parents of dying children would feel about being asked to donate the tissue. Shortly thereafter, Dylan came to Stanford, and his parents wanted to help doctors change the course of a disease his dad, John, called "a death sentence for kids."

Their generous donation and openness about sharing their story made a difference: Twenty-one families, many of whom learned of the need for donations by reading Dylan's story in *Stanford Medicine*, have now donated tumor tissue to Monje's lab.

With the donated tissue, Monje's team created the first cell line and mouse model of the tumor, which they have shared with scientists around the world. They've identified a candidate cell of origin for DIPG, learned that the tumor hijacks part of the brain's normal mechanism for neuroplasticity to promote its own growth, and identified an FDA-approved drug that extends the lives of mice with the disease. The team is now planning a clinical trial of this drug, panobinostat, to see if it will also help children.

Danah later met one family that donated tumor tissue after reading the story about Dylan: "I thought, 'Wow, this really encouraged another family to do this,'" she said. "It was a really good feeling."

Many families of DIPG patients have also raised money for Monje's research, contributing a total of more than $1 million to date.

"The story doesn't end when Dylan died," Danah said. "It feels good to know that my child's life wasn't just those five years. He's continuing to make a difference." ISM

MISHA GRAVENOR

Michelle Monje decided as a medical student to research diffuse intrinsic pontine glioma, a brain tumor that one father called "a death sentence for kids."

OF NOTE

reports on significant honors and awards for faculty, staff and students

ELIZABETH EGAN, MD, PhD, was appointed assistant professor of pediatrics, effective Oct. 1. Her clinical specialty is pediatric infectious diseases. Her research examines host-pathogen interactions in the parasitic disease malaria, with a focus on how genetic variation in human blood influences parasite biology and virulence.

PAIGE FOX, MD, PhD, was appointed assistant professor of surgery, effective Sept. 1. She specializes in disorders of the arm, armpit and shoulder in adults and children. In her research, she aims to optimize care for hand infection patients and to use tissue engineering to improve outcomes after hand and upper-extremity trauma.

ANSON LEE, MD, was appointed assistant professor of cardiothoracic surgery, effective Aug. 1. Lee leads the surgical arrhythmia program at Stanford, working closely with his colleagues who specialize in electrophysiology. Lee is also collaborating with the Stanford Cardiovascular Institute and the Department of Electrical Engineering to establish a basic and translational research laboratory that will explore the processes that underlie cardiac arrhythmias.

LINGYIN LI, PhD, was appointed assistant professor of biochemistry, effective Sept. 1. Li's research uses chemical biology to investigate the cancer-fighting mechanisms of innate immune pathways, an emerging field called chemical cancer immunology. Her lab aims to improve the understanding of these mechanisms so that more precise drugs can be developed to prevent or treat specific diseases.

VJ PERIYAKOIL, MD, clinical associate professor of medicine and director of palliative care education and training, received a Practice Innovation Challenge award from the American Medical Association and the Medical Group Management Association for the Letter Project. The project provides templates that help patients identify and communicate their wishes for end-of-life care to their doctors and families. The five winners, announced at the MGMA annual conference on Oct. 12, will receive $10,000 and will have the opportunity to disseminate their work through the AMA. ISM

Elizabeth Egan

Paige Fox

Anson Lee

Lingyin Li

VJ Periyakoil

NORBERT VON DER GROEBEN

Take in the architecture and fall colors

IIf you feel like you need an excuse to walk around campus while enjoying the fall colors, sign up for one of Lane Library's walking tours of the School of Medicine buildings. The tours trace the history of the school's architecture, highlighting some of the artistic and design choices that shaped the campus. The next tour is Nov. 18 at 2 p.m., and begins at the Stanford Hospital fountain. To register for the free tour, visit the Lane Library website.