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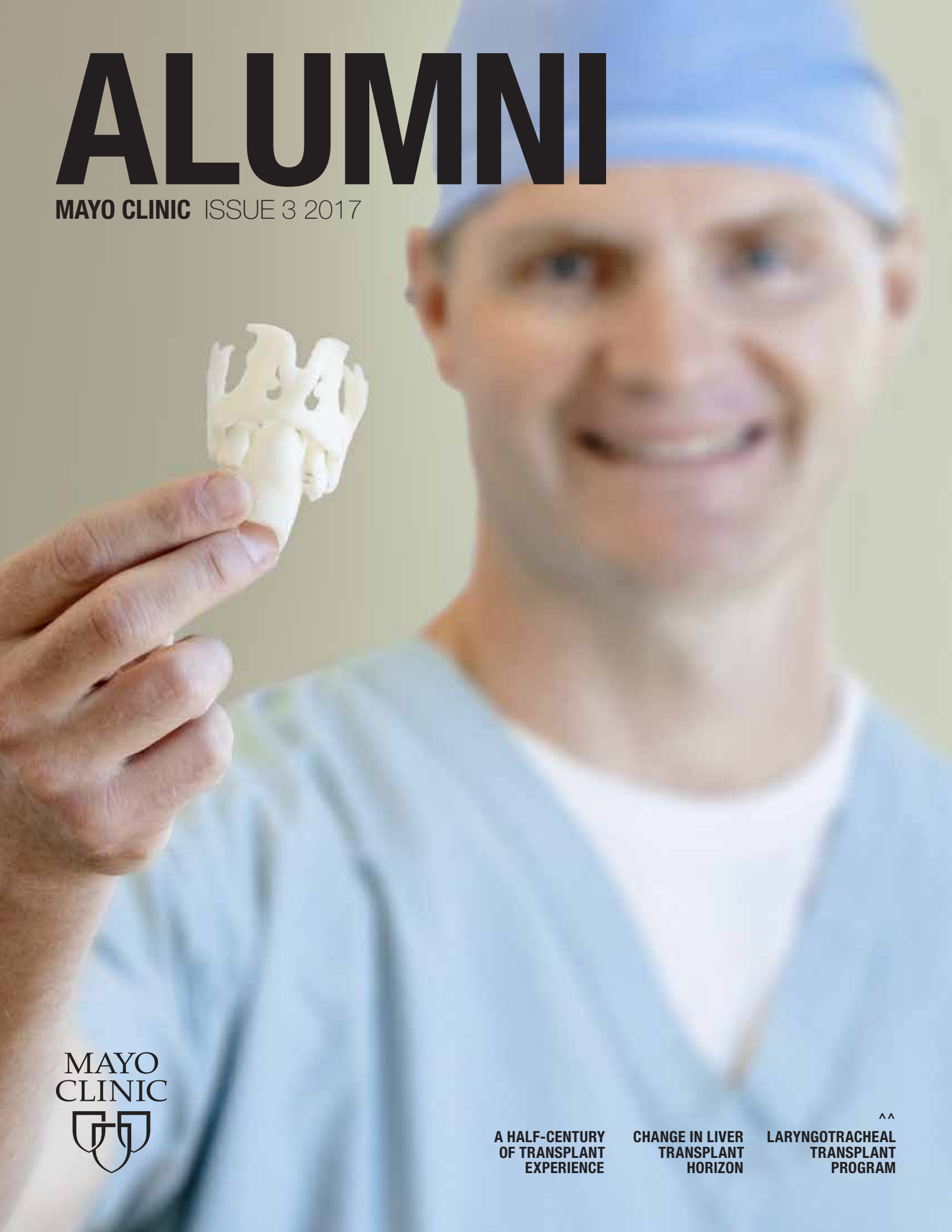
MAYO CLINIC ISSUE 3 2017



MAYO CLINIC

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A HALF-CENTURY OF TRANSPLANT EXPERIENCE

CHANGE IN LIVER TRANSPLANT HORIZON

LARYNGOTRACHEAL TRANSPLANT PROGRAM

LETTER FROM THE PRESIDENT

This letter is my last as president of the Mayo Clinic Alumni Association. In early October at the Biennial Meeting in Florida, I'll pass the gavel to Eric Edell, M.D. (THD '88). I know he'll do a marvelous job as president.

I want to take a moment to remind everyone of the importance of supporting our vital alumni network. We trained at the institution with the largest number of ACGME-accredited programs in the country — inarguably, an institution renowned for its excellence in producing physicians and scientists who are considered among the finest anywhere.

To a member, we take great pride in telling colleagues, patients and friends that we trained at Mayo Clinic — in bragging that our alma mater is ranked No. 1 in the U.S. We carry that Mayo pride with us our entire lives.

As such, we're called upon to give back to that institution. That may be through philanthropy in the Doctors Mayo Society, by being a mentor to a medical student through the Alumni Connect program, by paying our annual dues, by volunteering to serve on the Alumni Association Board of Directors or by attending Alumni Association events to stay in the know about all things Mayo Clinic.

We're all busy. It's not easy to find the time to do "extra things," but we all must do our part to keep our alumni network strong. The Alumni Association gives back to Mayo Clinic and its training programs, helping to keep it at the top of its game.

SUSHEELA BALA, M.D. (PAIM '87)

- President, Mayo Clinic Alumni Association
- Private Practice, Adult and Pediatric Allergy, Asthma and Immunology, San Bernardino, California
- Chief of Allergy, J.L. Pettis VA Medical Center, Loma Linda, California

In the year ahead, try to commit to supporting the Alumni Association in some way. I promise you'll reap benefits from affiliating with others who share your belief in the Mayo Model of Care — something no other medical institution's alumni experience quite the same.

Being involved in the Alumni Association Board of Directors has made me value our network of almost 30,000 alumni and the common bond we share even more. I'll treasure the experience always.

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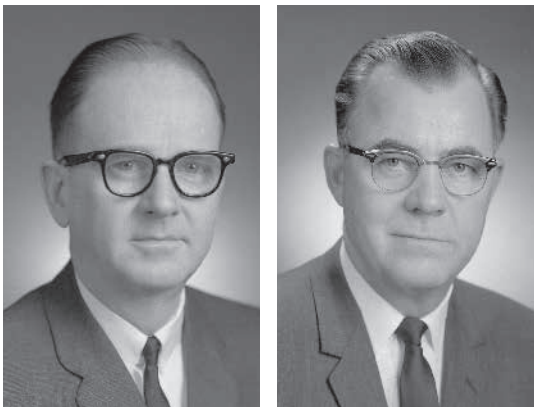
LEVERAGING A HALF-CENTURY OF TRANSPLANT EXPERIENCE

Transplant inroads and alternatives

Transplant medicine has evolved tremendously in the last 50 years, making it one of medicine's most compelling successes. Mayo Clinic's transplant medicine journey has been no less compelling, with Mayo a leader in new forays in transplant medicine and, importantly, regenerative medicine strides to avoid transplant altogether.



Mayo Clinic transplant surgery pioneers George Hallenbeck, M.D., Ph.D. (left), and James DeWeerd, M.D.

The early days

Mayo Clinic officially entered the field of transplant medicine in 1963, with a bone marrow transplant and a kidney transplant. George Hallenbeck, M.D., Ph.D. (S '42, PHYS '49), and James DeWeerd, M.D. (S '50, U '51), led the surgical team that performed that first kidney transplant. Dr. Hallenbeck devoted his full attention for two years to plan the operation. He subsequently led teams that performed kidney transplantations in 40 patients, including transplantations on two patients who received organs from one donor in 1968.

20,000 transplants later

Much has changed since those early years — including a track record of more than 20,000 transplants — but the pioneering spirit remains as strong as ever. Clinical and basic transplant research efforts emanating from Minnesota, Florida and Arizona continue to improve and expand organ transplantation and patient outcomes and put Mayo Clinic at the forefront of transplant research worldwide.

Ruud Krom, M.D., Ph.D. (S ’85) (left), and James D. Perkins, M.D. (S ’86), performed liver transplant surgery in 1986.

Today Mayo Clinic is the largest integrated transplant provider in the U.S., with 2,175 solid organ and bone marrow transplants in 2016 across its three locations. Last year, 4 percent of all transplants in the U.S. took place at Mayo Clinic.

With practices integrated and standardized across the enterprise, patients waiting for a transplant at one Mayo Clinic location can be transported to another location if it has a shorter wait and receive seamless care from site to site.

Unparalleled quality

Volume is one important qualifier for transplant programs; outcomes are an equally strong indicator of quality. Mayo's transplant programs have a history of strong performance. Mayo Clinic received top national rankings in July 2017 (the most recent period measured) from the Scientific Registry of Transplant Recipients (SRTR), the national database of transplant statistics, with more transplant programs in the upper tier than any other transplant provider in the country. In the last national reporting period, Mayo had six programs that were statistically better than expected — three in Rochester, two in Arizona and one in Florida.

"We consistently have more programs at statistically better-than-expected levels than any other transplant provider in the country," says David Douglas, M.D., practice chair of the Enterprise Transplant Center and director of the Transplant Center at Mayo Clinic in Arizona. "These outcomes confirm that ongoing convergence and quality efforts across the enterprise are working."

Program specifics

Mayo Clinic has preeminent adult and pediatric transplant programs in heart, liver, kidney, pancreas, lung, hand, face, and blood and bone marrow.

Specialized transplant care at Mayo Clinic includes:

- Innovative surgical techniques
- Laparoscopic donor nephrectomy
- Living-donor transplantation — about 250 per year
- Multidisciplinary team approach
- Multi-organ transplants
  - -Heart-kidney
  - -Heart-liver
  - -Heart-lung
  - -Heart-lung-liver
  - -Kidney-pancreas
  - -Liver-kidney
- Paired-kidney donation
- Pediatric services
- Reconstructive transplant surgery
- Novel strategies to prevent immune system rejection of donated tissue
- Access to clinical trials and new treatments

Site-to-site standardization

To ensure standardization of care from site to site and continuous improvement, Mayo Clinic has held an annual Transplant Summit since 2003. The 2017 summit attracted 170 staff members from all three locations who shared best practices over three days. In particular, the summits have been useful to standardize selection criteria and suppression protocols across the enterprise.

A future without transplant

Mayo Clinic isn't resting on its leadership-in-transplant laurels. Due to a nationwide organ shortage and a never-ending quest to find the best answers medical science can provide, Mayo Clinic researchers are studying alternatives to transplant including using stem cells to repair, replace or regenerate diseased cells in regenerative medicine (pages 10, 20).

Stem cell therapy may use adult cells that have been genetically reprogrammed in the laboratory (induced pluripotent stem cells), a patient's own stem cells that have been reprogrammed or cells developed from an embryo (embryonic stem cells). Researchers are examining how reprogrammed stem cells may be turned into specialized cells that can repair or regenerate cells in a patient's heart, blood, nerves and other parts of the body.

Transplant leadership

David Douglas, M.D. (GI ’92), practice chair of Enterprise Transplant Center; director, Transplant Center; Division of Gastroenterology and Hepatology; Mayo Clinic in Arizona

Charles Rosen, M.D. (MED ’84, S ’89, TRANS ’91), director, William J. von Liebig Center for Transplantation and Clinical Regeneration; Mayo Clinic in Rochester

C. Burcin Taner, M.D. (S ’04, TRANS ’06), chair, Department of Transplantation; chair, Division of Transplant Surgery; Mayo Clinic in Florida

DAVID DOUGLAS, M.D.

CHARLES ROSEN, M.D.

C. BURCIN TANER, M.D.

Mayo Clinic's transplant programs

Heart Transplant Program

- Began in 1988
- More than 85 heart transplants each year at all three campuses
- Two simultaneous heart transplants at Mayo Clinic in Arizona in 2016

Liver Transplant Program

- Began in 1985
- One of the largest and most experienced liver transplant programs in the U.S.
- 300 liver transplants per year at all three locations; more than 6,700 transplants since program was established
- More than 3,000 liver transplants at Mayo Clinic in Florida — a milestone few centers nationwide achieve
- Above-average patient survival rates

Kidney Transplant Program

- Began in 1963
- 600 kidney transplants per year at all three locations
- Among the largest programs, one of the largest living-donor kidney transplant programs and one of the largest paired-organ programs in the U.S. — 270 paired-kidney transplants since 2007

Laryngotracheal Transplant Program (page 10)

- Began in 2016
- The only UNOS-approved laryngotracheal program in the U.S.
- Conducting clinical trial of first 10 patients

Lung Transplant Program

- Began in 1990 in Rochester, 2001 in Florida and 2015 in Arizona
- More than 50 lung transplants per year at all three locations
- One of few medical centers that offers a full spectrum of options for lung transplantation, including heart-lung transplantation

- Future lung restoration capabilities at a lung restoration center on Mayo Clinic's Florida campus; perfusion procedures will make lungs acceptable for transplantation and increase the number of organs available for transplant

Pancreas Transplant Program

- Began in 1987
- More than 50 transplants per year at all three locations
- Leader of clinical trials in islet cell transplantation — a technique that gives people with type 1 diabetes needed insulin-producing cells without pancreas transplant
- Leader in major artificial pancreas study involving five U.S. and three European centers

Bone Marrow Transplant Program

- Formally established in 1982
- More bone marrow transplants than any other center in the U.S. — approximately 700 per year at all three campuses; almost 10,000 among all three campuses since program was established
- Includes advanced, nationally accredited Human Cellular Therapy Laboratory to prepare cells for transplant and produce safe cellular products for research and patient care
- Accredited to perform unrelated donor transplants by National Marrow Donor Program

Reconstructive Transplant Program (page 12)

Vascularized composite tissue allotransplantation (VCA) of multiple tissues such as muscle, bone, nerve and skin as a functional unit from a deceased donor to a recipient with a severe injury:

- Hand transplant
  - Approved in 2010
  - The first clinically approved hand transplant program in the U.S. at Mayo Clinic in Rochester
- Face transplant
  - Began in 2013
  - One transplant performed at Mayo Clinic in Rochester

Today Mayo Clinic is the largest integrated transplant provider in the U.S., with 2,175 solid organ and bone marrow transplants in 2016 across its three locations.

Transplant support services

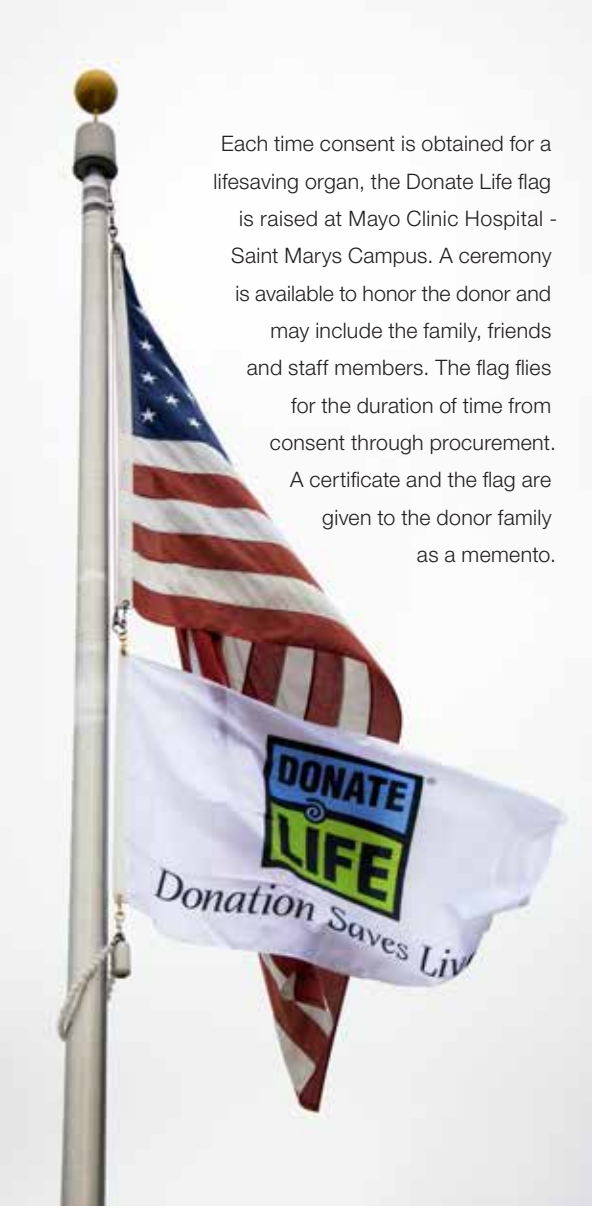
Transplant patients can have long waits — sometimes in the vicinity of their Mayo Clinic location and sometimes in the hospital. Mayo Clinic provides comprehensive services to support patients, their family members and living donors. Near each Mayo Clinic location is a lodging facility with low-cost housing for transplant patients and their families:

- Village at Mayo Clinic, Phoenix, Arizona: Three six-bedroom Southwestern-style casitas for patients having transplants (18 rooms)
- Gabriel House of Care, Jacksonville, Florida: 29-bedroom house
- Gift of Life Transplant House, Rochester, Minnesota: Two houses with 87 rooms total; the largest transplant house program in the country

Other care includes transplant social workers who meet with families early on to provide counseling, support and help with resources along the continuum of the transplant journey; weekly support groups for transplant patients; social work support for living donors as they contemplate donation and afterward; chaplains; pediatric child-life specialists; Caring Canines; massage therapists; and acupuncture.

Transplant milestones

1963	First bone marrow transplant First solid organ transplant — living related-donor kidney
1985	First liver transplant
1987	First kidney-pancreas transplant First liver-kidney transplant
1988	First heart transplant First solid organ transplant, Florida
1990	First lung transplant
1992	First heart-liver transplant
1993	First double-lung transplant
1994	First split-liver transplant First heart-double lung transplant
1999	First solid organ transplant, Arizona
2000	Mayo Clinic in Rochester Transplant Center established — now the William J. von Liebig Center for Transplantation and Clinical Regeneration
2003	Mayo Clinic in Florida Department of Transplant established — now the Gary and Dianne McCalla Center for Transplantation and Regenerative Care
2009	Mayo Clinic's Arizona Transplant Center established
2016	First face transplant, Minnesota ▲



Each time consent is obtained for a lifesaving organ, the Donate Life flag is raised at Mayo Clinic Hospital - Saint Marys Campus. A ceremony is available to honor the donor and may include the family, friends and staff members. The flag flies for the duration of time from consent through procurement. A certificate and the flag are given to the donor family as a memento.

Due to a nationwide organ shortage and a never-ending quest to find the best answers medical science can provide, Mayo Clinic researchers are studying alternatives to transplant including using stem cells to repair, replace or regenerate diseased cells in regenerative medicine.

LARYNGOTRACHEAL TRANSPLANT PROGRAM

Taking the flag and running with it — building the first laryngotracheal transplant program in U.S.

David Lott, M.D. (ENT '11), Department of Otolaryngology-Head & Neck Surgery/ Audiology, came to Mayo Clinic in Arizona in 2011 on a mission. He wanted to start a laryngotracheal transplant program — the first in the U.S.

Although two laryngeal transplants had been conducted in the U.S. and one in Europe, they were one-offs. No one had a full program or was investing the time, effort and financial resources necessary to get a program up and running.

Dr. Lott trained under Marshall Strome, M.D., who completed the first total human laryngeal transplant at Cleveland Clinic in 1998. During Dr. Lott's residency in otolaryngology-head and neck surgery, he worked in Dr. Strome's lab, and the two formed a lasting relationship. "I'm the trainee who took the flag from him in terms of laryngeal transplant and ran with it," says Dr. Lott.

After a fellowship in laryngeal surgery and professional voice at Harvard Medical School/ Massachusetts General Hospital in Boston, Dr. Lott joined the staff at Mayo Clinic in Arizona with the intention of starting the transplant program. "I'm an Arizona native, and Mayo has a great ENT department and reputation," he says. "The program progressed much more quickly than I had anticipated."

Dr. Lott recruited Dr. Strome, who is retired, to serve on the advisory board for Mayo's Larynotracheal Transplantation Program, which is now the only such program in the U.S. approved by the United Network for Organ Sharing (UNOS). "Dr. Strome's wisdom and guidance have been invaluable," says Dr. Lott. "We have been able to reach these heights because we are truly standing on the shoulders of a giant."

Patient need drives program investment

Why was Mayo Clinic willing to invest in establishing the first laryngotracheal transplant program when others weren't willing to take the risk? Because the needs of the patient come first.

"The need is there, and the technology works," says Dr. Lott, who estimates the potential patient population to be about 100,000 — patients who have had severe laryngeal scarring, trauma or a laryngectomy due to cancer. "This transplant program provides an opportunity to significantly improve the quality of life in patients with laryngeal or tracheal disease who have no treatment option other than laryngectomy. People who have their larynx removed not only cannot speak naturally but also are left with an opening into their lungs, making everyday activities risky."

DAVID LOTT, M.D.

Dr. Lott is embarking on a five-year clinical trial of 10 laryngotracheal transplant patients. "We have a handful of patients waiting for the trial to commence," he says. "Mayo wants to be at the forefront of transplant medicine, and this will be the world's first full-fledged laryngotracheal transplant program. We're excited to change the lives of these patients."

Larynx repair may supplant transplant

In addition to the laryngotracheal transplant program, which will use cadaver larynges, Dr. Lott and his team are working on a bioengineered larynx program. They'll use a patient's own adiopose-derived stem cells to create tissue to replace the damaged areas of the laryngotracheal system. Over several weeks of special treatment, the stem cells will grow new tissue on a patient-specific scaffold made on a 3-D printer in a new cell therapy laboratory at Mayo Clinic.

In the operating room, the patient's laryngeal tumor will be removed and the scaffold implanted in the patient — without a laryngectomy or transplant. Bioengineered organs have little risk of rejection and do not require lifelong immunosuppression therapy, making them a preferred alternative to cadaveric or donor allografts.

"Regenerative medicine is the future," says Dr. Lott, who hopes to have a human clinical trial for the bioengineered larynx underway in about a year. The trial will last five years. In addition to the larynx, the team also will be able to tissue engineer the trachea and esophagus. ▲

RECONSTRUCTIVE TRANSPLANT PROGRAM

Considering the ethics of a new branch of transplant medicine

Vascularized composite tissue allotransplantation (VCA), now known as reconstructive transplantation, emerged in the late 1990s, centering on upper extremities and the face. Mayo Clinic held back on developing a VCA program, taking a wait-and-see approach.

In addition to carefully evaluating all aspects of VCA, Mayo Clinic began a deep dive into ethical issues of this relatively new branch of transplant medicine. VCA is considered life-enhancing rather than lifesaving in most cases yet, like solid organ transplants, it requires lifelong immunosuppression therapy. The idea of subjecting patients to the potential adverse effects of immunosuppression for nonlifesaving treatment necessitated deliberate discussion and debate. Mayo Clinic didn't enter into these uncharted waters lightly.

'Kept our feet on the ground'

Any program Mayo would adopt would need to fit into the philosophy of putting patients' needs first. "We kept our feet on the ground by not doing anything that wasn't in the long-term best interest of the patient," says Hatem Amer, M.D. (NEPH '07), Division of Nephrology & Hypertension and medical director of the Reconstructive Transplant Program at Mayo Clinic in Rochester. "We believe we can innovate and be a leader in transplant medicine while still taking a conservative approach to these very sensitive programs."

Enter Kevin Reid, D.M.D. (OFP '96), Division of Orofacial Pain, Department of Dental Specialties at Mayo Clinic in Rochester. Dr. Reid has a master's degree in bioethics from the Medical College of Wisconsin in Milwaukee. He's been chair of Mayo Clinic's Transplant Center Ethics Advisory Board for the last eight years.

Obligations and ethical issues

"The goal of medicine is to do good, unconditionally. We have obligations to avoid doing harm, be good stewards of scarce resources for transplant and facilitate fully informed decision-making for our patients," says Dr. Reid. "Mayo Clinic takes those obligations very seriously, and we weigh all of those obligations and ethical issues before we embark on a new area of transplant medicine."

Mayo Clinic performed its first face transplant on Andy Sandness of Wyoming — a 56-hour procedure that was more than five years in the making.

Kevin Reid, D.M.D.

Among the ethical issues Mayo Clinic explored were:

- Face transplantation is relatively new, and long-term outcome data are very limited. How do medical professionals help an already-vulnerable patient make a wise decision about a transplant and adequately prepare a patient for the possible outcomes of face transplantation?
- Consider that a patient has one fuctioning hand and is otherwise healthy. Transplantation to replace the missing hand would require the patient to take immunosuppression medication for life. Is that a justifiable risk to endorse for a person who is otherwise healthy with a functioning hand?
- Should children be candidates for face transplantation?
- Is it reasonable to provide a male recipient with an available female graft or vice versa?
- Should people who are blind be candidates for face transplantation?
- Only 29 face transplants have been done in the world — 12 of them in the U.S. — so media often try to get access to patients. How do medical centers protect the confidentiality of patients, donors and donor families, and prepare them for the revelation of their transplant outside of the hospital? When is it OK for the medical center to publicize that it has undertaken a face transplant?
- Should these procedures be subsidized by federal health care dollars? If so, what are the criteria to be used for allocation of organs? What are the surgical, medical, psychological, occupational, recreational, social and quality-of-life outcomes that justify the risks and costs?

"We carefully considered all of these issues and more over seven years as we introduced our Reconstructive Transplant Program," says Dr. Reid. "We will continue to evaluate ethical issues as our program matures and transplant medicine evolves."

Hatem Amer, M.D.

"We believe we can innovate and be a leader in transplant medicine while still taking a conservative approach to these very sensitive programs." – Hatem Amer, M.D.

Careful patient selection

Dr. Reid explains that appropriate patient selection is paramount to ensuring Mayo Clinic's values are upheld. "We spare no time or energy in helping potential transplant patients understand what they might go through and what the medical, social and psychological outcomes might be. We must be convinced that the patient has the capacity to make a decision to proceed, will have adequate resources and caretakers after the procedure, and is not likely to engage in behaviors that would contribute to graft failure."

Mayo Clinic approved the hand transplant program in 2010 and has yet to proceed on a case. Mayo evaluated face transplant patients for three years before accepting the first patient in 2016.

"Our multidisciplinary Vascular Composite Tissue Allotransplantation Committee is deeply committed to ethical principles and steadfast in leaving no stone unturned in the patient selection process," says Dr. Reid. "If we have any doubt that someone won't have adequate caretakers, the ability to continue with immunosuppression therapy or adapt in other critical ways, we don't proceed with a transplant."

Dr. Amer says Mayo Clinic doesn't necessarily strive to do everything first. "Rather, needs of the patient come first. We developed our new Reconstructive Transplant Program after much deliberation and planning, and we proceed with patient cases only when we have no doubts."▲

Steven Moran, M.D.

Samir Mardini, M.D.

Origins of Mayo's VCA program

Ten years ago Steven Moran, M.D. (HAND '02), and Samir Mardini, M.D. (PLS '06) — both in the Division of Plastic and Reconstructive Surgery — requested that Mayo develop a clinical VCA program to serve patients whose needs weren't met by nontransplant advanced reconstructive techniques. The two worked closely with LifeSource, the federally designated organ procurement organization serving Minnesota and North and South Dakota, to ensure that face and hand procurement would proceed smoothly and not negatively affect the procurement of other solid organs.

Dr. Mardini, surgical director for face transplant, and his surgical team rehearsed the procurement and transplant of Mayo Clinic's first face transplant on 52 Saturdays in the cadaver dissection lab. In preparation for the first bilateral upper extremity transplant, Dr. Moran, surgical director for hand transplant, and his team also have rehearsed in the lab to ensure a successful result.

Quick facts about face transplantation

- Allografts include skin, bone, mucosa, salivary glands, arteries, veins, eyelids and tongue from human donors.
- The transplant is made in a single operation.
- Patients may experience improved quality of life, social interaction, self-image and function, including blinking, facial expression, oral continence and sensory function.
- Only five centers in the U.S. have performed face transplants.

Quick facts about hand transplantation

- Hand transplants are performed in only a few transplant centers around the world.
- The transplant involves the hand and a portion of the forearm from the deceased donor.
- A hand transplant may help patients regain some hand function and sensation.

Read about Mayo Clinic's first face transplant, perfromed earlier this year: mayo.edu/pmts/mc2300-mc2399/mc2386-3101.pdf

CHANGE IN LIVER TRANSPLANTATION LANDSCAPE ON THE HORIZON

Buying time and potentially improving organ health *ex vivo*

Can normothermic liver perfusion change the liver transplantation landscape by allowing donated livers to be stored longer and be healthier for transplant? Andrew Singer, M.D., Ph.D. (TRANS '14), Division of Transplant and Hepatobiliary Surgery at Mayo Clinic in Arizona, thinks so.

Dr. Singer is the principal investigator for Mayo's participation in an FDA-regulated multicenter clinical trial to test the safety and efficacy of a new portable *ex vivo* normothermic liver perfusion system,* which was developed at the University of Oxford in England.

The first transplant using the new system was in 2013 at King's College Hospital in London, England. All 20 transplants using the device were successful. The system has been through a second randomized clinical trial in four European countries, involving 220 liver transplants — half of them with the new perfusion system.

How it works

The perfusion system transports and stores a liver at normal body temperature for as long as 24 hours — double the maximal allowable time today. The current practice in liver transplantation is cold storage of the organ at 4° C, using a non-physiological perfusion solution to minimize liver degradation. Warm preservation, in contrast, creates an environment that mimics the human body. It does so by providing nutrition and continuously perfusing the organ at physiological pressures and flows with oxygen-carrying red cells at 37° C. The liver is functional during the preservation period, producing bile, metabolizing glucose and maintaining a physiological pH. This enables the transplant team to have an objective assessment of organ performance prior to transplant.

"Now, we have roughly 12 hours to transplant a liver and usually transplant within six," says Dr. Singer. "With this device, it may be possible

*[Note: Investigational device. Limited by Federal (or United States) law to investigational use]

to transport livers over longer distances — in fact, anywhere in the country. This may further minimize waitlist mortality by allowing transplant of the sickest patients with liver failure independent of the donor's location."

How it's revolutionary

Dr. Singer cites several paradigm changes in transplant medicine through the years: consensus on brain death; discovery of modern immunosuppression medications; and development of fluids in which organs can be stored for longer periods than historically possible, allowing for interstate transport of organs for transplant. He says this new perfusion system will likely find its place among those milestones.

"This technology will absolutely be a game-changer. Potentially being able to keep organs functional longer and better assess their quality prior to transplantation could increase the number of transplantable livers, maximize transplant outcomes and save lives," says Dr. Singer. "We're excited to be involved in the early phase of this cutting-edge technology."▲

Ex vivo lung perfusion coming to Mayo Clinic's Florida campus

In the summer 2016 issue of *Mayo Clinic Alumni*, we featured the in-the-works lung restoration center that will open on the campus of Mayo Clinic in Florida in about a year. The center will use *ex vivo* lung perfusion, similar to the liver perfusion system described here. This process reverses damage to lungs that otherwise are not suitable for transplant, making them clinically viable for transplant.

To read that story, visit alumniassociation.mayo.edu/wp-content/uploads/2016/04/2016-Issue-1-mc4409-1601.pdf

> **"With this device, it may be possible to transport livers over longer distances — in fact, anywhere in the country."** – Andrew Singer, M.D., Ph.D.

ANDREW SINGER, M.D., PH.D.

ENHANCED-RECOVERY PATHWAY FOR LIVER TRANSPLANT RECIPIENTS

Decreasing length of stay through practice innovation

Liver transplant recipients at Mayo Clinic in Florida have a median length of stay of only six days post-transplant. The U.S. median length of stay after liver transplant is 10 days. The Mayo program's median length of stay decreased significantly in the last three years. How was this achieved?

Mayo Clinic in Florida has a unique liver transplant practice. Since 2002 more than 50 percent of its liver transplant patients have been able to avoid a stay in the intensive care unit (ICU) post-transplant. The idea behind this practice is that medical care can be tailored to individual patient needs.

In 2014, using the same premise of individualized care and experience gained through the years, Mayo Clinic in Florida's Liver Transplant Program started a new continuous improvement initiative. This enhanced-recovery pathway protocol expedites dismissal from the hospital after liver transplantation. C. Burcin Taner, M.D. (S '04, TRANS '06), chair of the Department of Transplantation at Mayo Clinic in Florida, says it's the only program of its kind in the world.

"The protocol is appropriate for select patients who have limited medical comorbidities and a lower biological MELD (Model for End-Stage Liver Disease) score at the time of transplant," says Dr. Taner. "Many of our liver transplant patients are leaving the hospital within five days of transplant. Our patients and their families love getting out of the hospital sooner. Our success in this initiative requires multidisciplinary input and careful coordination. Our success over the many years as a progressive transplant center in delivering health care really depends on our team members' dedication and strong desire to make it better."

Key steps in the protocol include:

- Identifying appropriate patients by the transplant team
- Educating patients and families about the anticipated length of stay
- Communicating immediately after transplant to the care team about the length-of-stay expectation
- Identifying and addressing barriers to timely discharge, including medication availability, pain control and post-discharge care
- Following up with patients and caregivers within 48 hours after hospital discharge

The enhanced-recovery pathway doesn't compromise patient safety or increase hospital readmissions. By shifting some of the care from the inpatient to the outpatient setting, the program has resulted in significant cost savings. An added bonus — the median length of stay for liver transplant patients not included in the fast-track program has decreased, which Dr. Taner describes as a halo effect.

"Just because we have practiced medicine a certain way for a long time doesn't mean we have to continue doing it that way," says Dr. Taner. ▲

"With innovations such as this one, we can improve patient care beyond what we previously thought was imaginable."

– C. Burcin Taner, M.D.

HEPATO-WOW

Blazing trails in liver regenerative therapies

The only proven therapy for end-stage liver disease is transplant. Unfortunately there aren't enough organs to go around for those who need them. That is about to change. Major efforts are underway at Mayo Clinic to avoid transplant by using a liver support device, recellularization of livers and gene therapy to treat patients with their own cells to correct liver disease.

Scott Nyberg, M.D., Ph.D. (S '96), Division of Transplantation Surgery, is director of the liver program at the Mayo Clinic Center for Regenerative Medicine and head of Mayo Clinic's artificial liver program. He's trained as a transplant surgeon and biomedical engineer. Dr. Nyberg and his team have extensive experience in isolating and cultivating primary hepatocytes (liver cells) for use in cellular therapies.

He envisions this scenario within a decade: dialysis units for liver failure patients, cell therapies to treat metabolic diseases in utero and tissue-engineered livers to address the organ shortage. The result? Fewer people dying waiting for a liver transplant. Even growing a new liver from a patient's own cells isn't out of the realm of possibility.

Creating a blank canvas — donor liver recellularization

Sometimes a donated liver has a defect that makes it unusable. Dr. Nyberg is working with the regenerative medicine company Miromatrix Medical to remove all cells from these defective livers, leaving only a scaffold. He also works with Allan Dietz, Ph.D. (ONCL '02), director of Mayo Clinic's Immune, Progenitor, and Cell Therapeutics (IMPACT) lab (page 24), and Robert Huebert, M.D. (I '09, CI '10, GI '12, HEPAT '13), Division of Gastroenterology and Hepatology, to populate the scaffold with stem cells taken from a patient, creating a whole new organ — a tailor-made liver.

For now these livers are created by decellularizing and recellularizing newborn porcine livers — similar in size to a living donor liver.

The fast and simple decellularization process involves passing a mild detergent through an organ's native vascular system to remove all cellular components from the inside out, without any harm to the organ's structure. This creates a scaffold or biological matrix that retains the anatomical structure, architecture, mechanical properties and vascular network of the source organ or tissue. This

SCOTT NYBERG, M.D., PH.D.

retention is critical for the cellular interactions that facilitate recellularization to enable the growth of new tissue or a new organ.

New cells are then seeded on the resulting scaffold and by perfusion through the vasculature. This process facilitates the body's ability to repair and regenerate after liver injury. Because the patient's own endothelial cells are used, immunosuppression drugs are unnecessary.

"For many years, researchers and the medical community have sought a suitable scaffold to use as the building block for tissue engineering and regenerative medicine," says Miromatrix Medical's Jeff Ross, Ph.D. "Artificial and synthetic matrices or meshes for cells haven't succeeded due to an inability to reproduce the complex structure of a biological organ, particularly the vascular network. Our technologies encompass perfusion decellularization and recellularization and provide the appropriate matrix upon which a new liver can be built."

Correcting defective liver cells with gene therapy

In another regenerative medicine liver application, Mayo Clinic is testing an approach to correct metabolic disorders without whole-organ transplant.

The metabolic disorder in study is hereditary tyrosinemia type 1 (HT1), caused by an enzyme deficiency and commonly treated with medications. But the treatment is ineffective in many people, and the long-term safety of the drugs is unknown. Liver transplant is the only curable option for the progressive liver disease.

Mayo Clinic's gene therapy to correct the patient's own liver cells and transplant them into the diseased liver, causing enzyme production to occur, has resulted in the improvement of pigs with HT1 — they didn't progress to liver failure.

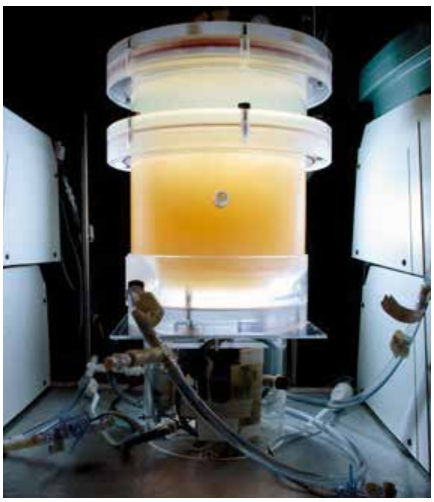
Cells are collected during removal of a small portion of the patient's liver and formed into clusters called spheroids. During this process, gene therapy corrects the genetic defect responsible for the patient's disease. The corrected hepatocytes are transplanted into the patient to regenerate the liver with normal hepatocytes. Because the patient's own cells are used, immunosuppression drugs aren't needed, according to Raymond Hickey, Ph.D. (S '16), Department of Surgery, a co-investigator who leads the gene therapy work.

Patients who will most benefit from the therapy are children who have inborn errors of metabolism such as urea cycle defects, phenylketonuria (PKU) and hereditary tyrosinemia.

Healing — and regenerating — ailing livers

Dr. Nyberg's lab has designed and tested bioartificial liver devices including the Spheroid Reservoir Bioartificial Liver. This device supports healing and regeneration of injured livers and aims to reduce mortality rates for patients with acute liver failure without requiring liver transplant. A bioartificial liver is intended as a stop-gap while someone awaits transplantation. Clinical studies are underway at Mayo Clinic to assess this approach as a long-term treatment option.

The Spheroid Reservoir Bioartificial Liver is a form of dialysis with healthy donor hepatocytes — currently from pigs raised in a special FDA-approved facility. A future source of human hepatocytes, according to Dr. Nyberg, will be genetically engineered pigs who will serve as incubators for the robust expansion of human hepatocytes. The liver dialysis process involves removing a patient's blood with a bedside device similar to a kidney dialysis machine, circulating the blood through the device and returning the blood to the body without the metabolic wastes that normally would be removed by a healthy liver.



The Spheroid Reservoir Bioartificial Liver supports healing and regeneration of injured livers.

Bioartificial liver device potential

- 40,000 Americans die of liver disease annually
- 150,000+ people on waiting list for donor livers
- 11 months average wait time
- 3 people die each day while waiting
- 25–50% of patients with acute liver failure could recover without transplant, freeing up more donor livers for others

In tests involving pigs with drug-induced acute liver failure or with liver failure after major liver resection, treatment with the bioartificial liver has resulted in improved survival and healthy livers by the end of the study. The device performed the functions of the liver and restored them to healthy functioning.

To obtain cells needed for this approach, Dr. Nyberg's team takes hepatocytes from a pig's liver and keeps them in a large bath that is rocked at a slow rate in an incubator. Overnight, the cells aggregate, forming fully functional hepatocyte spheroids. The spheroids are added to the device and the pig's blood is processed through the machine, passing the spheroids for detoxification and other liver functions.

"Our preclinical animal tests have shown liver regeneration after this supportive therapy," says Dr. Nyberg. "Some patients don't need a transplant but, rather, their livers could regenerate if they were stocked with healthy liver cells. This is the first study of its kind to show rescue of a large animal from liver failure where the control group all died and the treatment group recovered. To have this result occur in 100 percent of the subjects is an astounding finding.

"Although the artificial liver isn't yet cleared for use on humans, these findings show promise as an effective treatment option for diseases such as liver cancer and hepatitis. This may be a way to restore livers that are on the verge of failure or that have completely failed — bridge therapy while patients' own livers regenerate. A bioartificial liver device could allow us to treat and extend the livers of more patients, safely and cost effectively, with fewer risks."

Results of the preclinical trial were published in the *Journal of Hepatology*. Human trials could begin next year.

Mayo Clinic has licensed the rights to the Spheroid Reservoir Bioartificial Liver to Liver Cell Technologies for commercial development. ▲

Dr. Nyberg credits a junior-high science teacher with helping him dream big. Learn more: alumniassociation.mayo.edu/news/

Mayo in regenerative liver competition

Mayo Clinic's Scott Nyberg, M.D., Ph.D., and Allan Dietz, Ph.D., are on a team led by Miromatrix Medical's Jeff Ross, Ph.D., that is competing in the New Organ Liver Prize (neworgan.org). This international competition will award $1 million to the first team that creates a regenerative or bioengineered solution that keeps a large animal alive for 90 days without native liver function by the end of 2018. New Organ is an initiative of the Methuselah Foundation, which is dedicated to advancing regenerative technologies to reduce unnecessary suffering and extend healthy life.

IMMUNE, PROGENITOR, AND CELL THERAPEUTICS (IMPACT) LAB

Making patient-specific cellular drugs to help the body help itself

Great things are going on in the Immune, Progenitor, and Cell Therapeutics (IMPACT) lab at Mayo Clinic in Rochester. Patients with non-healing fistulas are getting relief — and healing. That's not all. The IMPACT lab is developing regenerative medicine therapies for more than a dozen conditions.

Cellular therapy uses specific types of stem cells to repair damaged tissues — a form of regenerative medicine. The IMPACT lab, part of the Department of Laboratory Medicine and Pathology, works with the Mayo Clinic Center for Regenerative Medicine to create patient-specific cellular "drugs" that expand or activate patients' own cells to treat their medical conditions.

Mayo Clinic's IMPACT lab is developing cellular therapies for:

- Amyotrophic lateral sclerosis (ALS)
- Crohns disease-related anal fistulas
- Cryptoglandular fistulas
- Degenerative disc disease
- Glioblastoma (newly diagnosed; recently relapsed)
- Laryngotracheal conditions
- Lymphoma
- Multiple system atrophy
- Osteoarthritis of the knee
- Ovarian cancer
- Pleural fistulas
- Recto-vaginal fistulas
- Renal stenosis
- Thyroid cancer
- Traumatic spinal cord injury
- Upper GI fistulas

A dendritic cell from the Mayo Clinic Immune, Progenitor, and Cell Therapeutics (IMPACT) lab.

Gastrointestinal applications

Mayo Clinic is leading a phase I clinical trial focused on testing the use of mesenchymal stem cells from a patient's own body to heal open wounds — perianal fistulas — caused by Crohns disease. These wounds, leading from the inside of the rectum to the outside of the body near the anus, develop when inflammation in the digestive tract causes an ulcer. The ulcer spreads through the intestinal wall, bores through muscle and skin near the anus, and causes a hole.

Perianal fistulas resist conventional treatment, which works less than half the time. Unhealed fistulas worsen and cause fecal leakage, abscesses, more fistulas and even cancer. Some cases require removal of the rectum and use of a permanent stoma and colostomy bag.

"These patients have had multiple procedures and have struggled to get their fistulas to heal," says Eric Dozois, M.D. (S '00, CRS '01), Division of Colon and Rectal Surgery.

Trial participants first receive therapy for existing infection in the fistula and general treatment for Crohns disease. Then Dr. Dozois performs a minor procedure to examine the patient's fistula tract and remove a small sample of fat from the abdomen. He sends the sample to the IMPACT lab, where the stem cells are isolated. When the cells proliferate, 20 million are embedded into a unique bio-absorbable plug. The lab work takes about six weeks.

In a subsequent operation, Dr. Dozois inserts the plug into the fistula and secures it in place by suturing the plug's cap to the interior lining of the rectum.

"Sending mesenchymal stem cells to the area of an open wound is what the body would do on its own if it hadn't been thrown off kilter by Crohns disease," says Allan Dietz, Ph.D. (ONCL '02), Division of Transfusion Medicine and director of the IMPACT lab. He believes the stem cells help to squelch inflammation in the area and draw cells with healing properties to the wound. Mesenchymal stem cells also promote the growth of new blood vessels. "You could compare this to administering steroids to a knee with osteoarthritis, but the way we administer stem cells is more directed — we're getting the entire dose right at the point of damage."

Researchers at other institutions have tried to treat fistulas with mesenchymal stem cells with varied approaches, including injecting donor stem cells into patients' fistulas. Mayo's researchers conceived the idea of implanting the patient's own cells into a fistula plug — a method that seems to be working well as evidenced by recently submitted data on patients' six-month follow-up results. The vast majority of patients' fistulas healed completely.

The trial has attracted patients from all over the country and involves a two-year follow-up period — a significant commitment.

"We're enthusiastic enough about the results of this ongoing trial that we're in the planning stages of a larger phase II trial," says William Faubion, M.D. (PDGI '98, GI '02), Division of Gastroenterology and Hepatology.

The researchers have received permission from the Food and Drug Administration (FDA) to use this protocol experimentally for people with cryptoglandular fistulizing disease and for children with Crohns-related fistulas. The Mayo Clinic team also is seeking approval to test the use of the stem cell-studded plug in people who develop fistulas after serious gastrointestinal surgery.

"If this approach continues to work as well as it has, it's going to become a first-line therapy, I think," says Dr. Faubion.

Pulmonary applications

Bronchopleural fistulas are wounds that cause holes between the large airways in the lungs and the membrane lining them. Traditional surgical treatment of these fistulas hasn't been effective. Mayo Clinic has tried a new wound-closure protocol, based on the ongoing trial investigating the same method to treat anal fistulas in Crohns disease.

Stem cells harvested from a patient's abdominal tissue were seeded into a bioabsorbable mesh. The mesh was surgically implanted at the site of the fistula. Imaging showed that the fistula was closed and remained healed — a first-in-human application of the protocol. More than 18 months later, the patient remained asymptomatic and had resumed normal activities.

“I think in the next 10 years we’ll be stunned at some of the applications as cells find their place in therapy. I think it’s the next big phase of medicine.” – Allan Dietz, Ph.D.

Mayo's researchers conceived the idea of implanting the patient's own cells into a fistula plug — a method that seems to be working well as evidenced by recently submitted data on patients' six-month follow-up results. The vast majority of patients' fistulas healed completely.


ERIC DOZOIS, M.D.


WILLIAM FAUBION, M.D.


DENNIS WIGLE, M.D., PH.D.

"To our knowledge, this case represents the first-in-human report of surgically placed stem cells to repair a large recurrent bronchopleural fistula," says Dennis Wigle, M.D., Ph.D. (TS '06), chair of the Division of General Thoracic Surgery and lead author of a paper about the case published in *Stem Cells Translational Medicine.* "The approach was well tolerated, suggesting the potential for expanded use."

Mayo Clinic is pursuing a clinical trial for this new application.

'Drug' development company

In these applications, the stem cells are the drug, produced by the IMPACT lab — a kind of drug development company. The cells are primarily for internal research and clinical purposes but also are produced for contract manufacturing.

"We are trying to meet unmet patient needs, where pharmaceuticals have failed," says Dr. Dietz. "In regenerative medicine, we use cells as drugs to regenerate wounded or diseased tissue, to delay or prevent transfer, among other reasons. These stem cells have the power to replace the local tissue. Skin is replaced with skin, bone replaces bone and cartilage is replaced."

Cells as drugs must be reviewed by the FDA, and an investigator needs FDA approval in the form of an investigational new drug (IND) exemption. To move an IND through the FDA requires regulatory knowledge and process management — expertise the IMPACT lab provides. The lab's scientists, regulatory specialists and lab techs have deep experience in cell biology, protocol development, clinical trial monitoring and regulatory environments, and have shepherded more than eight new protocols under INDs in the last 12 months.

Other applications — cancer vaccines, liver recellularization and ALS

The IMPACT lab also is working on cancer vaccines — boosting the immune system against cancers — an approach that is showing promise in clinical trials.

This process involves taking specific white blood cells from a patient and converting them, in the lab, into powerful dendritic cells that typically protect the body from infectious diseases.

"These cells flip on a switch that cranks up the immune system," says Dr. Dietz. "We started working on immune-based cancer therapies more than 15 years ago. By turning on the immune system, we now affect a patient's prognosis by getting the immune system to cooperate in attacking the tumor, not just trying to focus only on killing the tumor. This will change how we treat cancer. It's inexpensive, feasible and safe. We're seeing very good evidence of improvement in cancer patients' immune systems and evidence of long-term stable disease.

"In some cases, experience in the different approaches has been combined to produce novel therapies with unique properties. In one trial, we're using the measles virus to infect stem cells that home in on the tumor and deliver the virus to ovarian cancer."

Another IMPACT lab project involves recellularizing the liver (page 20), with a goal of being the first to transplant a fully functional, recellularized liver in a human.

And yet another focus is ALS. In three clinical trials the safety and tolerability of stem cell injections have been demonstrated, as well as signs of clinical impact — meaningful improvements in the rate of ALS progression for the six months following treatment.

Dr. Dietz points out that bone marrow transplant is one common, currently used cell-based therapy, and others such as these are on the way to becoming clinical staples as quickly as their usefulness can be demonstrated.

"There will be places where these therapies will be implemented relatively quickly, such as wound healing, because the cells seem to have a unique, powerful capacity to heal wounds," says Dr. Dietz. "I think in the next 10 years we'll be stunned at some of the applications as cells find their place in therapy. I think it's the next big phase of medicine." ▲

JOSEPH FIORE, M.D., FOUNDING MEMBER, DOCTORS MAYO SOCIETY

Heeding his father's advice — 'Give back more than you were given'

Joseph Fiore, M.D. (DERM '74), was around 7 years old when his father, a butcher in Brooklyn, New York, told him, "If you are ever given something, try to give back more than you were given. This advice will serve you well the rest of your life."

As a young adult Dr. Fiore considered various occupations, including becoming a professional drummer and pursuing business education. Remembering his father's advice, he thought about which career would involve serving others. "Medicine seemed like the proper calling at the time," he says. He applied to medical schools and was accepted at Georgetown University School of Medicine.

Dr. Fiore completed a residency in dermatology at Mayo Clinic in 1974 and set up a private practice in Fort Myers, Florida. Within a few years Harold Perry, M.D. (DERM '52, now deceased), then chair of the Mayo Clinic Department of Dermatology, contacted Dr. Fiore to become involved with the newly established Doctors Mayo Society. Specifically, Dr. Perry asked Dr. Fiore and his wife, Phyllis, to be founding members.

"I realized my Mayo training was a great gift, and I heeded my father's advice," says Dr. Fiore, who not only became a founding member of the Doctors Mayo Society but also started a clinical rotation for dermatology residents at his practice. For the next 15 years residents from Mayo Clinic in Rochester spent a week in Fort Myers, with expenses paid by the Fiores.

"The dermatology residents shadowed me around the clock for a week and got to see how busy a local physician in a nonacademic setting can be, including giving back to the community through Rotary and YMCA board membership," says Dr. Fiore. "I got to know almost every dermatology resident for 15 years."

Dr. Fiore's community service included 15 years as an on-air medical expert. In 1982 he approached the Fort Myers CBS affiliate to determine its interest in TV medical segments. The station manager liked the idea and assigned a cameraperson to Dr. Fiore. Away he went, covering topics ranging from liposuction and hair loss to ulcers and heart attacks in the feature called "To Your Health."

He also started an annual Video Health Fair in three counties, sponsored by their medical societies. The health fair aired on local TV and allowed viewers to call in to speak with physicians manning the phones. The popular feature attracted approximately 2,700 Southwest Florida callers each year for 16 years.

> **"I ask physicians if they're proud of having trained or worked at Mayo Clinic and if they promote that fact in their local communities. When they say yes, I introduce them to the Doctors Mayo Society."** – Joseph Fiore, M.D.

Back to Mayo after private practice

In 1994 Dr. Fiore retired from private practice and joined the Department of Dermatology at Mayo Clinic in Rochester for five years. Then he continued in the department at Mayo Clinic in Arizona and retired in 2015. Today he and Phyllis live in Park City, Utah, and are active advocates for Mayo Clinic and the Doctors Mayo Society.

"I was chair of the Mayo Clinic Alumni Association Committee on Development for more than 25 years and learned there's an art to asking for money," he says. "I ask physicians if they're proud of having trained or worked at Mayo Clinic and if they promote that fact in their local communities. When they say yes, I introduce them to the Doctors Mayo Society. Many people are comfortable committing to giving $1,000 per year for 10 years, including many of the former dermatology residents who did rotations in my Florida practice. It's a wonderful way to show your dedication and gratitude to Mayo — for learning the art and science of medicine, including putting the needs of the patient first.

"Phyllis and I contribute to Mayo because that's what our lives are about: giving back more than we've been given. She grew up with a single parent; I'm the son of a butcher. We're very grateful for the opportunities we've been given and the influence Mayo has had on our lives." ▲

mayoclinic.org/giving-to-mayo-clinic/ways-to-give/alumni-giving

RICHARD EHMAN, M.D.

From playing with carburetors in Canada to inventing MRE at Mayo Clinic

Richard Ehman, M.D. (R-D '85), Department of Radiology at Mayo Clinic in Rochester, comes by his penchant for medical innovation naturally. His mother was a nurse educator. His father was a teacher who became immersed in the post-Sputnik movement to reinvent science education in North American schools.

When Dr. Ehman was a preschooler in a tiny town in Saskatchewan, Canada, his parents noticed he was consumed with understanding how things worked. They often found door latches and other home objects disassembled. In defense of their home, Dr. Ehman's parents brought home old carburetors from the local service station, put them in a bowl and gave their son a screwdriver, encouraging him to take them apart.

"They fostered curiosity about how things work and encouraged me to use tools and learn by experimentation how to make things," says Dr. Ehman, who majored in physics at the University of Saskatchewan and planned to pursue a Ph.D. in physics. "When I was growing up, my dad participated in summer programs in physics education at places including Stanford and the University of Colorado, and the whole family went along. I was fascinated by the experiments he developed for his high school classes. By age 7, I had set up my own lab in the basement, pursuing experiments with electricity and chemistry."

He describes his earliest "invention" — an electronic book. "I had the idea to embed a network of tiny conductors in the pages of books, which would interconnect the sections in a logical way. I built a prototype with a wired stylus that could be touched to various points in the pages, providing a flexible way to navigate through the topic. This was before the advent of personal computers, but the idea was similar to the current use of hypertext links in online documents."

In the early 1970s Dr. Ehman became fascinated by a new algorithm that made it possible to analyze signals with computers using mathematical techniques that were previously thought to be too complex to be practical. The Cooley-Tukey algorithm was originally developed as a tool for processing seismic signals to detect Soviet nuclear testing.

Tinkerer extraordinaire Richard Ehman, M.D., in one of his workshops on the Mayo Clinic Rochester campus.

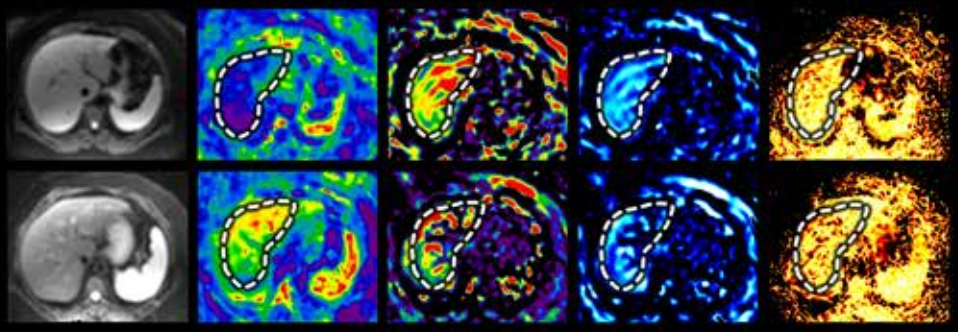
"It seemed to me that algorithms like this, in combination with computers, would have a huge impact in medicine," says Dr. Ehman. "As it turned out, these advanced digital signal-processing techniques are now a basic component of many thousands of products that are used every day. So I learned as much as I could and pursued some undergraduate projects exploring how they might be used to analyze signals obtained in neuroscience and pulmonary medicine."

A change in career direction

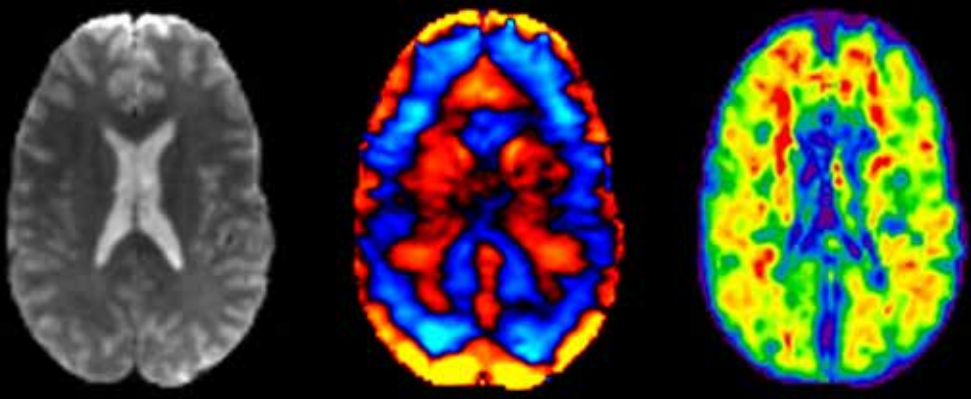
An encounter at a conference in Toronto led to a change in plans: a career in medicine. "I told Harold Johns, Ph.D., a pioneer in medical physics, about my interests, and he suggested I consider medical school. I took his advice and was accepted at the University of Saskatchewan College of Medicine."

Dr. Ehman spent the summer at the University of Saskatchewan taking a required biology course. It was there that he met his future wife, Margaret Houston, M.D. (EPID '89, FM '90), who also was preparing to enter medical school. Dr. Ehman completed a residency in diagnostic radiology at the University of Calgary, Alberta, Canada. During his final year of residency, he spent three months at Mayo Clinic in Rochester as a visiting resident.

"I was interested in learning about the emerging field of body-computed tomography, and radiologists at Mayo were the world leaders in that area," he says. Then, during a research fellowship at the University of California, San Francisco, he became fascinated with the potential of a new imaging technology known as magnetic resonance imaging (MRI). Mayo had just installed a prototype MRI scanner and was



Liver images of two different patients (each on a different row). At far left are conventional MR images. The colored images are MRE, showing stiffness and other mechanical properties of the tissue.



(from left)
A conventional MR cross-sectional image through the head; an MRE image showing mechanical waves through the brain; an elastogram showing the mechanical stiffness of brain tissue.

looking for someone with experience in the technology. Dr. Ehman returned to Mayo Clinic as a clinical fellow in 1984 and joined the staff in 1985.

The dawn of MRI

"When I came to Mayo Clinic, the field of MRI was at a very early stage," says Dr. Ehman. "I came in during evenings and weekends when the scanner was not being used for clinical work to do experiments to explore the physics and mathematics underlying some of the problems that we were encountering in our patient examinations."

Working closely with colleague Joel Felmlee, Ph.D. (BPHY '91), Dr. Ehman began to develop solutions to problems such as flow artifacts — image degradation caused by motion of blood in vessels.

"We invented and tested a solution to the flow artifact problem in early 1985," he says. "Mayo Clinic filed a patent application on the technology, and then we showed it to an MRI manufacturer."

Within a year that technology, called spatial presaturation, was being used to improve diagnostic quality in MRI examinations around the world. "That experience taught me about the power of focusing on real problems encountered in patient care," says Dr. Ehman.

A subsequent discovery — a method to correct the effects of patient motion during imaging — also was made available to MRI manufacturers and has been widely adopted in diagnostic patient care.

In recent years Dr. Ehman, who has more than 70 patents for his inventions, has focused on developing MRI-based methods for determining the mechanical properties of tissue — a technology that he named magnetic resonance elastography (MRE). His basic discovery that enabled the technology was published in *Science* in 1995.

The possibilities of MRE

"Today the main application of MRE is diagnosing liver fibrosis," says Dr. Ehman. "This common condition doesn't cause any obvious abnormality in the anatomy, so it can't be detected with conventional imaging technologies. In the past a liver biopsy was required. Now, MRE provides many patients with a safer, less expensive and more comfortable alternative to a biopsy for diagnosing liver fibrosis."

Richard Ehman, M.D.

Consultant, Division of Diagnostic Radiology,
Department of Radiology; Department of Physiology
and Biomedical Engineering
Blanche R. & Richard J. Erlanger Professor of Medical Research
Professor of Radiology
Mayo Clinic, Rochester

- **Fellowships:** Clinical, Mayo Clinic School of Graduate Medical Education; Research, University of California, San Francisco
- **Residency:** Diagnostic Radiology, University of Calgary, Alberta, Canada
- **Medical school:** University of Saskatchewan College of Medicine, Canada
- **Undergraduate:** University of Saskatchewan
- **Native of:** Saskatoon, Saskatchewan

Awards and distinctions

- President, Radiological Society of North America (2017)
- Fellow, National Academy of Inventors (2016)
- National Institutes of Health MERIT Award (2016)
- Mayo Clinic Distinguished Investigator (2014)
- Past-president, Academy of Radiology Research (2012-2014)
- Emeritus member, Mayo Clinic Board of Trustees
- Mayo Clinic Board of Governors (2006-2014)
- Member, National Academy of Medicine (2010)
- Past-president, International Society for Magnetic Resonance in Medicine (2003)
- Gold Medal, International Society for Magnetic Resonance in Medicine (1995)

Family loyalty to and gratitude for Mayo Clinic

The life of the grandmother-in-law of Richard Ehman, M.D., was saved at Mayo Clinic in 1932.

Mary Belcher was the grandmother of Margaret Houston, M.D. (EPID '89, FM '90), Dr. Ehman's wife, Department of Family Medicine at Mayo Clinic in Rochester. At age 38 Mary and her husband, Stanley, had a small farm in Saskatoon, Saskatchewan, Canada, and three young children. Mary became ill, and X-rays showed a huge tumor mass in her chest. Physicians advised that there was nothing that could be done and that Mary had only a few months to live. Mary and Stanley refused to accept that fate and traveled to Mayo Clinic by train. At the time, Mayo Clinic was pioneering the field of thoracic surgery, made possible by new technology. Mary had one of the first operations of its kind to remove the tumor. She recovered and returned home to raise her family.

"Mary was able to live a long life — to age 92 — because of the care she received at Mayo Clinic," says Dr. Ehman. "My wife's family had intense loyalty to and gratitude for Mayo, which added to our attraction to want to practice there."

Mary Belcher

Dr. Ehman and his team are developing many other applications of MRE. Already the technology is aiding Mayo neurosurgeons in planning operations to remove some types of brain tumors. MRE is being used to study degenerative brain conditions, where patterns of altered tissue stiffness show promise for discriminating between Alzheimers disease and other diagnostic possibilities. Applications of MRE for detecting breast, pancreatic and prostate cancer also are being explored.

MRE spin-off

In 2010 Mayo Clinic founded a start-up company called Resoundant to make Dr. Ehman's MRE technology available to patients around the world. Resoundant was incorporated as an external Mayo-owned company in 2013. Dr. Ehman serves as president and CEO of the company on behalf of Mayo Clinic. Resoundant provides expertise, specialized algorithms and licensing to help MRI manufacturers upgrade their machines to allow MRE scanning. Resoundant also manufactures specialized hardware necessary for MRE and supplies these key components — made in Rochester — to MRI manufacturers. Approximately 1,000 MRI scanners around the world have been equipped with the MRE technology developed at Mayo Clinic.

"Another part of our mission with Resoundant is investing in and pursuing research to expand the capabilities and applications of this new technology," says Dr. Ehman. "The Resoundant model is a new way to support our research at Mayo Clinic. We have projects underway with implications that might have been the subject of science fiction in the past. For instance, we have preliminary evidence that MRE may provide us with the ability to observe some of the dynamic changes in the brain that are associated with learning."

Dr. Ehman served as a member of the Mayo Clinic Board of Governors from 2006 to 2014. In 2010 he led a task force that resulted in new policies designed to foster entrepreneurship among employees.

"Mayo has a rich history of pursuing and adopting medical innovations that benefit patients," he says. "Mayo encourages inventions by its employees more effectively than most other medical organizations. It also has been very successful at licensing technologies that have been invented at Mayo. The new policies are designed to harness the power of entrepreneurship to make Mayo innovations available to more people around the world. A major factor in Mayo's success is our very effective system for managing conflicts of interest, which is based on

ethics, and is focused on protecting scientific integrity and the interests of patients."

In 2016 Dr. Ehman received a RAVE (Recognizing, Awarding, and Valuing Entrepreneurs) award from the Journey to Growth, Rochester Area Economic Development and 504 Corporation of Rochester, Minnesota. The program recognizes start-up companies for attracting people, investment opportunities and jobs to Rochester.

"Resoundant has outgrown our original space and moved to a larger facility. We now have five full-time employees and a contract with Mayo Clinic for the part-time effort of six Mayo employees," says Dr. Ehman. "RAVE was a nice recognition of our progress."

Emphasis on fun

Dr. Ehman's love of innovation and building doesn't end at the clinic. He has a workshop at home where he fixes and builds things. One year over the winter holidays, he and his three children built a 12-person maple-top dining room table with a welded steel structure.

His love of medicine and discovery has rubbed off on the children. The couple's oldest son, Eric (MED '11, RGI '17), graduated from Mayo Clinic School of Medicine, pursued a residency in radiology at the University of California, San Francisco, and is completing a fellowship in abdominal imaging at Mayo Clinic. He will join the Mayo Clinic staff at the conclusion of his fellowship. Son Jeffrey recently accepted a position as a systems engineer at Mayo Clinic. Daughter Katherine is a second-year student at the University of Minnesota Medical School, Duluth campus.

"I encouraged my kids to pursue something they love," says Dr. Ehman. "I tell others interested in innovation and invention the same thing — it's important to have fun. I'm in my laboratory office by 5:30 most mornings. When I wake up in the morning, I can't wait to get back to it." ▲

Dr. Ehman's advice to would-be inventors

1. Proactively seek out mentorship.
2. Engage colleagues and students in your ideas. Students often make extraordinary contributions.
3. Tap the power of multidisciplinary team science. Many opportunities for innovation are located in the boundary regions between scientific fields. The ability to readily engage colleagues from very different disciplines is a special advantage for inventors at Mayo Clinic.
4. Cultivate creativity and intuition.
5. Be prepared to follow your instincts, and be persistent.
6. Recognize and learn from failures. Know when to walk away.
7. If an idea seems promising but doesn't work initially, set it aside for a time; retest it later.
8. Keep things in perspective.
9. Have fun.

(from left) Richard Ehman, M.D., Margaret Houston, M.D., Eric Ehman, M.D., Katherine Ehman and Jeffrey Ehman. Photo Courtesy of Pietricola Photography.

MAYO CLINIC UPDATE

Exclusively online

Check the Alumni Association website for even more stories:

- "Kidney donation to strangers — the ultimate gift." Mayo's Philip Fischer, M.D. (PD '99), and James Haemmerle, M.D. (OR '78), have donated kidneys altruistically. "Bit by bit, we recognize that we're all in the same huge family," says Dr. Haemmerle.
- "It can be done — Mayo Clinic School of Medicine evolves as it accommodates a student's disabilities." Not a single person in the graduating class of Leah Grengs Thompson, M.D. (MED '17), will look at a person with a disability the way they would have without her in their class, according to the director of Health, Disability & Accommodations for Mayo Clinic School of Medicine.

alumniassociation.mayo.edu/news

Philip Fischer, M.D., (left) and James Haemmerle, M.D.

Leah Grengs Thompson, M.D., with Fredric Meyer, M.D.

Save the date

Alumni Association International Meeting

June 21–23, 2018
Berlin, Germany
Hotel Adlon Kempinski

- Five-star historic hotel adjacent to Brandenburg Gate
- Saturday, June 23, scientific sessions in Horsaal Lecture Hall at historic Kaiserin Friedrich Haus
- Robust speaker lineup
- Post-conference weeklong tour beginning in Berlin

Correction

In issue 2 we incorrectly listed the division of which Robert Brown, M.D., is chair. It is the Division of Stroke and Cerebrovascular Disease. We regret the error.

Private Facebook group for alumni

Have you wanted to communicate with other Mayo Clinic alumni in a private forum? You can ask questions, post jobs, seek advice and much more in the Alumni Association's new private Facebook group.

Go to facebook.com/groups/mayoclinicalumni/, and click on "Join."

Mayo Clinic ranked among Best Children's Hospitals

Mayo Clinic Children's Center was ranked as the top-performing children's hospital in Minnesota, Iowa, North Dakota and South Dakota in *U.S. News & World Report's* 2017-2018 Best Children's Hospitals rankings.

Rankings of almost 200 pediatric centers identify the top 50 in each of 10 specialties. Only 81 children's hospitals were ranked in at least one pediatric specialty. Mayo Clinic Children's Center ranked as a top-performing children's hospital in nine of 10 pediatric specialties:

- Cancer (No. 19)
- Cardiology and heart surgery (No. 22)
- Diabetes and endocrinology (No. 20)
- Gastroenterology and GI surgery (No. 48)
- Neonatology (No. 37)
- Neurology and neurosurgery (No. 20)
- Orthopedics (No. 27)
- Pulmonology (No. 38)
- Urology (No. 34)

Among the cutting-edge programs Mayo Clinic Children's Center offers are the Fetal Care Center, proton beam therapy for childhood cancer and stem-cell treatment for children with heart disease.

Obituaries

Charles Barbee, M.D. (S '70), died Oct. 9, 2016.

Milton Cooper, M.D. (I '56), died April 29, 2017.

Paul Gannon, M.D. (S '61), died July 6, 2017.

Wayne Goodson, M.D. (OR '03), died June 24, 2017.

Donald Gordon, M.D. (S '55), died May 18, 2017.

Barry Handwerger, M.D. (RHEU '81), died March 31, 2017.

David Hathaway, M.D. (I '66, NEPH '67), died Dec. 15, 2016.

Keith Kelly, M.D. (PHYS '67, S '68), died July 25, 2017.

Caroline Klein, M.D., Ph.D. (PND '99, N-EMG '00, N '01), died April 27, 2017.

Robert G. Lee, M.D. (NPHY '68), died March 31, 2017.

Archie Miller, M.D. (I '59), died June 6, 2016.

Richard Perry, M.D. (OR '62), died July 7, 2016.

Myron "Tim" Potter, M.D. (I '66), died April 2, 2016.

James Regan, M.D. (DERM '72), died June 27, 2016.

Charles Thoen, D.V.M., Ph.D. (M '71), died May 8, 2017.

Jay Tichelaar, Ph.D. (MBIO '95), died May 22, 2017.

Renato Travelli, M.D. (R-D '64), died June 19, 2017.

Kenneth Woolling, M.D. (I '52), died April 16, 2017.

alumniassociation.mayo.edu/people
Complete obituaries and alumni news

Mayo Clinic Alumni magazine is published quarterly and mailed free of charge to physicians, scientists and medical educators who studied and/or trained at Mayo Clinic, and to Mayo consulting staff. The magazine reports on Mayo Clinic alumni, staff and students, and informs readers about newsworthy activities throughout Mayo Clinic.

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Mayo Clinic is committed to creating and sustaining an environment that respects and supports diversity in staff and patient populations.

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Mayo Clinic was again named the best hospital in the country in the *U.S. News & World Report* annual list of top hospitals. Mayo has ranked at or near the top of "Honor Roll" hospitals through the history of the *U.S. News & World Report* Best Hospitals rankings.

Other highlights:

- Mayo Clinic's Arizona campus ranked No. 20 among hospitals nationwide.
- Mayo Clinic ranked No. 1 in Arizona, Florida and Minnesota.

Mayo Clinic also ranked No. 1 in six specialties:

- Diabetes and endocrinology
- Gastroenterology and GI surgery
- Geriatrics
- Gynecology
- Nephrology
- Neurology and neurosurgery

No. 2 in four specialties:

- Cardiology and heart surgery
- Orthopedics
- Pulmonology
- Urology

No. 3 in one specialty:

- Cancer

No. 4 in one specialty:

- Ear, nose and throat

Hospitals are measured for factors including safety, survival, patient services and reputation with other specialists.