Joslin Science

The power of the big picture in diabetes research
The pandemic of diabetes now affects more than 11 percent of all adults in the U.S. and almost 300 million people worldwide.

This rising tide may afflict as many as one in three people in this country by 2050.

Joslin Diabetes Center continues to lead the fight to find a cure with its unique tradition of research excellence and its unrivaled team of world-class scientists.

Joslin is accelerating the fight against diabetes with the power of the big picture in diabetes research.
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Joslin Science is produced by the Communications Department at Joslin Diabetes Center.

Joslin Diabetes Center is the world’s pre-eminent diabetes research and clinical care organization. Joslin is dedicated to ensuring that people with diabetes live long, healthy lives and offers real hope and progress toward diabetes prevention and a cure. Founded in 1898 by Elliott P. Joslin, M.D., Joslin is an independent, nonprofit institution affiliated with Harvard Medical School. For more information about Joslin, visit www.joslin.org, www.facebook.com/joslindiabetescenter and twitter.com/JoslinDiabetes.

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A conversation with George King, M.D.

How much progress are we making globally in diabetes research?
Worldwide, we’re turning out a lot more new treatments than we did ten years ago. The new treatment for diabetic macular edema, which builds on research at Joslin, can halt it twice as often as the previous treatment, for instance. In type 2 diabetes, there are at least two new types of glucose-lowering agents coming into the market in the next year or two. And for people who are on insulin, continuous glucose monitoring can make control a lot easier—still difficult, but a lot easier.

Obviously we have not won the war; we don’t have a cure. But in research, the tide’s definitely turning.

What are some recent Joslin contributions?
Joslin laid the foundation for the treatment for diabetic macular edema. We made a finding in 1994 that the protein VEGF may increase in the back of the eye in humans, and tested it in our lab at the cellular level to confirm its biological importance. Dr. Lloyd Paul Aiello went on to confirm it in animal studies, and he pioneered one of the clinical trials that showed that inhibitors of VEGF could prevent the late stages of diabetic eye disease. So the Joslin research went from the clinic to the lab and back to the clinic and then into treatment.

That’s just one of our many studies whose results have been applied to clinical care.

One major project is the Joslin 50-Year Medalist Study, looking at patients who have had type 1 diabetes for many years with surprisingly few complications. We’re identifying factors that might protect other patients with diabetes from getting eye or kidney disease. We’re also studying methods that could potentially regenerate the insulin-producing beta cells. [See page 22.]

In type 2 diabetes, Dr. Steven Shoelson’s basic work on inflammation identified a small molecule that worked well in animal models. That has translated now to collaborating with Dr. Allison Goldfine on a national trial of salsalate, an existing generic anti-inflammatory drug, to decrease inflammation and prevent or treat diabetes, and perhaps also to lower cardiovascular risks. [See pages 5 and 16.]

There’s also the recent finding that brown fat, which can burn calories, can be active in adults. [See page 14.]

How important is brown fat?
It’s one of the most exciting discoveries in the past 10 years in type 2 diabetes and obesity, because of its promise to help in controlling weight. But if you double the amount of brown fat in adults, will that have any impact on weight gain? We need intervention treatments and trials to see.

What are the trends in getting federal research funding?
It’s always easier when you have great ideas.

In general, obtaining federal funding is becoming more difficult. Joslin will be impacted by the decrease in National Institutes of Health funding. Thus it is even more important now for our faculty to keep having great ideas, writing papers and getting published.

How critical is funding from foundation grants and personal philanthropy?
It’s absolutely necessary. It supports much of our most important and innovative work. We’re incredibly grateful for what it allows us to do.

In what ways do Joslin scientists work with industry?
We collaborate with pharmaceutical, biotech and device companies to translate our ideas into clinical practice, and we want to do more of that. We have streamlined our process to push our ideas into commercialization quicker, which can improve patient treatments and help with Joslin’s overall financial picture.

Overall, what distinctive role does Joslin play in diabetes research?
Joslin has an outstanding reputation with scientists in the study of diabetes nationally and internationally, due to our productivity and longevity.

Joslin has the biggest group of diabetes researchers under one roof in the world, and we have wonderful critical mass. We can carry out many studies, both at the basic science and the clinical levels, with in-house collaborators.

But in addition, we’re situated in a hub of scientific activity of many, many types that multiply what we can offer here. For example, if we need a cardiovascular collaborator, all we have to do is go across the street to Brigham & Women’s Hospital or Beth Israel Deaconess Medical Center. If we want to do stem cell studies, we can collaborate with the Harvard Stem Cell Institute, where many of our faculty are members.

In addition to basic research, we do clinical studies on a large scale, we do outcomes research for adult and pediatric patients, we identify better ways for teaching patient compliance and increasing the knowledge base of care providers. The list of projects is very long. All of them are incredibly important and can lead to new therapies and potential cures for diabetes, which is our mission.
Joslin has the biggest group of diabetes researchers under one roof in the world, and we have wonderful critical mass.”

Joslin research by the numbers

35+ independent investigators

300 research staff

$40 million research budget

120+ scientific papers published a year in peer-reviewed journals

150+ clinical studies underway

120+ M.D. and Ph.D. fellows in training
Joslin’s clinical research programs are broad, deep, demonstrably successful and absolutely critical

Testing treatments

Nothing gets better in diabetes care without clinical research. Whether it’s a molecular biologist making a surprising finding that clarifies a key step in diabetes, or a doctor looking at how her patients respond to treatment, or a biostatistician spotting a key pattern in a group of patients, the most powerful insights from research will be tested in the Joslin Clinical Research Center. Some discoveries will lay the foundation for improved therapies and potential cures worldwide.

At any given time, more than 150 studies with human subjects are underway at Joslin, all done with exquisite care and great attention to volunteer rights and requirements. Here are quick snapshots of a handful of representative clinical projects.
For people of Asian descent, standard diabetes management methods don’t always work, and the problem begins with diagnosis. "Sometimes when a healthcare provider takes care of Asian patients, it’s hard to tell whether the patients are at risk for diabetes or what type of diabetes they might have because of their relatively low body weight," notes William Hsu, M.D., co-director of Joslin’s Asian American Diabetes Initiative. The standard blood tests for detecting type 2 diabetes are not accurate in Asian patients. Dr. Hsu and his colleagues have found a candidate that may prove to be a better clinical indicator for insulin resistance in this population.

He and his co-workers recently completed a four-year study in which Asian and Caucasian volunteers with similar risks of developing type 2 diabetes were asked to consume eight weeks of a traditional Asian diet and then transitioned to eight weeks of a typical Western diet. "We wanted to ask two fundamental questions," explains Dr. Hsu. "First, is the traditional Asian diet beneficial for people at risk for diabetes? Furthermore, do Asians and Caucasians respond differently to the changes in the diet?" Preliminary analyses indicate that everyone gained weight on the Western diet—but all lost weight on the Asian diet. Both groups showed significant improvements in processing glucose and insulin levels with the Asian food. "We are actively looking into how we could translate this finding in clinical care," says Dr. Hsu.

Increased inflammation occurs in patients with both diabetes and heart disease. Salsalate, an anti-inflammatory drug used for many decades to treat the pain of arthritis, is being examined in several Joslin studies to treat patients with either type 2 diabetes or heart disease. The studies stem from basic research by the lab of Steven Shoelson, M.D., Ph.D. [See page 16.]

Preliminary results "indicate that salsalate may provide an effective, safe and inexpensive new avenue for diabetes treatment," comments Allison Goldfine, M.D., Joslin’s director of clinical research, who co-leads the studies with Dr. Shoelson. “Of course we are excited about a drug that might be used to treat diabetes, but we are also working with patients with heart disease because many patients with diabetes die of this complication. Thus we are now studying whether the drug will also be helpful in people who have heart disease.” The clinical trials are being funded by the National Institutes of Health, because salsalate, a generic drug, is not the most appealing candidate for pharmaceutical companies.

Dr. William Hsu points out that Asian Americans may be at risk of developing diabetes even when standard clinical measurements don’t show it.

Is the traditional Asian diet beneficial for people at risk for diabetes?"
**Clinical research**

“**Our group focuses on designing and evaluating clinical trials aimed at improving diabetes management and overall health for children and teens with diabetes,**” says Dr. Lori Laffel.

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**Designing and evaluating interventions for children with diabetes**

**W**e are fortunate to have patients and families who are partners with us in our clinical research projects at Joslin,” says Lori Laffel, M.D., M.P.H., chief of Joslin’s Pediatric, Adolescent, and Young Adult Section.

One major project is the CHEF (**C**ultivating Healthy Environments in **F**amilies with Diabetes) study, which examines the behavioral and medical effects of an intense intervention on the diets of children and adolescents with type 1 diabetes. Earlier Joslin research showed that parents of these children sometimes may choose less healthy packaged foods because these foods are labeled with their carbohydrate content, presumably making “carb counting” and glucose management a little simpler. “In this project, we aim to encourage children and teens with diabetes along with their families to resume healthy eating with the addition of whole foods like fresh fruits, vegetables and whole grains,” she says.

Another major research effort is the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study. “This is by far the largest study of youngsters with type 2 diabetes, with more than 700 patients in 15 centers across the U.S.,” says Dr. Laffel. The TODAY study is comparing three kinds of treatment, all employing the common type 2 drug metformin. One group of subjects is taking metformin, a second group is using metformin plus a drug that helps insulin work better, and a third is combining metformin with intensive lifestyle treatments. After the study’s first round is completed, researchers will continue tracking the natural history of type 2 diabetes in this very large sample of young people.

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**Looking AHEAD for improved cardiovascular health**

**E**xercise, lose weight and reduce your risk of cardiovascular disease.

For most people with type 2 diabetes, this prescription is straightforward but extremely difficult to carry out. The Look AHEAD (Action for Health in Diabetes) national clinical trial, for which Edward Horton, M.D., heads Joslin’s participation, is taking a wide and long look at how well an intensive lifestyle intervention works in helping people bring about this change.

After four years, an early answer is in: Very well. “A lifestyle intervention is very effective in reducing cardiovascular risk factors,” reports Dr. Horton. Those participants who stayed with the intervention did better than a control group with normal diabetes support and education in weight, fitness, hemoglobin A1C levels, blood pressure and high-density cholesterol levels. Look AHEAD is spinning off a number of ancillary studies, in which Joslin researchers are cooperating with outside colleagues to study the benefits of such interventions for everything from improved bone density results to the health of women with gestational diabetes.

Dr. Edward Horton notes that the national Look AHEAD trial has underlined just how much lifestyle interventions can aid in minimizing cardiovascular risks.

**“A lifestyle intervention is very effective in reducing cardiovascular risk factors.”**
Type 2 diabetes begins with insulin resistance, but how does that condition progress to the full-blown disease? The Joslin cohort study, run by Mary-Elizabeth Patti, M.D., and Allison Goldfine, M.D., addresses this question by looking at volunteers along the spectrum of insulin resistance, from no signs of the condition all the way to full-blown type 2 diabetes.

Once people have diabetes, their metabolism changes so much “that it becomes very unclear whether the changes you observe are resulting from the diabetes or are causing the diabetes,” explains Dr. Patti. “If we can identify factors that are different in people at risk for diabetes, those factors may play a causal role in diabetes development.”

The project examines the family histories of the volunteers along with analyses of their blood as well as muscle and fat tissues. As Dr. Patti and her colleagues find more about changes in gene and protein expression as well as body metabolism among these various populations, they follow up with lab studies in cells and animal models. The approach is sparking a number of significant discoveries, including new targets for therapies to prevent or treat the disease.

“Understanding how people understand self-management”

RIGHT NOW WE HAVE A ONE-SIZE-FITS-ALL APPROACH TO DIABETES EDUCATION,” says Katie Weinger, Ed.D., R.N. “But instead of trying to adapt people to our treatments, including education, we want to adapt our approaches to people and their particular strengths and weaknesses.”

Dr. Weinger is interested in executive function—the ability of people to organize, plan and solve problems. In a new project, she plans to supplement interviews and paper-based surveys with functional magnetic resonance imaging (fMRI) brain scans. Volunteers will receive fMRI brain scans before and after taking diabetes self-management courses, and their success in self-management will be followed closely for six months. This study will bring a new set of neurocognitive and neuropsychological information to the ongoing effort “to figure out ways for people to make it less stressful and yet still accomplish enough on their lifestyle recommendations that they can live healthily and well with diabetes,” says Dr. Weinger.

“We are seeing what we can do for people who are struggling with diabetes but are still coming to their appointments and their education sessions,” says Dr. Katie Weinger.
Ever since Dr. Elliott P. Joslin began documenting his patients’ experiences in the late 1800s, physician-scientists at Joslin Diabetes Center have been poring over clinical data to improve care and patient outcomes. Whether stored in Dr. Joslin’s fabled “black books,” paper charts or computers, this information has helped doctors pose and answer questions about the disease and its life-threatening complications.

But researchers’ ability to evaluate this trove of clinical data—the largest on diabetes in the world—could be significantly expanded if the system were upgraded with new hardware, software and staff.

Joslin leaders plan to transform the center’s current repository of patient information, its electronic medical record (EMR) system, into a premier tool for clinical research. “We have a tremendous opportunity to advance knowledge about diabetes health-care delivery and improve patient outcomes, and to do it in a cost-effective way,” says Lori Laffel, M.D., M.P.H., chief of the Pediatric, Adolescent and Young Adult Section.

Healthcare providers around the country are moving toward leveraging health information technology like EMR systems to save lives and reduce costs, and the federal government has designated billions of dollars to help stimulate these moves. Joslin was an early adopter when it launched its EMR initiative in 2004 using NextGen Healthcare software. Today, the system maintains data on about 40,000 adult and pediatric patients.

Among its clinical benefits, the EMR tracks patient visits to Joslin Clinic, helps generate treatment plans, and signals when someone is overdue for services or uses a piece of medical equipment that has been recalled.

It is also valuable for quality improvement efforts. For example, the Joslin Clinic used the database to quickly identify and contact patients and providers who were using the glucose-lowering drug rosiglitazone after a 2007 scientific report suggested the drug might place patients with type 2 diabetes at higher risk for heart attacks.

Joslin leaders knew from the start that, in addition to facilitating care, its EMR would be a goldmine for research into type 1, type 2 and gestational diabetes. There are currently more than 150 clinical studies taking place at Joslin to examine the natural history of diabetes and evaluate treatment options such as lifestyle interventions, educational programs, medications and new technologies. Some of these studies tap information from the EMR with patients’ identifying information removed to protect privacy. (All studies receive appropriate oversight to maintain national and institutional privacy standards.)

But the current EMR system has limitations for patient-based research. Laboratory and clinical data are located in different portions of the EMR, making them harder to access. In addition, Joslin investigators must wait for the database’s software programmer to handle their requests.

Aiming for “research-ready”

“We have used the system for six years and identified what people
want to change to make it more effective for both patient care and research,” notes pediatric endocrinologist Sanjeev Mehta, M.D., M.P.H., physician champion for the center’s EMR initiative.

To make the EMR more “research-ready” and allow investigators to design and conduct studies in a smoother and standardized way, Joslin scientific leaders are working with Joslin chief information officer Edward Charbonneau on a three-pronged plan that involves:

1. Creating a clinical “data warehouse” that would integrate and regularly update clinical information stored in three different systems.
2. Analyzing the quality of the EMR’s existing data and then creating a system for maintaining its quality.
3. Developing a “user interface” that enables investigators to search the data contained in the warehouse.

Allison Goldfine, M.D., who heads Joslin clinical research and is co-leading the initiative, believes a more flexible EMR system will help doctors assess how well patients are achieving current care goals and identify patterns among patients who do or don’t achieve these goals.

“By looking at people who came to Joslin over the years and asking, ‘Who develops eye complications or kidney complications?’ or ‘What role does smoking or a specific gene play?’ we can better understand the physiology and problems associated with diabetes,” Dr. Goldfine says. “Finding patterns in outcomes might lead to new treatment strategies and also help us target therapies to those who would benefit most—and avoid adverse effects in those who wouldn’t.”

“We hope the EMR will generate new questions that will then lead to answers for improving care and finding cures,” she adds.

Patient information boosts understanding of kidney disease

Andrzej Krolewski, M.D., Ph.D., has shed considerable light on the mechanisms of late diabetic complications, particularly diabetic kidney disease. Drawing on the large Joslin Clinic patient population, he created a modern population research laboratory that combines a very large database of clinical information captured from medical records and special examinations of patients attending the Joslin Clinic. Backing up this clinical data are banks of their DNA and biological samples collected over two decades of follow-up. His research uses epidemiological, genetic and proteomic methods and has been a model for efforts in translational medicine.
Joslin researchers lead in pursuing several strategies to replenish the insulin-producing beta cells destroyed in type 1 diabetes

The problem of not enough beta cells

Here’s how it’s supposed to work: Sprinkled throughout the pancreas, tiny collections of beta cells generate the small amount of insulin needed each day, with their production exquisitely calibrated minute-by-minute with blood glucose levels.

But in type 1 diabetes, an autoimmune attack seeks and destroys these important but fragile cells.

Joslin scientists are leading the way in the quickly advancing research to find new sources for beta cells—including “progenitor” cells located in the pancreas that can morph into beta cells—and to develop innovative ways to make more copies of surviving cells.

Just as critical are efforts to ensure that any newly formed beta cells are fully functional and that they can survive the ordeal of transplantation.

An alternate source?

Susan Bonner-Weir, Ph.D., and her colleagues have amassed evidence of an important potential source of new beta cells within the pancreas. Her lab showed that in rats and mice that are neonatal or have had pancreatic injury, cells in the nearby pancreatic ducts, which act like pipes for digestive enzymes, can differentiate into beta cells and the other pancreatic cells.

“But which cell in the duct tree is the progenitor?” Dr. Bonner-Weir asks. Working with both mice and human cells, her lab is puzzling out exactly which cells can switch, and what signals those cells to make the transition and then proliferate.

Replicating success

Gordon Weir, M.D., looks at the replication of existing adult human beta cells. In one effort funded by the Juvenile Diabetes Research Foundation, he experiments with human islets that are transplanted into mice whose immune systems have been shut down, examining potential ways to make them

Answers in a capsule

For decades, type 1 diabetes researchers have struggled to package pancreatic islets containing beta cells and other hormone-producing cells within a membrane so that they are guarded against autoimmune attack after transplants. “Encapsulation continues to be a maddening and attractive concept,” says Dr. Gordon Weir. “You lock the cells up in a membrane that screens out the cells that attack the islets, and yet the holes are big enough that nutrients and oxygen get in perfectly well, and insulin gets out.”

Today, the Weir lab has high hopes for its joint work with the lab of Massachusetts Institute of Technology’s Drs. Robert Langer and Dan Anderson, testing innovative capsules (right) built of materials derived from seaweed using nanotechnology engineering.
divide more quickly. “This is the only way you really can look at human tissue in an in vivo situation,” he explains.

The lab of Rohit Kulkarni, M.D., Ph.D., creates genetically engineered mouse models that help to understand beta-cell regeneration issues related to both type 1 and type 2 diabetes, particularly looking at the replication of surviving cells. “We can clearly show that beta-cell replication occurs in diet-induced obesity and pregnancy in mice,” Dr. Kulkarni says. “That’s why we pursue the strategy of replication, because if it’s happening naturally, we can target that to push it up.”

Growing in maturity

Both Dr. Kulkarni and the team of Arun Sharma, Ph.D., and Dr. Bonner-Weir work on the issues involved in making replacement beta cells fully functional—able to release sufficient amounts of insulin when prompted by glucose in the blood.

“Insulin-producing cells must go through several steps, which eventually result in a mature glucose-responsive beta cell,” notes Dr. Sharma. His work has shown that a protein known as MafA, a transcription factor (master gene regulator), regulates the ability of beta cells to produce insulin in response to glucose. In newborn mice and diabetic mice, levels of MafA activity are much lower than in adult mice, but if the scientists boost MafA levels in these mice, they can kick-start the production of insulin in response to glucose.

Dr. Kulkarni works in collaboration with SysCODE (the System-based Consortium for Organ Design and Engineering), systematically sweeping through all the genes and proteins that may be important in beta-cell maturation from embryonic to newborn to adult stages. “We’ve come up with some very interesting candidates that may help to get a much better beta cell that can secrete more insulin in response to glucose,” he says.

Inducing insulin

In parallel, Dr. Kulkarni is working to derive insulin-secreting cells by engineering skin cells obtained from patients with type 2 diabetes. “This approach will allow accelerating therapies on an individualized basis for patients with type 2 diabetes who have no autoimmune problems,” he says.

Overall, Joslin continues to be a major driver in the quest to find a suitable source of beta cells and to eventually cure type 1 diabetes. “I won’t tell you that a cure will happen next year, because the challenges are difficult and there are always surprises,” says Dr. Weir. “But we know where we need to go, and we’ve got to be impressed by these kinds of advances.”
In the autoimmune attack behind type 1 diabetes, you can think of T cells as an improperly trained SWAT team that hones in on insulin-producing beta cells rather than pathogens. Research at Joslin seeks to sort out the diabolically complicated details of their attack and to work toward steps that can be taken to stop it.

In one project, Thomas Serwold, Ph.D., employs mouse models to understand the cells within the thymus that help T cells to develop, and whether these cells can be altered to prevent autoimmune T cells from developing in the first place.

“Throughout life, T cells are produced in the thymus, each with a unique receptor that can bind only to certain protein fragments derived from pathogens,” explains Dr. Serwold. “Also within the thymus, epithelial cells act like teacher cells for the T cells, preventing those that might target the body’s own cells from graduating and leaving the thymus. Developing techniques to manipulate the functions of these teacher cells will tell us a lot about how the autoimmune T cells that drive type 1 diabetes come to develop, and how they might be eliminated.”

In related Joslin work, Tihamer Orban, M.D., is a principal investigator in TrialNet and the Immune Tolerance Network, national networks dedicated to translating basic research into wider clinical application for prediction, prevention and intervention for type 1 diabetes autoimmunity. A novel vaccine developed by Dr. Orban, designed to induce an immune response that calls in regulatory T cells that protect against the type 1 attack, is in clinical trials.

Studying autoimmunity some years back, Myra Lipes, M.D., made a surprising discovery when she genetically modified mice to express a high-risk human type 1 diabetes susceptibility gene. “In addition to developing diabetes, the mice developed autoimmune heart disease,” she says. Following up, her lab has identified a molecule that may spark this autoimmune attack, potentially pointing toward a new approach to diagnosing and treating heart disease in patients with type 1 diabetes.

“Curing an autoimmune disease such as type 1 diabetes is like solving a very difficult jigsaw puzzle,” says Aldo Rossini, M.D., Mary K. Iacocca Senior Visiting Scholar. “With every little piece of the puzzle, we’re getting closer and closer to understanding the problem. Today Joslin is building up the immunobiology group with bright young researchers from multiple fields. One day, the final pieces of the puzzle will be there.”
All too often, people with type 1 diabetes find their blood glucose levels bouncing from too high to too low and back. The continuous glucose monitoring (CGM) devices now coming into the mainstream can help to provide better control, and both the adult and pediatric clinics at Joslin participated in major nationwide trials that proved their usefulness. Clinical researchers now are finding the best ways to help users deal with the devices, and employing the devices to learn more about diabetes management.

“We can substantially reduce the risk of complications with best use of today’s advances in diabetes management such as CGM,” says Howard Wolpert, M.D. “At the same time, today’s CGM is still fairly rudimentary technology and there are a lot of frustrations that go along with using it.”

“Despite its imperfections, CGM represents extraordinary progress,” says Lori Laffel, M.D., M.P.H., Chief of Pediatrics. While the national trial funded by the Juvenile Diabetes Research Foundation didn’t demonstrate its effectiveness among adolescents, “CGM can improve anyone’s glycemic control, independent of their age or stage of development, if it’s used consistently,” she says.

In one project, Dr. Laffel and her colleagues are examining the use of CGM by adolescents, with half of those studied getting an intense behavioral intervention to help them overcome problems associated with CGM use.

Dr. Wolpert is leading two studies with adult volunteers whose glucose levels are carefully controlled during experiments within Joslin’s Clinical Research Center. One project aims to see if CGM, which reads glucose levels in “interstitial” fluids just under the skin, offers a better measure of brain glucose levels and cognitive abilities than do the standard blood fingerstick readings.

A second adult study looks to define exactly how much extra insulin adults require when they eat a high-fat meal, and how that insulin can best be delivered. “We’re aiming to give people much more scientifically based recommendations on how to adjust their insulin for changes in fat in a meal, and this could cause a shift in nutrition guidelines,” says Dr. Wolpert. “The work also could be helpful in focusing people on the importance of controlling their fat intake as a way of optimizing their glucose control.”

Diabetes equipment suppliers “often focus on developing the hardware, and they may not have the expertise, the focus and the long-term perspective to provide the clinical implementation, training and all the support tools that one really needs for people to use the new technology safely and effectively,” he adds. “Joslin’s clinical insight and experience can be critical in helping people manage these new tools effectively.”
What does it take to burn off the extra weight that puts so many people at risk of type 2 diabetes and related diseases? How about just turning down the thermostat—can a cool room burn off a handful of chocolate candy or a side of French fries? That’s one question Joslin researchers are asking as they follow up on their 2009 discovery of energy-burning brown fat in adults.

Brown fat works opposite to white fat. White fat infamously stores extra calories as overflowing bellies, muffin tops, love handles and plump thighs. In neat contrast, brown fat expends energy in the form of heat. That’s very handy for maintaining body temperature in newborns, but brown fat takes up so little space that until recently most doctors believed adults had none.

Joslin’s C. Ronald Kahn, M.D., Aaron Cypess, M.D., Ph.D., and their colleagues looked for brown fat in the radiology scans of adults who had undergone the testing for other reasons. They found small collections of brown fat in the neck and around the collarbones that tended to show up in younger, leaner adults examined in cooler seasons, while these collections were not seen in older, obese individuals. Women had detectable brown fat twice as often as men.

Other papers published in the same issue of the New England Journal of Medicine and elsewhere since then have confirmed and extended these original observations.

In the desperate search for more effective tools to combat the twin epidemics of obesity and type 2 diabetes, the surprising possibilities of brown fat represent a potential metabolic bonanza. But this enticing idea requires a lot of fleshing out, a task in which the Kahn and Cypess labs are joined by the lab of Yu-Hua Tseng, Ph.D.

Feeling the burn

Obesity happens when energy intake exceeds energy expenditure. Brown fat may help balance the equation, if scientists can harness the energy-burning power for clinical application.

“Brown fat is not a cure for obesity,” cautions Dr. Cypess, “but burning off a hundred or more extra calories a day could add up.”

Additionally, studies in mice show that brown fat activity appears to reduce the metabolic complications of obesity, such as high blood sugar levels and low insulin sensitivity, even if the mice don’t lose weight. “We don’t know if that’s true in humans,” Dr. Kahn says.

What Dr. Cypess calls the Joslin “fat
team” is at the center of a hub of projects across many labs designed to understand the epidemiology, biology and clinical utility of brown fat.

Among the open questions, exactly how much energy does brown fat burn? In preliminary experiments by Drs. Cypess and Kahn, normal-weight people who sit in a 59-degree room for two hours with summer clothing seem to chew up energy at a rate of 100 to 250 calories per day.

Many collaborations are filling in such gaps in knowledge as who has brown fat (in one group of kids, about 40 percent between ages 5 and 21), where it exists in adults (intermixed with white fat and muscle in some samples) and the best ways to stimulate it (so far, cold seems to work better than known drugs).

One challenge is finding a better way to measure brown fat in humans. Radiation-based imaging exposes people to small but cumulatively harmful risks. Magnetic resonance imaging (MRI) is expensive. In his office, Dr. Cypess demonstrates a bulky handheld infrared camera he’s testing. The manufacturer sells it to identify heat leakage from homes but in people it might reveal telltale brown fat hot spots.

**Fat opportunities**

One year before the blitz of studies trumpeting brown fat in adults, Dr. Tseng and her co-authors reported that BMP-7, a molecule used after spinal fracture surgery to promote bone growth, could expand brown fat when injected into mice. With the help of an orthopedic surgeon, she and Dr. Cypess are evaluating changes in brown fat in people undergoing spinal surgery followed with BMP-7 treatment.

Dr. Tseng is also looking for brown fat precursor or starter cells, with an eye toward the possibility of extracting a person’s own cells and transforming them for cell therapy.

“Not all the brown fat cells in the body are the same,” she says. “Brown fat from different anatomical positions may come from different sources.”

In an unexpected direction, the team is also exploring the potential of white fat cells to increase their energy-burning potential and be more like brown fat cells. Brown fat gets its distinctive color from its uniquely dense mitochondria, the tiny cellular power plants that convert oxygen and food energy into cell energy or, in the case of brown fat, heat. “White fat needs more mitochondria, and it needs the special mitochondrial protein, UCP1, found only in brown fat,” Dr. Kahn says.

Most recently, Tseng’s lab has identified “progenitor” cells in white fat tissue and skeletal muscle in mice that can be induced to become mature brown fat cells, complete with the UCP1 marker. The results were published in the Proceedings of the National Academy of Sciences in December 2010.

As their findings pile up, the team is rethinking all fat. “I collect fat,” Dr. Cypess remarks. “We’re making a fat map, an atlas of the entire human adipose tissue depot. Fat may be a bunch of mini-organs that have different behaviors depending where they are.”

In the meantime, Dr. Kahn wistfully calculates that stimulation of his brown fat might be equivalent to his 35-minute strenuous workout on an elliptical trainer. But when her friends ask Dr. Tseng for weight-loss advice, she tells them the best evidence supports diet and exercise. “Our research is really to benefit people with metabolic disorders who need to lose weight to restore their metabolism to a normal state,” she says.
For most scientists, discoveries in the lab do not translate directly into medical uses. But for the Joslin researchers investigating inflammation as a troublemaker in type 2 diabetes, the road to the clinic has run smoothly so far. Unexpected plot twists are popping up, however, in their search for the drug’s elusive underlying molecular mechanisms.

Ten years ago, Steven Shoelson, M.D., Ph.D., and his co-authors reported that salicylates, a family of anti-inflammatory agents that includes aspirin, could boost insulin sensitivity, lower blood glucose levels and even reduce blood lipids in rodents. The drug seemed to work by blocking a specific low-grade inflammatory pathway activated by weight gain and obesity. The paper provided a plausible way that obesity promoted insulin resistance—and suggested a way to intervene.

The findings set the stage for tests in people of a stomach-sparing formulation called salsalate, an inexpensive generic drug widely prescribed for rheumatoid arthritis joint pain. The multi-center clinical trial was co-headed by Dr. Shoelson and Allison Goldfine, M.D.

Positive results from the first stage of this trial were reported in 2010. There are also two large ongoing trials of salsalate—one to further confirm treatment of type 2 diabetes and another for cardiovascular disease, specifically to alter plaque built up in blood vessels and to prevent heart attacks. Results of the diabetes trial are expected in late 2011. Those for the heart disease trial will follow by several years.

That gives the salicylate family the strange honor of being among the oldest and newest experimental remedies for type 2 diabetes and for one of its major complications, since scattered reports of its usefulness date back to 1876.

“The clinical path has been unusually straightforward,” Dr. Shoelson says. “The surprise is its efficacy. But trying to figure out exactly how it works has been a challenge.”
Teaming up with the lab of Harvard Medical School’s Diane Mathis, Ph.D., the Joslin colleagues discovered that abdominal fat in lean rodents held T regulatory cells (“Tregs,” known as the guardians of the immune system) with a distinctive molecular signature. Further study showed that in obese rodents and people, these lean-fat–specific Treg cells dwindled while destructive macrophages piled in. But in obese mice, salicylate seems to prevent this switch.

The immunological framework holds promise for revealing how obesity correlates not just with type 2 diabetes but with Alzheimer’s disease, asthma and certain cancers. “Obesity seems to affect the immune system everywhere,” Dr. Shoelson says.

**Stress testing**

However, as Dr. Shoelson and his colleagues probe the molecular and cellular diorama of salicylate activity in mice and people, unexpected anomalies have cropped up: Their recent comprehensive evaluation showed that inflammatory pathways don’t account for all of the salicylate effects.

The scientists knew that plants make salicylate in response to bacteria, fungi, extreme temperatures, drought and other stresses. Could salicylate also activate a stress response in people?

To find answers, Drs. Shoelson and Lee are teaming up with Joslin’s T. Keith Blackwell, Ph.D., who works in C. elegans, a tiny worm that serves as a fundamental biological discovery tool. In early work in both worm and mammalian cells, Dr. Blackwell says, “we see that salicylate acts on a stress defense mechanism that may be critical for its anti-inflammatory function and effects on insulin resistance.”

“Salicylate is doing something important and quite wonderful,” Shoelson sums up. “It reduces levels of chronic inflammation, and thus suppresses the collateral damage caused by that inflammation. And at the same time salicylate protects against a variety of cellular stresses.”

“For us to make the next leap, we need to figure out how the inflammation and stress response pathways are interrelated and regulated,” he says. “The clues are there, we just need to be a bit smarter.”
The overall genetic approach for studying cardiovascular risks in type 2 diabetes “has changed dramatically in the past few years,” says Dr. Alessandro Doria.

Knowing that their risks are particularly high can help people to make lifestyle changes that may be beneficial.”

Genetic analyses help to unravel the complexities of coronary artery disease

Decoding the connections between diabetes and heart health

If we can find genes that predispose people with type 2 diabetes to cardiovascular complications, we will learn more about the mechanisms responsible for the disease,” says Alessandro Doria, M.D., Ph.D., M.P.H.

“Even genetic variants that have minor effects on risk may be important,” Dr. Doria adds, “because they may highlight targets for drug interventions. If we find variants with larger effects, we also could use this information to create genetic tests that can identify people whose cardiovascular risk is particularly high.”

“The way we do these studies has changed dramatically in the past few years,” he notes, “We now have the ability to screen the entire genome systematically for association with a disease. In this way you can come across genes and molecular processes that are completely unsuspected.”

“There’s a lot of potential for novelty, but discovery is not as easy as it might seem,” Dr. Doria adds. “The first step is to find which regions of the genome are associated with the disease. Next is to find which genes in those regions are responsible for the association. And once you have those genes, the third step is understanding the mechanisms by which they influence cardiovascular disease. So the initial genetic study is just the beginning of a long march.”

In one early result of that march, he and his colleagues showed that a common genetic variant that increases coronary artery disease in the general population is particularly worrisome when it shows up among people with diabetes that is under poor control. “If you have both of these problems, the risk skyrockets,” says Dr. Doria. “Knowing that their risks are particularly high, however, can help people in this situation to make lifestyle changes that may be beneficial.”
Type 2 diabetes is a disease that increases in incidence with age and is associated with significant stress, and many Joslin research projects seek to understand the connection between these risk factors and development of diabetes. Two principal investigators lead basic research projects—one on adult stem cells and one on worms—that explore these related mechanisms, helping to move toward therapies that may slow the progression of the disease or minimize its effects.

Amy Wagers, Ph.D., studies tissue repair and regeneration in aging, focusing primarily on the role of two types of stem cells, one that makes blood and another that makes skeletal muscle. Her lab has documented the ways in which these stem cells lose functionality over time, and also has demonstrated that components in the blood of young mice may help to revive stem cells in old mice.

“We’re noticing an increasing number of similarities in tissue function between aging individuals and individuals with diabetes,” says Dr. Wagers. “Many of the cells and systems that are altered in old mice are also altered in mice we’ve made diabetic.”

Wagers’ work will aid in understanding how diabetes advances, how its effects may be accelerated by age-related factors, how tissues damaged by diabetes might be repaired, and how the deficits in cell production that accompany aging might be slowed.

T. Keith Blackwell, M.D., Ph.D., studies how cells and organisms protect themselves against stress, and the relationship to aging and chronic diseases such as diabetes. His lab works with the C. elegans worm, which is all of a millimeter long.

“The worm is a great animal for this work because we can do sophisticated genetic manipulations on a large scale to identify molecular processes that are involved in handling stress,” says Dr. Blackwell. “It helps us in discovering ‘wiring diagrams’ for fundamental mechanisms that then can be looked at in higher organisms such as mice and humans.”

Some projects in the Blackwell lab study stress in the endoplasmic reticulum—a structure in the cell that folds up proteins before they can do their work, and gets a real workout in beta cells. “It’s hard for beta cells to pump out lots of insulin, particularly under conditions such as type 2 diabetes,” he says. “We look at mechanisms that defend the cell against this type of stress.”

Additionally, his lab examines the defensive mechanisms that guard against oxidative stress, in which a toxic form of oxygen builds up in tissues. This is another major contributor to the damage inflicted on beta cells and other cells impaired in diabetes, Dr. Blackwell explains.
How does exercise help treat type 2 diabetes?

“Exercise has profound effects throughout the body,” points out Laurie Goodyear, Ph.D. “One effect is that exercise can lower blood glucose concentrations, in part by increasing glucose uptake into skeletal muscles. Another important effect is that after exercise, muscles are more sensitive to the actions of insulin, which can result in a lowering of insulin concentrations. Those effects are very desirable for people with type 2 diabetes.”

Dr. Goodyear’s lab is working to understand the connections between the beneficial effects of exercise and diabetes by studying the molecular mechanisms that regulate the signals that stimulate glucose uptake into cells. Proteins that have a main function in the regulation of glucose transport can be targets in the development of pharmaceutical therapies for type 2 diabetes.

The Goodyear lab has demonstrated that a protein called AMP activated protein kinase (AMPK) is increased in people when they exercise and has an important role in metabolic regulation in many types of cells throughout the body, including muscle, heart and fat cells.

“Work we’ve done in collaboration with the pharmaceutical company Merck showed that metformin, which is probably the number one diabetes drug in the world, works through this AMPK mechanism that exercise activates,” adds Dr. Goodyear. “So research on exercise has led to improved understanding of how a major drug works. Now many pharmaceutical companies are trying to develop AMP activators for diabetes, some with success.”

In other work, Dr. Goodyear’s studies focus on proteins related to AMPK that are triggered by exercise to improve glucose uptake. For one project, her lab has found a way to record images of the movement of crucial proteins that transport glucose in contracting muscles of living mice.

“We’re also doing studies on adaptations to exercise and exercise training,” she says. “If you train a human or animal to exercise, there are chronic adaptations that occur in the muscle and throughout other parts of the body, and we investigate some of these effects. The effects that occur in skeletal muscle make it better able to perform work. There also are effects on the heart, fat cells and throughout the whole body that are very important to overall health.”
Mary Loeken, Ph.D., has found crucial clues to the causes of birth defects that may occur in pregnancies of women with diabetes. Her research follows in the legacy of Joslin’s Dr. Priscilla White, a trailblazer in improving the health of women with diabetes during their pregnancies and the health of their babies. Dr. Loeken’s work may help in learning how to better manage any form of diabetes in pregnancy (including gestational diabetes) and eventually in detecting and treating birth defects at an early stage.

The Loeken lab has shown how high blood glucose levels can decrease production of a key protein called Pax3, and that this event can trigger problems in forming the brain and spinal cord and the heart. Recently, she and her colleagues have discovered that Pax3 helps to control another protein called p53 that plays a crucial role in cell life and death. This suggests a scenario in which less Pax3 is produced and p53 then becomes more active and helps to kill cells needed in normal development.

Additionally, Dr. Loeken investigates why the offspring of women with gestational or long-term diabetes are at increased risk of eventually developing obesity and type 2 diabetes. Her lab developed a mouse strain that is genetically diabetic. During pregnancy, their fetuses are exposed to high blood glucose levels. As the offspring of these mice age, they develop characteristics of type 2 diabetes, and the researchers are investigating how this process occurs.

Another Joslin scientist, Mary-Elizabeth Patti, M.D., studies the causes of type 2 diabetes. As part of her work, she pursues a different angle in exploring how the risk of developing the disease can be handed down to following generations in ways that are not based simply on copying parental DNA.

In one effort, “we examine the effects of poor maternal nutrition on their babies’ risks for diabetes and obesity,” Dr. Patti says. “Many factors contribute to this increased risk, including problems in muscle, fat and pancreatic islets. We’ve been largely interested in how obesity develops, because it occurs very early in life. Human babies exposed to an abnormal intrauterine environment are already fat, and they have less muscle in relation to fat.”

In a recent project, Dr. Patti examined the role of muscle stem cells in this heightened risk of disease down the road. Mice born after poor maternal nutrition or given an overly rich diet as newborns produce a smaller number of muscle stem cells, setting the stage for reduced muscle mass, which in turn may be linked to later development of diabetes as well as obesity.

“There’s an important public health message here about maternal nutrition and fitness,” Dr. Patti comments. “We know that obesity begets obesity. If you are planning to become pregnant, you really want to try to improve your health as much as possible before the pregnancy, so your baby is exposed to a healthy metabolic environment. Fortunately, women in pregnancy are very open to ideas.”
This is an exceptional group—we’re still learning just how exceptional.

Many of the people who have been awarded a Joslin 50-Year Medal still are producing insulin, decades after being hit by the type 1 diabetes autoimmune attacks that destroy insulin-producing beta cells.

And in a recent detailed study of hundreds of Medalists, 43% of the group remained free of proliferative diabetic retinopathy, 39% were free from nerve damage, 52% free of cardiovascular disease and 87% free of kidney disease.

What gives—or rather, what doesn’t give way to diabetes in this select group of survivors?

“They are phenomenal,” says Hillary Keenan, Ph.D., co-principal investigator for the Joslin 50-Year Medalist study, which formally started in 2005 and is creating an ever-longer string of innovative research projects.

Beta cells that keep coming

A paper published in 2010 providing definitive proof that some Medalists still possess functioning beta cells, both growing and dying in the pancreas, was especially remarkable. “After 70 or 80 years, these cells are still constantly reproducing themselves, which is very exciting,” says George King, M.D., Joslin’s Chief Scientific Officer and principal investigator for the Medalist study.
**Medalist for philanthropy**

In 2008, Thomas J. Beatson, Jr. asked four Joslin principal investigators to present him with compelling proposals for research on type 1 diabetes. Inspired by all four proposals, in 2009 he decided to help fund each, splitting a $1-million gift evenly between the four labs. An avid cyclist who has cycled more than 100,000 miles, Mr. Beatson added a rider to his gift: The first funded researcher to publish a paper with a significant outcome in a peer-reviewed journal would win the Beatson Challenge—and a special yellow cycling jersey. In 2010, Dr. Hillary Keenan and her colleagues grabbed the jersey.

More recently, part of a $3.2 million gift given by the Thomas J. Beatson, Jr. Foundation in 2010 will fund a tissue regeneration program that is part of the Medalist study. The program is helping to identify biological factors that either contribute to or help prevent diabetes complications.

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“The autoimmune process is still going on, but somehow these beta cells are resistant,” adds Dr. Keenan.

**Studying “diabetes in a dish”**

Another groundbreaking project involving this exceptional group of patients is underway under the direction of Rohit Kulkarni, M.D., Ph.D., and Amy Wagers, Ph.D. The scientists are using skin cells from Medalists to create induced pluripotent stem (iPS) cells, which have the potential to differentiate into any type of cell in the body.

“With the iPS cells, we’ll generate insulin-secreting beta cells, and cells typically involved in complications that develop in patients with longstanding type 1 diabetes including vascular cells, kidney cells and eye cells,” says Dr. Kulkarni. These cells then can be analyzed for clues to their uncanny survival skills in Medalists.

The diabetic iPS cells “will model diabetes in a dish,” says Dr. Wagers. Previous Medalist research has identified a number of candidate molecular pathways to examine, she adds, and “the nice thing about having the iPS cells is that one can test out those individual pathways in the exact genetic background of the individual in which they’ve been identified. It gives us a much more controlled system to test the importance of genes that are associated with protection from diabetic complications.”

**Finding safety factors**

Other researchers in the Medalist study will examine more deeply how the cells that become involved in cardiovascular, eye and kidney disease may differ in that population.

Among these projects, Andrzej Krolewski, M.D., Ph.D., is leading an effort to compare all the protein-coding genes in two groups of people with diabetes: Medalists without serious eye or kidney complications, and others who developed serious complications within the first 25 years of diabetes. Genes that are produced in greater numbers in the first group will be investigated further to identify factors that may protect against the complications.

Additionally, the study will compare the health histories of Medalists with those of other populations, including the parents of Medalists, another long-lived group.

Yet another project will take a look at their psychological profiles—one of the most common attributes, apparently, is that Medalists like to dance!

Taken all together, the Medalist projects demonstrate Joslin’s unique strengths across the board in diabetes research. Only Joslin, declares Dr. King, can put together a study with this breadth and depth, with so many collaborations drawing on researchers with such a broad range of expertise, and with such promise for major impact on type 1 diabetes.
Beginning in the 1960s, the laser photocoagulation technique pioneered by William P. Beetham, M.D., and Lloyd M. Aiello, M.D., became the worldwide standard of care for reducing vision loss from diabetes. Joslin’s eye research team, which still carries the leadership torch, today is energized by important new results.

Joslin scientists are identifying factors that trigger molecular changes in the eye and finding promising ways to halt these processes. Researchers also are seeking biological factors that aid in early detection or actively protect against eye disease. Additionally, in global telemedicine, Joslin is developing online tools to offer diabetes patients the highest standards of care wherever they live.

New drug for diabetic macular edema

In diabetic retinopathy (damage to the retina in the back of the eye), loss of vision occurs in two primary ways.

With proliferative, or advanced, diabetic retinopathy— afecting more than 700,000 U.S. patients—blood vessels grow in the eye where they don’t belong. Laser treatment generally works well to treat this disease.

Diabetic macular edema, which afflicts more than 500,000 patients, results from leaking of blood vessels that causes swelling in the macula, the area of the retina responsible for our sharpest vision. Left untreated, about a quarter of people with diabetes eventually suffer vision loss from macular edema.

“Laser treatment has been the gold standard intervention for diabetic macular edema over the past 25 years, but now we have an even better therapy that can be used alone or in conjunction with laser—injecting a drug called ranibizumab,” says Lloyd Paul Aiello, M.D., Ph.D., director of Joslin’s Beetham Eye Institute and head of Joslin’s eye research initiatives. The drug targets a key player in blood vessel growth—a protein called vascular endothelial growth factor (VEGF).

Dr. Lloyd Paul Aiello led the basic research that took the first steps toward this treatment, which was endorsed by a landmark clinical study by the Diabetic Retinopathy Clinical Research Network in 2010. In the 1990s, Dr. Aiello and George L. King, M.D., Joslin’s Chief Scientific Officer, observed heightened activity of VEGF in patients with diabetic eye disease and undertook basic research studies to understand the process.

The 2010 clinical study shows anti-VEGF drugs can dramatically reduce vision loss and improve the chance of vision gain, actually stopping leakage in half the patients. Additional clinical trials are being launched to see if similar but less costly anti-VEGF drugs will provide a comparable effect.

Protecting against inflammation

VEGF is only part of the equation, perhaps accounting for about half of diabetic macular edema cases. To illuminate the other cases, Edward P. Feener, Ph.D., is studying the breakdown of the retina’s protective barrier and the subsequent march of inflammatory proteins into the retina.

Using proteomics, the large-scale study of protein structure and function, Dr. Feener identified a troublemaking non-VEGF pathway triggered by a protein called plasma kallikrein. In addition to its role in diabetic macular edema, this protein is part of a potent inflammatory system involved in high blood pressure, kidney disease and stroke. “By identifying promising new drugs that target plasma kallikrein and other proteins involved, we hope to find ways to reduce retinal swelling and possibly benefit other inflammatory conditions,” says Dr. Feener.
Prevention and prediction

Remarkably, some Joslin 50-Year Medalists, who have survived with diabetes for more than five decades, still have little or no diabetic retinopathy, notes Jennifer K. Sun, M.D., M.P.H. A large majority of these patients maintain perfect or excellent vision despite having lived with diabetes for 50 years or more.

“We are investigating factors that may have been involved in their long survival and protected them from diabetic eye complications and vision loss over the long term,” says Dr. Sun. “By identifying key molecules or pathways that protect these unique patients and understanding how they prevent diabetic eye disease, we hope to create novel treatments that can benefit all patients with diabetes, including those who are naturally more susceptible to eye complications.”

She and her colleagues also are seeking ways to predict which patients with diabetes will develop retinopathy by correlating the presence of eye complications with biological markers (substances that can help to indicate a condition), measurements of retinal blood flow and retinal thickness, and ultra-high-resolution images of the various layers of the retina.

Sharing vision with the world

With their state-of-the-art eye care, most Joslin patients retain 20/20 or better vision. How can this success be replicated worldwide—especially 20 years from now, when more than 400 million people will have diabetes?

The Joslin Vision Network, which was formally established in 1998 by Dr. Lloyd M. Aiello and Sven E. Bursell, Ph.D., may hold the answer. With specialized cameras, software and digital data securely transmitted online, the network allows patients to be evaluated from any location worldwide.

Images and other key patient data, including blood pressure and blood glucose measurements, can be transmitted to Joslin in Boston, where an expert ophthalmology team evaluates the images and provides treatment guidance, explains Paolo S. Silva, M.D., assistant chief of telemedicine.

On the horizon, Joslin is seeking funds to expand the network and bring Joslin’s level of diabetes eye care to patients worldwide.

A notable goal is to create an automated portable helmet that patients wear for 15 minutes, capturing and transmitting eye and other medical data to an ophthalmology team in another part of the world who guide their care, says Dr. Lloyd M. Aiello, whose entrepreneurial spirit continues to catapult Joslin’s eye research to new heights.

“We have made great strides in preserving vision and preventing blindness because we’re willing to take risks,” he says. “But to take risks and be successful, you must be dedicated and understand the disease and the needs of our patients. That’s Joslin’s legacy and model for the future.”

Current beneficiaries of the Joslin Vision Network include children at a pediatric endocrine clinic in Caracas, Venezuela. “These patients ages 3 to 21 don’t have access to eye care, so we provide their care by interpreting data sent online to ophthalmology specialists at Joslin, who advise the patients’ local doctors and nurses,” says Dr. Lloyd M. Aiello, who launched the Joslin Vision Network at the endocrine clinic in 2005.

“In addition to providing clinical studies to understand early retinopathy and offering preventive strategies, this experience is helping Joslin’s clinical teams learn how to integrate specialty services within another country’s culture and medical system,” Dr. Aiello emphasizes.
There is an epidemic of kidney disease caused almost entirely by diabetes,” declares Robert Stanton, M.D. “About half a million people in the United States are on dialysis or having kidney transplants. This shortens lives, decreases quality of life and comprises 6.5% of the Medicare budget. And while current treatments appear to have slowed down the progression of kidney disease associated with diabetes, they’re not curing it.”

The Stanton lab, however, is taking promising steps toward stopping the disease.

In diabetes, a toxic form of oxygen builds up in tissues, a damaging condition known as oxidative stress. Dr. Stanton has shown that diabetes reduces the activity of a crucial enzyme called G6PD that produces the body’s main antioxidant, a molecule that guards against oxidative stress called NADPH. This stress leads to kidney and blood vessel damage. Lack of G6PD also may play a role in accelerating the progression of type 2 diabetes itself, by destroying insulin-producing beta cells.

Dr. Stanton now is working with Joslin colleagues and outside collaborators on “exciting ideas about treatments that could boost G6PD production,” he says.

In related work at Joslin, epidemiologist Andrzej Krolewski, M.D., Ph.D., does large-scale studies of people with kidney disease, which affects more than 10% of people with type 2 diabetes and more than 30% of those with type 1 diabetes.

The traditional diagnostic marker of microalbumin (small amounts of a protein called albumin that may leak into urine) doesn’t seem to do a good job predicting risk of kidney disease, says Dr. Krolewski. His lab is researching novel candidates for more effective diagnostic tools.
People with diabetes are at a greater risk for developing Alzheimer’s disease and other neurological conditions, as well as more extensive damage from strokes caused by bleeding. Researchers at Joslin are taking significant steps to understand what drives these risks and to work toward preventive mechanisms.

Gail Musen, Ph.D., examines whether warning signs for Alzheimer’s disease can be detected among people with insulin resistance, who are at higher risk for developing the grim neurodegenerative disease. “This study will help us begin to identify how insulin resistance increases risk for Alzheimer’s, and to identify people who are at risk so that we can try early interventions to decrease that risk,” Dr. Musen says.

She explains that people developing Alzheimer’s may show unusual patterns in the brain’s “default network,” a set of areas of the brain that get busier when the brain is relatively quiet. Importantly, these brain changes can be detected when cognition is still entirely normal. Dr. Musen and her colleagues will employ functional magnetic resonance imaging (fMRI) to examine brain activity in people with various levels of insulin resistance, both while they are mentally “at rest” and when performing memory tasks.

Joslin’s Edward Feener, Ph.D., is making key discoveries about strokes that involve intracerebral hemorrhage (bleeding in the brain). There are no effective treatments to control such bleeding, and diabetes and high blood glucose levels are associated with increased bleeding and worse clinical outcomes.

But studies in the Feener lab have pinpointed a new mechanism involving a protein called plasma kallikrein that interferes with the normal clotting process in the brain following blood vessel injury in people with diabetes. Given the prevalence of strokes and the damage they inflict, “these were exciting results,” says Dr. Feener. The finding raises the possibility of developing drugs that act as preventive measures in people with diabetes or others at high risk for stroke.

In 2010, work at Joslin also produced a surprising finding about another aspect of brain function: diabetes can affect how much cholesterol the brain can make.

The brain produces its own cholesterol and won’t function normally if it doesn’t churn out enough. Investigators in the lab of C. Ronald Kahn, M.D., found that brain cholesterol synthesis drops below normal levels in several mouse models of diabetes.

“This decrease in cholesterol could affect how nerves function for appetite regulation, behavior, memory and even pain and motor activity,” says Dr. Kahn. “Thus, this has broad implications for people with diabetes.”
Philanthropists with a special role in scientific progress

The Iacocca family

Philanthropic support of Joslin can happen in many ways: events, annual gifts, direct mail campaigns, endowed funds, and many other special fundraising initiatives. Two generations of the Iacocca family have supported Joslin for 34 years in every way possible and today the family remains one of our most important and influential partners.

In 1975, Mary Iacocca began receiving treatment at Joslin for her type 1 diabetes. The Iacoccas’ first donation to Joslin was in 1977 and ignited a decades-long crusade to support Joslin and its research efforts. In 1981, Lee and Mary Iacocca established the Mary K. Iacocca Fellowship, which provides annual support for research fellows to receive training and mentoring at Joslin. This was the first of several fellowship programs that the family established. Fellows continue to make advances in diabetes research and have gone on to hold prestigious positions at prominent institutions worldwide. In addition to these fellowship programs, the Iacocca family established the Mary K. Iacocca Professor of Medicine, an endowed professorship currently held by C. Ronald Kahn, M.D., and the Mary K. Iacocca Director of the Laboratory of Advanced Genetic Technologies, an endowed position in diabetes genetic research. To date, the Iacocca family has contributed over $8 million to support Joslin’s mission. We are deeply grateful to Lee Iacocca, Ned and Kate Iacocca Hentz, and Victor and Lia Iacocca Assad, for their vision and leadership, which have had a lasting impact on the lives of people with diabetes around the world.
In 2008, Joslin was given a $2,000,000 commitment from the Moses D. Nunnally Jr. Charitable Trust of Richmond, Virginia. This gift was given in memory of Dianne Nunnally Hoppes by her family to name the Dianne Nunnally Hoppes Laboratory for Diabetes Complications. Dianne Nunnally Hoppes was a long-time Joslin friend, supporter and patient who died of cancer in 2008. Her family’s gift in her memory supports a laboratory that focuses on understanding, preventing and reversing the long-term complications of diabetes. Under the direction of George King, M.D., Joslin’s Chief Scientific Officer, scientists in the Dianne Nunnally Hoppes Laboratory for Diabetes Complications will continue their crusade against diabetes complications—an effort that has produced major advances in recent years. This gift is the first time a Joslin lab has been named to honor a benefactor and testifies to the confidence our donors have in our world-class research programs.

The family of Dianne Nunnally Hoppes

The Joslin connection to the Lowerre family stretches back to founder Dr. Elliott P. Joslin, who cared for Paul’s father, Henry. In gratitude for the care that both have received, Paul and his wife, Ursula Lowerre, have been generous philanthropic partners with Joslin for close to two decades. The Bettina Garthwaite Lowerre Endowment Fund, established in 1998 through a bequest, honors Paul’s mother’s memory and furthers the activities and programs of Joslin. The Lowerre’s generosity includes not only general organizational support through the High Hopes Fund, events and auctions, but also contributions to advance Joslin’s stem cell research initiatives. Most recently, Paul and Ursula opened their home in New York City for a cultivation event in honor of Stanley Mirsky, M.D. Joslin is most indebted to Paul and Ursula Lowerre for their ongoing dedication to Joslin research and the Joslin mission.

The Griffin Drury family

The Maria Griffin Drury Fund was created by the Griffin Drury family in honor of their beautiful daughter Maria, who had type 1 diabetes and died just a month after her seventh birthday. For the past nine years, this very special Joslin family has built a team of community supporters and runners who make it their mission year after year to run in the Boston Half-Marathon and raise funds to support Joslin’s pediatric research and the work of Lori Laffel, M.D., M.P.H. The Griffin Drury family, including daughters Grace and Caroline, continues to put together other fundraising events throughout the year totaling more than half a million dollars.
Affiliated with Harvard Medical School, Joslin’s lead scientists bring an enormous range of achievements

Lloyd M. Aiello, M.D., who has pioneered breakthroughs in the management of diabetes eye complications including laser photocoagulation, now seeks ways to broaden better eye health care worldwide through advances in telemedicine. He is the Founding Director of the Beetham Eye Institute, an Investigator in the Section on Vascular Cell Biology and a Clinical Professor of Ophthalmology.

Jerry Cavallerano, O.D., Ph.D., concentrates his research primarily around the Diabetic Retinopathy Clinical Research Network initiatives at the Beetham Eye Institute and clinical applications of the Joslin Vision Network. He is assistant to the Beetham director and an Associate Professor of Ophthalmology.

Lloyd Paul Aiello, M.D., Ph.D., works to determine the biochemical and molecular mechanisms underlying diabetic retinopathy and other retinal vascular disorders, and to develop and test novel therapeutic interventions and clinical trial research. He is Director of the Beetham Eye Institute, co-head of the Section on Vascular Cell Biology and a Professor of Ophthalmology.

Aaron Cypess, M.D., Ph.D., looks at the role of energy-burning brown fat, which may offer help in the battle against obesity, and at what makes this fat become active in various groups of people. He is an Assistant Investigator in the Section on Integrative Physiology & Metabolism and an Assistant Professor of Medicine.

T. Keith Blackwell, M.D., Ph.D., studies how cells and organisms protect themselves against stress, and the relationship to aging and chronic diseases such as diabetes, working with the simple animal model C. elegans. He is co-head of the Section on Islet Cell & Regenerative Biology and a Professor of Pathology.

Alessandro Doria, M.D., Ph.D., M.P.H., studies the genetic mechanisms that predispose people with type 2 diabetes to cardiovascular complications, helping to identify diagnostic tools and potential therapies, and investigates the genes involved in a form of diabetes called MODY. He is an Investigator in the Section on Genetics & Epidemiology and an Associate Professor of Medicine.

Susan Bonner-Weir, Ph.D., does research on pancreatic islet cells, with a main focus on a search for new sources of insulin-producing beta cells. She is a Senior Investigator in the Section on Islet Cell & Regenerative Biology and a Professor of Medicine.

Edward Feener, Ph.D., examines the mechanisms underlying complications that diabetes can produce in blood vessels, with a current focus on characterizing the role played by a protein called plasma kallikrein in the retina and the brain. He is an Investigator in the Section on Vascular Cell Biology and an Associate Professor of Medicine.

A. Enrique Caballero, M.D., studies the impact of multiple medical, psychological, socioeconomic and cultural factors on diabetes care among Latinos, and ways to improve that care. He is an Investigator in the Section on Clinical, Behavioral & Outcomes Research and an Assistant Professor of Medicine.

Om Ganda, M.D., explores the connections between type 2 diabetes and cardiovascular disease and related complications in clinical trials. He is an Investigator in the Section on Clinical, Behavioral & Outcomes Research and an Associate Clinical Professor of Medicine.
Ann Goebel-Fabbri, Ph.D., seeks to better understand how eating disorders affect long-term medical complications in women with diabetes and what types of interventions might help improve health outcomes in these high-risk patients. She is an Investigator in the Section on Clinical, Behavioral & Outcomes Research and an Assistant Professor of Psychiatry.

Allison Goldfine, M.D., studies the ways in which genetic predisposition, obesity, lifestyle and other risk factors interact in the development of diabetes and the cardiovascular complications of the disease. She is head of the Section of Clinical, Behavioral & Outcomes Research and an Associate Professor of Medicine.

Laurie Goodyear, Ph.D., works to understand the connections between the beneficial effects of exercise and diabetes by studying the molecular mechanisms that regulate the signals that stimulate glucose uptake into cells. She is co-head of the Section on Integrative Physiology & Metabolism and an Associate Professor of Medicine.

Osama Hamdy, M.D., Ph.D., looks at the metabolic and cardiovascular benefits of short- and long-term weight reduction in obese individuals with diabetes. He is Medical Director of the Obesity Clinical Program and an Assistant Professor of Medicine.

Edward Horton, M.D., leads clinical studies focusing on ways to minimize the risk of developing cardiovascular disease among people with diabetes. He is a Senior Investigator in the Section on Clinical, Behavioral & Outcomes Research and a Professor of Medicine.

William Hsu, M.D., works to understand the causes of diabetes among Asian Americans, and to create medical tools and management approaches to appropriately diagnose and treat that population for the disease. He is an Investigator in the Section on Vascular Cell Biology and an Assistant Professor of Medicine.

C. Ronald Kahn, M.D., studies how insulin acts in the body, how insulin resistance (a precursor to type 2 diabetes) progresses, and the role of obesity mechanisms, with an emphasis on how fat cells develop. He is a former President of Joslin, co-head of the Section on Integrative Physiology & Metabolism, and a Professor of Medicine.

Hillary Keenan, Ph.D., is an epidemiologist who is co-principal investigator on the Joslin 50-Year Medalist Study. She is a research associate in the Section on Vascular Cell Biology and an Instructor in Medicine.

George King, M.D., studies the molecular mechanisms by which high blood glucose levels and insulin resistance may lead to long-term complications. He is Joslin’s Chief Scientific Officer, co-head of the Section on Vascular Cell Biology and a Professor of Medicine.

Andrzej Krolewski, M.D., Ph.D., explores the mechanisms of late diabetic complications, particularly diabetic kidney disease, using epidemiological, genetic and proteomic methods. He is head of the Section on Genetics & Epidemiology and an Associate Professor of Medicine.
Rohit N. Kulkarni, M.D., Ph.D., focuses on the ways in which insulin-producing beta cells can be regenerated, work that applies both to type 1 and type 2 diabetes. He is an Investigator in the Section on Islet Cell & Regenerative Biology and an Associate Professor of Medicine.

Sanjeev Mehta, M.D., M.P.H., looks at the impact of nutrition on the health of youth and young adults with type 1 diabetes, and works to improve the use of electronic medical records for research and clinical purposes. He is a Research Associate in the Section on Genetics & Epidemiology and an Instructor in Pediatrics.

Lori Laffel, M.D., M.P.H., works to optimize diabetes management approaches that preserve the health, normal growth, development and family functioning of children, adolescents and young adults with diabetes. She is head of the Joslin pediatric clinic; an Investigator in the Section on Genetics & Epidemiology; and an Associate Professor of Pediatrics.

Gail Musen, Ph.D., explores the effects of diabetes on the central nervous system, with a focus on whether warning signs for Alzheimer’s disease can be detected among people with insulin resistance. She is an Assistant Investigator in the Section on Clinical, Behavioral & Outcomes Research and an Instructor in Medicine.

Jongsoon Lee, Ph.D., explores the role of inflammation in obesity, type 2 diabetes and cardiovascular disease. He is an Assistant Investigator in the Section on Pathophysiology & Molecular Pharmacology and an Assistant Professor of Medicine.

Tihamer Orban, M.D., focuses on developing immune therapies for type 1 diabetes, including clinical testing of a novel type 1 diabetes vaccine. He is an Assistant Investigator in the Section on Immunobiology and an Instructor in Medicine.

Myra Lipes, M.D., studies the underpinnings of autoimmune disease, currently focusing on an autoimmune attack that weakens heart muscle and may be particularly prevalent among people with type 1 diabetes. She is an Investigator in the Section on Islet Cell & Regenerative Biology and an Assistant Professor of Medicine.

Mary-Elizabeth Patti, M.D., works to identify cellular and molecular mechanisms that increase the risk of diabetes, particularly those that begin during pregnancy and early life, and to speed the development of therapies to reduce this risk. She is an Investigator in the Section on Integrative Physiology & Metabolism and an Assistant Professor of Medicine.

Mary Loeken, Ph.D., seeks to understand the causes of birth defects that may occur in pregnancies of women with diabetes. She is an Investigator in the Section on Islet Cell & Regenerative Biology and an Associate Professor of Medicine.

Aldo Rossini, M.D., is the acting head of the Section on Immunobiology, a Mary K. Iaccoca Senior Visiting Scholar and Professor Emeritus at the University of Massachusetts Medical School.
Thomas Serwold, Ph.D., seeks to understand the cells that help T cells to develop, and whether these cells can be altered to prevent autoimmune T cells from developing and then launching the attacks that cause type 1 diabetes. He is an Investigator in the Section on Immunobiology and an Assistant Professor of Medicine.

Arun Sharma, Ph.D., investigates the issues involved in making insulin-producing replacement cells fully functional—able to release sufficient amounts of insulin when prompted by glucose in the blood. He is an Investigator in the Section on Islet Cell & Regenerative Biology and an Assistant Professor of Medicine.

Steven Shoelson, M.D., Ph.D., looks at the connections between inflammation and the development of obesity, insulin resistance, type 2 diabetes and cardiovascular disease. He is head of the Section on Pathophysiology & Molecular Pharmacology and a Professor of Medicine.

Robert C. Stanton, M.D., probes the damaging role of oxidants in diabetes complications, especially related to kidney disease, and looks for ways to prevent the damage. He is an Investigator in the Section on Vascular Cell Biology and an Associate Professor of Medicine.

Jennifer Sun, M.D., M.P.H., carries out clinical research to understand the factors behind diabetic eye disease and potential treatment approaches. She is an Assistant Investigator in the Section on Vascular Cell Biology and an Assistant Professor of Ophthalmology.

Yu-Hua Tseng, Ph.D., investigates how brown fat and white fat develop and function. She is an Assistant Investigator in the Section on Integrative Physiology & Metabolism and an Assistant Professor of Medicine.

Amy Wagers, Ph.D., focuses on understanding the mechanisms that regulate the function of blood-forming and muscle-forming adult stem cells, to aid in the eventual treatment of diabetes and other diseases. She is an Investigator in the Section on Islet Cell & Regenerative Biology and an Associate Professor of Stem Cell and Regenerative Biology.

Katie Weinger, Ed.D., R.N., examines barriers to effective self-management for diabetes and determines ways in which diabetes clinicians and educators can best incorporate psychological techniques to improve patient adherence and outcomes. She is an Investigator in the Section on Clinical, Behavioral & Outcomes Research and an Assistant Professor of Psychiatry.

Gordon Weir, M.D., studies potential sources of new insulin-producing beta cells and methods of successfully transplanting these cells or regenerating them in people with type 1 diabetes. He is co-head of the Section on Islet Cell & Regenerative Biology and a Professor of Medicine.

Howard Wolpert, M.D., leads clinical trials that help to analyze the best ways to adopt technology for type 1 diabetes management. He is an Investigator in the Section on Clinical, Behavioral & Outcomes Research and an Assistant Professor of Medicine.
A decade of discovery

In recent years, Joslin’s scientific team has made broad and deep progress in the fight to find cures. Here is a sampling of major research achievements between 2000 and 2010.

2000

› Researchers discover a way to encourage pancreas cells that do not normally produce insulin to become insulin-producing cells.

SUSAN BONNER-WEIR, PH.D., AND GORDON C. WEIR, M.D.

› Insulin signaling in the brain is linked to type 2 diabetes, appetite control, obesity and even infertility.

C. RONALD KAHN, M.D. AND COLLEAGUES

2003

› Researchers find that mice genetically altered to have fat that did not respond to insulin could overeat without gaining weight, becoming protected against obesity and type 2 diabetes.

DR. KAHN’S LAB

› Investigators discover in patients with type 1 diabetes that early signs of kidney disease (microalbuminuria) can be reversed to normal with proper medical screening and diabetes control.

ANDRZEJ KROLEWSKI, M.D., PH.D., AND BRUCE PERKINS, M.D., M.P.H.
Scientists demonstrate that when people gain weight, they activate a “master switch” (known as NF-kB), which triggers the inflammation pathway that leads to insulin resistance. Aspirin-like anti-inflammatory drugs can turn off this response.

STEVEN SHOELSON, M.D., PH.D.

Research shows that poor prenatal nutrition permanently damages the function of insulin-producing cells in the pancreas, raising the risk that the child will later develop type 2 diabetes.

MARY-ELIZABETH PATTI, M.D.

A Joslin-led study documents for the first time subtle changes in the gray matter of the brains of patients with type 1 diabetes compared to control subjects who did not have diabetes.

ALAN JACOBSON, M.D.

Joslin researchers discover a protein that causes blood vessel leakage in eyes with diabetic retinopathy.

EDWARD FEENER, M.D.

Investigators show that salsalate, an inexpensive anti-inflammatory drug similar to aspirin, may prevent and help to treat type 2 diabetes by lowering blood glucose and reducing inflammation.

ALLISON GOLDFINE, M.D., AND DR. SHOELSON

Joslin researchers demonstrate that a protein known for its role in inducing bone growth can also help promote the development of brown fat, a “good” fat that helps in the expenditure of energy and may play a role in fighting obesity.

YU-HUA TSENG, PH.D.

Scientists show that insulin-producing pancreatic beta cells can form after birth or injury from adult stem cells within the pancreas that are not beta cells.

DR. BONNER-WEIR’S LAB

Researchers demonstrate that adult humans still have energy-burning brown fat, a finding that could pave the way for new treatments both for obesity and type 2 diabetes.

DR. KAHN’S LAB AND AARON CYPESS, M.D., PH.D.

Scientists discover a key route by which high blood glucose levels can damage eyes, suggesting new drug targets for diabetes complications.

GEORGE KING, M.D., AND COLLEAGUES

In separate efforts, Joslin researchers identify two mechanisms that can kill insulin-producing cells in diabetes—one when the cells themselves can’t import insulin properly and another when high blood glucose levels damage a key enzyme.

ROHIT KULKARNI, M.D., PH.D., AND ROBERT STANTON, M.D.

Salsalate passes the next clinical hurdle in an FDA phase 2/3 trial for treatment of patients with type 2 diabetes.

DR. GOLDFINE’S LAB AND DR. SHOELSON’S LAB

A national clinical trial confirms the effectiveness of ranibizumab (Lucentis) eye injections, often in combination with laser treatment, as a standard treatment for diabetes-associated swelling of the retina. Joslin basic research laid the foundation for this improved therapy.

LLOYD P. AIELLO, M.D., PH.D., AND DR. KING’S LAB

Joslin research shows that insulin guards against artery damage and atherosclerosis, major causes of death in patients with type 1 or type 2 diabetes.

DR. KING’S LAB

Scientists at Joslin conclusively demonstrate that a surprisingly high percentage of people with type 1 diabetes who have had the disease for 50 years or longer may still have insulin-producing islet cells and/or islet cell antibodies.

DR. KING’S LAB AND HILLARY KEENAN, PH.D.

Researchers identify adult stem cells in white fat tissue and skeletal muscle that can be transformed into brown fat cells.

DR. TSENG’S LAB
Joslin offers the power of the big picture in diabetes research.

Joslin’s endocrinologists, clinical researchers, molecular biologists, geneticists, statisticians, development biologists, clinical nurses, bioinformatics specialists, technicians and other personnel make up the largest collection of diabetes researchers under one roof.

Every one is dedicated to finding a cure and realizing our vision of a world without diabetes.