

NOVEMBER 2016

THE LEADING MAGAZINE FOR ● ENDOCRINOLOGISTS

Endocrine news

Diabetes DISCOURSE

ENDOCRINOLOGISTS ARE AT THE FOREFRONT OF DIABETES TREATMENT AND RESEARCH AND WILL UNDOUBTEDLY PLAY A VITAL ROLE IN FINDING A CURE. THIS MONTH, *ENDOCRINE NEWS* PUTS A UNIQUE FOCUS ON SOME OF THE MORE ATYPICAL COMPONENTS OF THIS BURGEONING EPIDEMIC.

- The underappreciated complication between diabetes and bone health.
- Addressing the growing impact of diabetes technology on patients and physicians.
- Will a diabetes cure be found through pancreas donors?
- A look at the Endocrine Society's efforts to reduce and prevent hypoglycemia.

WHY ENDOCRINOLOGY?

How Bryan A. Wilson was liberated to a life of science.

HEART ON YOUR SLEEVE:

Is there a role for wearables in patient care?

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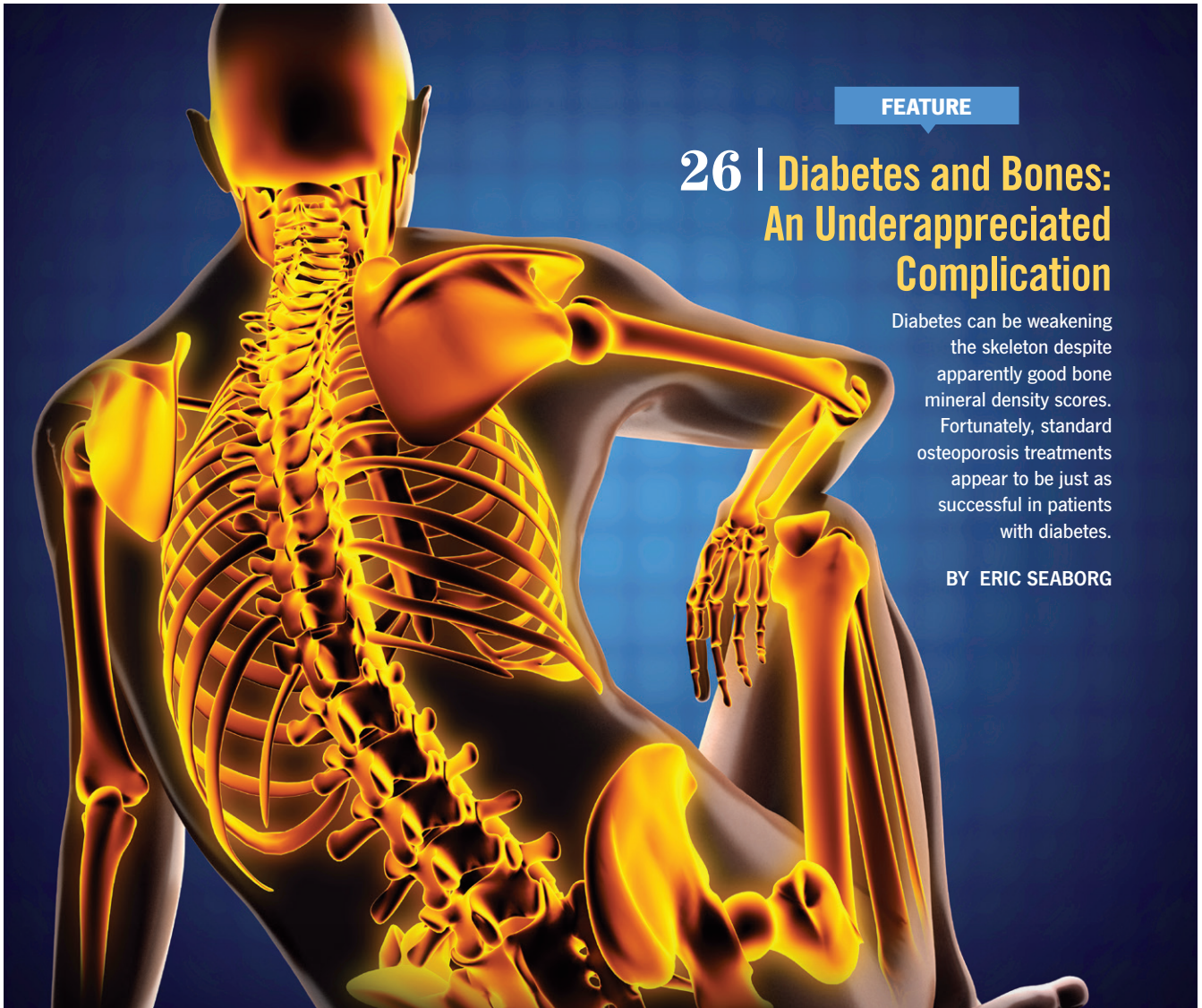
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FEATURE

26 | Diabetes and Bones: An Underappreciated Complication

Diabetes can be weakening the skeleton despite apparently good bone mineral density scores. Fortunately, standard osteoporosis treatments appear to be just as successful in patients with diabetes.

BY ERIC SEABORG

FEATURE

20 | Pancreas Donors: A Key to a Cure?

If you haven't heard of the JDRF Network for the Pancreatic Organ Donor with Diabetes aka nPOD, you will. nPOD is not just a research lab or a clearing house for pancreas tissue from donors with diabetes, it's on the front lines to finding a cure.

BY DEREK BAGLEY

FEATURE

30 | Priming the Pump

Insulin pumps and continuous glucose monitors are changing quickly — and their impact is only expected to grow. Details on how these devices should be used with patients are outlined in a new Endocrine Society Clinical Practice Guideline.

BY ERIC SEABORG

SPECIAL SECTION

35 | Hypoglycemia: A Comprehensive Approach in the U.S.

This special 10-page section is devoted to the Endocrine Society's efforts in addressing hypoglycemia in the U.S. and includes a detailed "blueprint" for how to reduce "the incidence of hypoglycemia and ensure that patients and providers receive the tools they need to prevent and manage the complication."



FROM THE **EDITOR**


Putting the Unique Aspects of Diabetes Front and Center

THE ENDOCRINE SOCIETY AND *ENDOCRINE NEWS* ARE FOCUSING ON diabetes for November to coincide with the heightened awareness of this disease around the world — National Diabetes Month, World Diabetes Day (November 14), American Diabetes Month. To that end, this issue has a number of articles that approach diabetes from unique perspectives.

On page 26, Eric Seaborg explores the link between diabetes and bone health in “Diabetes and Bones: An Underappreciated Complication.” In the article, Mishaela R. Rubin, MD, an associate professor of medicine at Columbia University Medical Center in New York, discusses how skeletal deterioration can also be another complication from diabetes. “We know that these advanced glycation end-products accumulate in other tissues and can harm them,” she says. “It is possible that the same thing is happening in the skeleton. We understand that patients who have poorly controlled diabetes are going to have worse bone quality, and that will predispose them to an increased fracture risk.”

For a look at the importance of diabetes technology, Seaborg also writes about the new clinical practice guideline the Endocrine Society recently published that focuses on insulin pumps and continuous glucose monitors. In “Priming the Pump” on page 30, he discusses which patients are ideal candidates for the devices as well as tailoring the technology needs to individual patients’ situations. He spoke with Anne L. Peters from the Keck School of Medicine at the University of Southern California in Los Angeles who says that providers shouldn’t tell patients they “‘must go on the pump because your control will get better,’ but rather, ‘a pump is one way to treat diabetes, these are your options,’” she explains, adding “It is always the user who makes the device work.”

Associate editor Derek Bagley has written an in-depth feature on the JDRF Network for the Pancreatic Organ Donors with Diabetes (nPOD). In “Pancreas Donors: A Key to a Cure?” (p. 20), Bagley not only gives us the details on nPOD but also elaborates on some of its recent research findings as well as the network’s future plans as it hopes to play a major role in finding a cure for diabetes. . . even if it’s to nPOD’s detriment. “The big breakthrough would be finding a cure [for diabetes],” says Irina Kusmartseva, PhD, director of nPOD’s Organ Processing and Pathology Core. “But I wouldn’t mind.”

Finally, this issue features a special 10-page section devoted to the Endocrine Society’s efforts in addressing hypoglycemia in the U.S., beginning on page 35. Aside from commentary from Rep. Diana DeGette (D-CO), co-chair of the Congressional Diabetes Caucus, and a Q&A with Griffin P. Rodgers, MD, MACP, and Judith E. Fradkin, MD, from the National Institute of Diabetes and Digestive & Kidney Diseases, there is also a detailed “blueprint” for how the Endocrine Society and other diabetes stakeholders can work in concert to reduce “the incidence of hypoglycemia and ensure that patients and providers receive the tools they need to prevent and manage the complication.” 

— **Mark A. Newman**, Editor, *Endocrine News*

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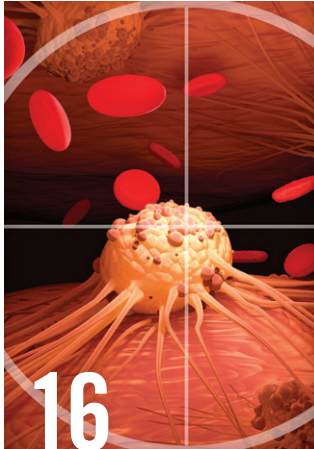
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The Endocrine Society Leads the Way in Tackling Diabetes Around the World

ADDRESSING THE GLOBAL DIABETES EPIDEMIC has been a key priority for the Society since its inception. As we move into the first year of our next hundred years, this work will be even more critical given that more than 422 million people worldwide suffer from the disease. November is Diabetes Month and World Diabetes Day is Observed on November 14, and this provides an opportunity to highlight the impact of the disease and identify strategies to make a difference. We should be proud of the significant headway we have made in ensuring that patients with diabetes have access to treatment and prevention programs and are aware of the impact of hypoglycemia on health outcomes and cost. The following are just some examples of the work our Society is doing:

DIABETES PREVENTION — In an effort to help reduce the number of new cases of diabetes, the Society has long advocated for Medicare coverage of the National Diabetes Prevention Program (NDPP), which has demonstrated that moderate weight loss can prevent or reduce the onset of diabetes by 71% in older adults. Our members have met with Congress and federal agencies, and helped pass a resolution at the American Medical Association's House of Delegates to underscore the importance of Medicare coverage for this program. As a result, the Centers for Medicare and Medicaid Services has announced its intention to cover the NDPP in 2017. This important win highlights how we can work together to affect change, and we are pleased that Medicare has recognized the value of the NDPP.

REDUCING HYPOGLYCEMIA — Recognizing the importance of addressing hypoglycemia to improve outcomes and to reduce unnecessary costs has been a key priority. To this end, the Society established the Hypoglycemia Quality Collaborative, a working group comprised of representatives from provider groups, patient organizations, federal agencies, payers, and industry, to develop a comprehensive approach to addressing hypoglycemia. Together we developed a blueprint, which is included in this issue of

Endocrine News (page 35), to provide recommendations for advancing research, raising awareness, educating clinicians and patients, and supporting delivery reform. We look forward to engaging our members as we identify and prioritize areas for future work.

DEVICES — The Endocrine Society has issued a Clinical Practice Guideline providing guidance on the standard of care for diabetes technologies, including insulin pump therapy and the use of continuous glucose monitors in patients with type 1 and type 2 diabetes. We also continue to advocate for access to much-needed diabetes devices and therapies to ensure that patients receive the

appropriate care. Our members have been heavily involved in building support for the Medicare CGM Access Act of 2015, which would provide Medicare coverage for continuous glucose monitoring. As a result of our advocacy, the legislation has garnered the support of 269 representatives and 49 senators. I urge you to join this effort and make sure your voice is heard by visiting endocrine.org/advocacy.

PATIENT INFORMATION — The Hormone Health Network has developed several patient resources for individuals and their caregivers managing diabetes at hormone.org. One highlight is D.A.I.L.Y. (Diabetes Awareness Information for Loved ones and You). This online portal provides resources that are tailored to an individual patient's needs and can be shared with healthcare professionals to encourage a collaborative approach to

diabetes management. We've also launched *Managing Patients with T1DM*, a new activity for clinical fellows that explores important aspects of patient-centered care, such as exercise and mental health.


ADVANCING RESEARCH — Endocrine Society members made major contributions to diabetes research programs over the past year. C. Ronald Kahn's lab showed how insulin resistance in the brain can lead to anxiety and depressive-like behaviors in

“
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mice. Mitchell Lazar's group shed light on potential precision approaches to treating type 2 diabetes by showing how genomic variation can affect metabolic health and therapeutic response to certain drugs. Barbara B. Kahn's research identified lipids that can improve glucose control; future research could help better inform future studies of therapeutic potential. These and other important research advances are summarized in National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK's) Recent Advances and Emerging Opportunities document.

GLOBAL EFFORTS — This past August, we launched the Society's first global outreach program for patients and providers, EndoCares: Diabetes in Lima, Peru. EndoCares was possible through the collaboration with three local organizations: Sociedad Peruana de Endocrinología, Asociación Peruana de Diabetes, and Liga de Lucha Contra la Diabetes, and the sponsorship of Sanofi Peru. Endocrine Society members, Agustín

Busta, MD, Lisa Fish, MD, and Guillermo Umpierrez, MD, led a provider-focused session on treating diabetes, that reached an audience of over 1,000 healthcare providers, including primary care physicians, advanced practice professionals, and medical students. The patient-focused sessions focused on managing both type 1 and type 2 diabetes in two simultaneous day-long programs which reached more than 600 patients and their families. EndoCares brings together many of the Society's most recent strategic initiatives: addressing health disparities, serving as a global partner and champion of the field, and fostering the next generation of endocrinologists.

For more information about the Society's work in diabetes, please visit our special Centennial Page for November at escentennial.org. 

— **Henry M. Kronenberg, MD**, President, Endocrine Society

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Hormone Science to Health

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ENDOCRINE SOCIETY

Five Members Elected to Society Governing Council

Members of the Endocrine Society have elected five new Officers and Council members to lead the world's oldest and largest global membership organization representing endocrinologists, who are dedicated to research on hormones and the clinical practice of endocrinology.

The new Officers and Council members are:

- **Susan J. Mandel, MD, MPH:**
President-Elect
- **Genevieve Neal-Perry, MD, PhD:**
Vice President, Basic Scientist
- **Cesar L. Boguszewski, MD, PhD:**
Council Member, Clinical Scientist Seat
- **Anthony Hollenberg, MD:**
Council Member, At-Large Seat
- **Clifford Rosen, MD:**
Council Member, At-Large Seat



MANDEL will serve as president-elect in 2017 – 2018 and then as president in 2018 – 2019. She is professor of medicine and radiology, and associate chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Pennsylvania's Perelman School of Medicine in Philadelphia. A

Society member for more than two decades, she has served as vice president and as a council member representing physicians in practice. She has served on numerous Society committees, most recently as chair of the Knowledge Integration Task Force. Her awards and honors include the Endocrine Society's 2011 Distinguished Educator Award, the H. Jack Baskin MD Endocrine Teaching Award, and the Louis Duhring Award for Outstanding Clinical Specialist from the University of Pennsylvania Health System.



NEAL-PERRY will serve a three-year term as vice president, basic scientist (2017 – 2020). She is an associate professor of obstetrics and gynecology, and directs the University of Washington Medicine Reproductive Endocrinology and Infertility Center at the University of Washington in

Seattle. Neal-Perry has been a member of the Endocrine Society since 2001 and has served on the Special Programs Committee, the Research Affairs Core Committee, and the editorial board for *Endocrinology*. She has been recognized by the Faculty of 1000 and honored with the Endocrine Society's Young Investigator Mentor Award and the AMA Women Physicians Section Physician Mentor Award.



BOGUSZEWSKI will serve a three-year term in the clinical scientist-designated seat on Council (2017 – 2020). He is a professor of endocrinology in the Federal University of Parana's Department of Internal Medicine in Curitiba, Brazil. A Society member for 20 years, he serves on the Society's

Scientific and Educational Programs Core Committee and previously served on the Scientific Statements Task Force and Research Affairs Core Committee. Boguszewski is associate editor for South America for the *European Journal of Endocrinology* and serves on the editorial board for *Archives of Endocrinology and Metabolism*. He is chair of the Brazilian Society of Endocrinology and Metabolism's International Committee and was chair of the Executive Committee of the Brazilian Congress of Endocrinology and Metabolism 2014. He serves on the Board of Directors of the Pituitary Society and is a member of the Program Organizing Committee of the European Congress of Endocrinology 2017 in Lisbon, Portugal.



HOLLENBERG will serve a three-year term as an at-large member of council (2017 – 2020). He is chief of the Division of Endocrinology, Diabetes and Metabolism at Beth Israel Deaconess Medical

Center; a professor of medicine at Harvard Medical School and director of Clinical and Translational Research Training Programs at Harvard Catalyst in Boston. He is an associate editor for *Endocrinology* and previously served on the Society's Annual Meeting Steering Committee and the *Molecular Endocrinology* editorial board. His honors include being selected to deliver the David Owen Segal Lecture at Mount Sinai School of Medicine, the Gerald N. Burrow Memorial Lecture at the University of Toronto, and the Rosalind Pitt-Rivers Lecture to the British Endocrine Society in Edinburgh, U.K.



ROSEN will serve a three-year term as an at-large member of council (2017 – 2020). He is the director of clinical and translational research and a senior faculty scientist at Maine Medical Center

Research Institute in Scarborough, Maine, and a professor of medicine at Tufts University School of Medicine in Boston. Rosen is an associate editor of *The New England Journal of Medicine* and *Endocrine Reviews*. He currently serves on the Society's Laureate Awards Committee and has previously served on the Annual Meeting Steering Committee and Scientific and Educational Programs Core Committee. His honors include the Society's Glenn Foundation Award and the American Society for Bone and Mineral Research's Larry Raisz Award.

The new officers and council members will assume their new positions at **ENDO 2017** in Orlando, Florida, from April 1 to 4, 2017.



Endocrine News Associate Editor Speaks at ATA Conference

On September 22, *Endocrine News* associate editor Derek Bagley spoke at the 86th Annual Meeting of the American Thyroid Association in Denver, Colo., during the Basic Trainees Lunch Session as part of the E. Chester Ridgway Trainees Conference.

The goal of the session was to have an informal discussion over lunch on the career paths available to basic science fellows. The panelists represented tracks from academia, translational, industry, and science writing.

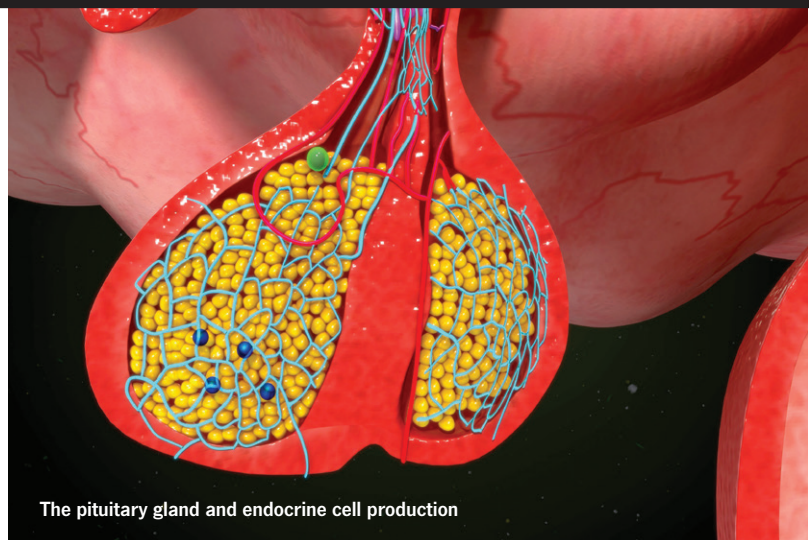
"I sort of felt like the odd man out since I don't have as much of a science background as the other panelists," Bagley says. "But the attendees still seemed interested in what I had to say. A few even approached me after and said they appreciated a different perspective."

Other panelists included Grant Anderson, PhD, head of the Department of Pharmacy Practice and Pharmaceutical Sciences at the University of Minnesota; Giulia Kennedy, PhD, chief scientific officer at Veracyte; and Paul Davis, MD, director of the Ordway Research Institute in Albany, N.Y. The discussion was moderated by David S. Sharlin, PhD, assistant professor in the Department of Biological Sciences at Minnesota State University, Mankato. Each panelist briefly described his or her career path and then opened the floor for questions from the room full of graduate students and post-doc fellows still navigating their career paths.

Bagley's inclusion on the panel speaks well of the Endocrine Society's reputation among other medical associations, according to *Endocrine News* editor, Mark A. Newman. "Derek was invited to speak to these early career professionals because the organizers of the conference trusted the Endocrine Society as well as *Endocrine News* to such a degree that they knew he could offer a unique and relevant perspective," he says. "The science and research that the Endocrine Society is known for is so well-respected that Derek and the magazine's reputation preceded him."

While a much smaller conference than ENDO, the Endocrine Society's annual conference, Bagley was able to speak to several of the Society's members between sessions.

Endocrine Society Issues Clinical Practice Guideline on Hypopituitarism



The pituitary gland and endocrine cell production

A Clinical Practice Guideline that recommends treating insufficient hormone levels in individuals with hypopituitarism by replacing hormones at levels as close to the body's natural patterns as possible has been published by the Endocrine Society.

The guideline, titled “Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline,” was published online and will appear in the November 2016 print issue of *The Journal of Clinical Endocrinology & Metabolism (JCEM)*.

“Hypopituitarism can manifest as low levels of a variety of hormones, including cortisol, thyroid hormone, estrogen, testosterone, and growth hormone,” says Maria Fleseriu, MD, FACE, of Oregon Health & Science University in Portland, Ore. Fleseriu chaired the task force that developed the guideline. “The goal of treatment should be to restore hormone levels as close to healthy levels as possible. The interactions between these hormones also are very important, and patients might require dose changes of one or more of the replacement hormones after starting or discontinuing another one.”

In recommending treatment options, the guideline task force followed the overriding principle of using hormone replacement therapy dose size and timing to mimic the body's natural functioning as closely as possible.

Accurate and reliable measurements of hormones play a central role in diagnosing hypopituitarism and monitoring the effectiveness of treatments, Fleseriu says. Healthcare providers need to keep in mind technical considerations to ensure the testing procedure is as accurate as possible.

The guideline addresses special circumstances that may affect the treatment of patients with hypopituitarism, including pregnancy care, post-surgical care following pituitary or other operations, treatment in combination with anti-epilepsy medication, and care following pituitary apoplexy — a serious condition that occurs when there is bleeding into the gland or blood flow to it is blocked.

Recommendations from the guideline include:

- ▶ Measurements of both free thyroxine and thyroid-stimulating hormone are needed to evaluate central hypothyroidism, a condition where the thyroid gland does not produce enough hormones because it isn't stimulated by the pituitary gland.
- ▶ People who have central hypothyroidism should be treated with levothyroxine in doses sufficient to raise levels of the thyroid hormone free thyroxine to the upper half of the reference range.
- ▶ Growth hormone stimulation testing should be used to diagnose patients with suspected growth hormone deficiency.

“**Accurate and reliable measurements of hormones play a central role in diagnosing hypopituitarism and monitoring the effectiveness of treatments.**”



Pete Myers Recognized by NIEHS

On November 1, Endocrine Society member John Peterson (Pete) Myers, PhD, was recognized by the National Institute of Environmental Health Sciences (NIEHS) as one of 12 individuals to receive the inaugural Champion of Environmental Health Research Award.

Myers is a biologist, and founder, CEO, publisher, and chief scientist of the nonprofit foundation Environmental Health Sciences. With Dianne Dumanoski and Theo Colborn, he also co-authored the book *Our Stolen Future*, which described the science of endocrine disruption and brought attention to the fact that endocrine-disrupting chemicals (EDCs) can interfere with fetal development. Myers was recognized by the Endocrine Society with the 2016 Outstanding Public Service Laureate Award, citing his key role in changing the relationship between scientists and the press, and improving the accuracy of scientific reporting.

The NIEHS Champion of Environmental Health Research Awards recognize “outstanding researchers, leaders, and communicators that have contributed to the NIEHS mission to discover how the environment affects people in order to promote healthier lives.”

- ▶ People who have proven cases of growth hormone deficiency and no contraindications should be offered growth hormone replacement as a treatment option.
- ▶ Premenopausal women who have central hypogonadism, a condition where the sex glands produce minimal amounts or no hormones, can undergo hormone treatment, provided there are no contraindications.
- ▶ People producing abnormally large volumes of dilute urine should be tested for central diabetes insipidus — a rare condition that leads to frequent urination — by analyzing the concentration of their blood and urine.
- ▶ For patients who have low levels of glucocorticoid hormones, hydrocortisone can be given in a daily single or divided dose.
- ▶ All hypopituitarism patients should be instructed to obtain an emergency card, bracelet, or necklace warning about the possibility of adrenal insufficiency.
- ▶ Patients who are suspected of having an adrenal crisis due to secondary adrenal insufficiency should receive an immediate injection of 50 to 100 milligrams of hydrocortisone.
- ▶ People who have central adrenal insufficiency should receive the lowest tolerable dose of hydrocortisone replacement on a long-term basis to reduce the risk of metabolic and cardiovascular disease.

Other members of the Endocrine Society task force that developed this guideline include: Ibrahim A. Hashim, PhD, of UT Southwestern Medical Center in Dallas, Texas; Niki Karavitaki, MSc, PhD, FRCP, of the University of Birmingham and Birmingham Health Partners in Birmingham, U.K.; Shlomo Melmed, MD, of Cedars-Sinai Medical Center in Los Angeles, Calif.; M. Hassan Murad, MD, of the Mayo Clinic in Rochester, Minn.; Roberto Salvatori, MD, of Johns Hopkins University School of Medicine in Baltimore, Md.; and Mary H. Samuels, MD, of Oregon Health & Science University in Portland.

This guideline was co-sponsored by the American Association for Clinical Chemistry, the Pituitary Society, and the European Society of Endocrinology.

The guideline was published online at www.endocrine.org/hormonalreplacement ahead of print.

In Memoriam: Melvin M. Grumbach, MD

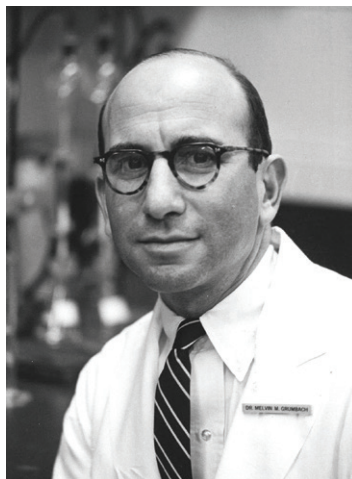
Endocrine Society past-president (1981 – 1982) Melvin Malcom Grumbach, MD, known to the world as Mel, passed away October 4, 2016, at the age of 90. Mel was the Edward B. Shaw Professor of Pediatrics, Emeritus, and former chairman of the Department of Pediatrics (1966 – 1986) at the University of California, San Francisco (UCSF), and was a world leader in every phase of pediatrics and endocrinology.

Born December 21, 1925, Mel received his MD from Columbia University, New York City, New York, in 1948, and after three years of pediatric residency in New York and two years in the U.S. Air Force, joined Lawson Wilkins' legendary program in pediatric endocrinology at Johns Hopkins University. After two short years and 10 publications at Hopkins, Mel returned to Columbia University before moving to University of California – San Francisco as chair of Pediatrics in 1966, where he morphed a regional clinical program into one of the preeminent academic departments in the country.

Mel had a tremendous impact on the specialty of pediatric endocrinology. From 1956 to 1990, he supervised the training of 82 fellows from 15 countries on five continents. Of these, 42 became professors, 40 became division chiefs, 14 became department chairs, and two became deans. No single individual trained as many leaders or had a broader impact on pediatric endocrinology.

Mel was known as the world's foremost pediatric endocrinologist. His early work delineated chromosomal dynamics and chromosomal disorders, then, with the late Selma Kaplan, MD, and his longtime friend Felix Conte, he studied the hormonal basis of sexual differentiation, growth, and puberty in children. His work defined much of our present knowledge of the hypothalamic-pituitary axis and the clinical management of its disorders. Overall, Mel published 389 research papers, reviews, and book chapters.

Mel was a ubiquitous force in academic leadership. He protected the time of young faculty, encouraged them to get grants, and fought for lab space. He was elected president of the Association of Medical School Department Chairs (1973),



the Lawson Wilkins Pediatric Endocrine Society (1975), the Western Society for Pediatric Research (1978), the Endocrine Society (1981), and the American Pediatric Society (1989).

Mel's research, teaching, and leadership were widely recognized: He received the Endocrine Society's Fred Conrad Koch Lifetime Achievement Award (1992), its highest award; the Lifetime Achievement Award from the American Academy of Pediatrics (1996); the John Howland Award from the American Pediatric Society (1997), the highest award in

American pediatrics, and was the first recipient of the Judson J. Van Wyk Prize for career achievement from the Lawson Wilkins Pediatric Endocrine Society (2006). He was elected to the Institute of Medicine (1983), the American Academy of Arts and Sciences (1995), and the National Academy of Sciences (1995); he received honorary doctorates from the University of Geneva (1991), the University of Paris 5 (René Descartes) (2000), and the University of Athens (2008), and was awarded the UCSF Medal in 2010.

Mel always believed that his legacy was not in the papers he wrote or awards he received, but in the people he taught. He created a vibrant, dynamic Pediatric Endocrine Program and Department of Pediatrics at UCSF. The staying power of this program speaks volumes for Mel. Beyond UCSF, his training of deans, chairs, and chiefs is unequalled; his influence unmatched; his impact all-pervasive. One cannot write the history of endocrinology or of UCSF without writing of Mel.

Walter L. Miller, MD
Distinguished Professor, Emeritus
University of California, San Francisco
Emeritus Chief of Endocrinology
UCSF Benioff Children's Hospitals

Gifts to honor Grumbach's life may be donated to the UCSF Foundation, UCSF Department of Pediatrics, 550 16th Street, San Francisco, CA 94158-2549, attn: Grumbach Research Award.

John W. Funder Awarded 15th Endocrine Regulations Prize



John W. Funder, MD, Prince Henry's Institute Victoria, Australia, was awarded the 15th Endocrine Regulations Prize of the Fondation IPSEN for his pioneering work on the endocrine aspects of arterial hypertension,

specifically on primary aldosteronism (PA) at the ICE-CSE (International Congress of Endocrinology – Chinese Society of Endocrinology), in Beijing on September 1.

Funder served as the chair of the task force that created the recently published article “The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline,” which was featured in the September issue of *Endocrine News*.

“In the past eight years, we have come to recognize that primary aldosteronism, despite being quite common, frequently goes undiagnosed and untreated,” Funder says in the article. “This is a major public health issue. Many people with primary aldosteronism are never screened due to the associated costs. Better screening processes are needed to ensure no person suffering from primary aldosteronism and the resulting risks of uncontrolled high blood pressure goes untreated.”

Over the past decade, Funder's contributions have been largely in the field of primary aldosteronism. His current activities are two-fold: a re-examination of the prevalence of PA combining evidence from around the world that its true prevalence may be of the order of 50%, and to show that even at the currently accepted prevalence <1% of hypertensives are ever screened, and thus that >99% of PA patients are never appropriately treated, leading to a reasoned case for inclusion of a low-dose Mineralocorticoid receptor antagonist in the first-line therapy for all hypertensives.

“The Fondation IPSEN Endocrine Regulations Prize is a true honor,” Funder says. “I am delighted to be counted among the recipients for this prestigious award.”

UNCOMMON STRENGTH

Rare Endocrine Diseases Highlighted in New Awareness Campaign

A new global campaign has been launched by Alexion Pharmaceuticals, Inc., to raise awareness of bone disorder hypophosphatasia (HPP), metabolic disease lysosomal acid lipase deficiency (LAL-D), and other rare diseases.

Launched in September, Uncommon Strength celebrates the extraordinary resilience and inner strength of individuals impacted by these diseases. Aside from HPP and LAL-D, the other diseases highlighted are genetic deficiency atypical hemolytic uremic syndrome (aHUS) and blood disorder paroxysmal nocturnal hemoglobinuria (PNH). Alexion will provide support with educational information as well as interactive social media elements to unite the community.

People living with rare diseases, and their families, must demonstrate “uncommon strength” as they persevere to find answers about their diseases. Reaching a diagnosis for a rare disease can be a long and challenging experience because the conditions are often unknown, misunderstood, or misdiagnosed. In fact, the average time from a person's first symptom to receiving an accurate diagnosis of a rare disease is nearly five years, during which he or she may visit more than seven physicians, according to a 2013 article in the *Journal of Rare Diseases*.

“At Alexion, we are inspired by patients and families living with rare diseases and recognize the inner strength and perseverance they must have to face the ongoing challenges they encounter, such as receiving an accurate and timely diagnosis and appropriate medical care,” David Hallal, CEO, Alexion, says in a statement. “...Patients with rare diseases are true heroes, and it is our hope that the Uncommon Strength campaign will amplify their voices and generate the much needed awareness to reach more patients and families who are still seeking answers.”

For more information, go to www.UncommonStrength.com. 

Parathyroid and Osteoporosis 2016

Philadelphia, November 11

Participants will discuss and debate difficult cases including cost-effective management of osteoporosis, management of hypoparathyroidism, and surgical treatment of parathyroid disorders. This course is designed for all specialists working in general and endocrine surgery, endocrinology, otolaryngology, medical imaging, pathology, and family medicine.

jeffersoncme@jefferson.edu

PPTOX V

Fukuoka, Japan, November 13 – 16

The international summit of Prenatal Programming and Toxicity (PPTOX) is dedicated to cutting-edge discussion of environmental hazards during early life and long-term consequences. PPTOX is one of the premier international venues for scientists to evaluate current knowledge and guide forward momentum for this burgeoning field.

www.pptoxv.com

Translational Reproductive Biology and Clinical Reproductive Endocrinology

New York, N.Y., November 17 – 20

The objective of this conference is to offer an authoritative update for reproductive clinicians and researchers, focusing on new translational developments in the field of reproductive biology and physiology, as well as clinically relevant patient-care issues. The goal is to offer both basic scientists and clinicians a place to share ideas and to inform them of paradigm changes and significant developments that they may not hear about anywhere else.

<http://frm.cme-congresses.com/>

Saudi Arabia Highlights of ENDO

Al-Khobar, Saudi Arabia, November 30 – December 1

Held in conjunction with the Saudi Diabetes & Endocrine Association (SDEA), this two-day intensive conference covers some of the many highlighted sessions featured at **ENDO 2016** in Boston in April. Among the topics covered are diabetes, thyroid, osteoporosis and bone health, pituitary disorders, women's and men's health, and adrenal disorders. This program has been tailored specifically for practicing clinicians, clinical scientists, and early career and in-training clinicians.

www.endohighlights.com



Orlando, Florida



Orlando, Fla., April 1 – 4, 2017

The Endocrine Society holds its annual meeting within arm's reach of the "happiest place on Earth" in Orlando. With over 9,000 attendees, nearly 3,000 abstracts, and over 200 other sessions, it is the leading global meeting on endocrinology research and clinical care. The meeting also hosts other satellite and pre-conference events, such as our Early Career Forum and Hands-On Thyroid Workshops.

www.endocrine.org/endo-2017

14th Annual World Congress on Insulin Resistance Diabetes and Cardiovascular Disease

Universal City, Calif., December 1 – 3

The WCIRDC presents the cutting edge of metabolic research and helps clinicians translate both preclinical and clinical data into their approach to day-to-day clinical practice. The distinguished global faculty, combined with the congress' unique bench-to-bedside approach, has culminated in a state-of-the-art program. These expert and creative faculty help promote a new understanding for metabolic diseases.

www.wcir.org

9th World Congress on Prevention of Diabetes and Its Complications

Atlanta, December 2 – 4

This congress combines theory and practice providing a forum for physicians and scientists worldwide to disseminate and discuss new

information on causes, prevention, best practices, and standards of care. Because of the diverse nature of the target audience, educational formats will include didactic lectures, panel debates, case presentations, and concurrent sessions allowing the participant to choose from a wide range of topics and formats.

www.wcpd9.com/home.php

Sixth International Conference on Endocrinology

Dallas, Texas, December 5 – 7

This year's annual congress highlights the theme "New recommendations and practical approaches in the treatment of endocrine disorders," which reflects the emerging progress being made in endocrine disease research as discoveries in the lab are translated into treatments in an increasingly targeted and precise manner.

<http://endocrinology.conferenceseries.com/>

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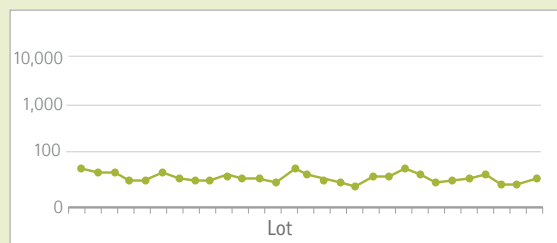


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WHY ENDOCRINOLOGY?

Liberated to a Life of Science

BY **BRYAN A. WILSON, PHD, MBA**, SPIRE Postdoctoral Fellow, McAllister Heart Institute, University of North Carolina at Chapel Hill

My passion for science and research was initially inspired by my mother. I grew up in a single-parent home and was fortunate to have a loving and strong mother who reinforced my dreams. She was the first person to expose me to science. In her efforts to motivate my science inquisitiveness, I remember receiving Christmas gifts in the form of a Smithsonian chemistry set and my first microscope. At that time, I did not fully understand her actions, but I would later come to realize that my mother was liberating me to a life of science. She gave me the confidence to believe in myself and assured me that it was okay to be different. More importantly, she assured me it was okay to love science.

My first introduction to the field of endocrinology occurred in the summer of 2007 when I participated in the Wake Forest School of Medicine's Excellence in Cardiovascular Sciences program. During the eight-week program, I was mentored by Mark C. Chappell, PhD.

Working with him laid the foundation of my science career trajectory and gave me the motivation to apply to graduate school. After graduating from Louisiana State University in 2008 with a bachelor's degree in biological/nutritional sciences, I returned to Wake to complete a one-year NIH-NIGMS-sponsored Post Baccalaureate Research Education Program (PREP). My experience in this program was a defining moment, one in which I could truly envision myself becoming an independent investigator and making a difference. In 2010, I was successfully admitted and matriculated as a graduate student at Wake Forest School

of Medicine. Dr. Chappell served as my thesis adviser, and my research focused on understanding mitochondrial and intracellular signaling of the renin-angiotensin system (RAS), which is a classic endocrine system that regulates blood pressure and fluid homeostasis. More specifically, my studies sought to elucidate how dysregulation of the RAS leads to uncontrollable hypertension and cardiovascular disease. Currently, I am a postdoctoral fellow in the lab of Monte S. Willis, MD, PhD, MBA, at the University of North Carolina at Chapel Hill. My research project specifically investigates a muscle-specific protein (MuRF-1) that directly regulates muscle mass size and is involved in mitochondrial function and exercise performance in vivo.

“
Positive change begins with a plan and can only be successful if one has the courage to embrace new directions and the persistence to overcome any obstacle.
”


My graduate school research opened many career doors and prompted me to attend my first ENDO meeting in 2013. During this meeting, I won a travel award and was selected as a Presidential Poster Competition Award Winner. I just remember feeling completely at home at the ENDO meeting. Everyone I met was very friendly and engaging, and the researchers there seemed just as interested in me as a person as well as my research. I especially remember my first interactions with the Committee on Diversity and Inclusion and its various sponsored activities. The Endocrine Society's associate director, professional development Kirsta Suggs and chief program officer Wanda Johnson were some of the first individuals I met along with Rocio I. Pereira, MD. During this meeting, I also attended a special workshop where I learned about the Future Leaders Advancing Research in Endocrinology (FLARE) program, and in 2014, I was selected

To celebrate 100 years of the Endocrine Society, throughout 2016 *Endocrine News* is running a “Why Endocrinology?” column in each issue. If you'd like to share your story with our readers, contact Mark A. Newman at mnewman@endocrine.org.

as a fellow. Becoming a FLARE fellow was life changing for me because it gave me the opportunity to serve the Society and its various initiatives. Often times in life, we are looking for ways in which an opportunity or person could serve us, however, a person can gain so much more by serving others. As a FLARE intern, I worked very closely with the Minority Access Program (MAP) and recruited undergraduates at the Annual Biomedical Research Conference for Minority Students (ABRCMS).

Aside from my research explorations, my long-term goals involve developing a creative niche in endocrinology by applying innovative approaches toward biotechnology and promoting the discovery of novel technologies. To facilitate these pursuits, I earned a dual PhD/MBA degree. With this unique training, I hope to flourish within a career that will

allow me to foster improved communication and relationships between industry and academia with a focus on treating endocrine disorders. Ultimately, I would like to facilitate the creation of standardized academic curricula and professional training by which students, clinicians, and researchers are exposed to business applications.

Positive change begins with a plan and can only be successful if one has the courage to embrace new directions and the persistence to overcome any obstacle. My mother and the aforementioned experiences have contributed to my commitment to pursue a career that leverages both my endocrinology research and business knowledge. Indeed, I believe these experiences have strengthened my resolve to develop a successful science career to continue my scientific contributions and mentorship of future trainees. 



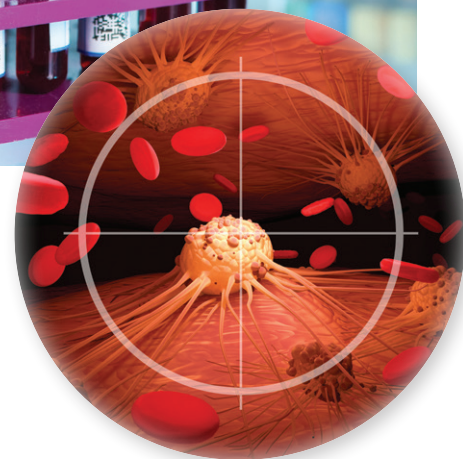
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100 YEARS
OF HORMONE SCIENCE TO HEALTH

BY DEREK BAGLEY

Blood Biomarkers Identified in Drug-Resistant Cancer Tumor Cells



While searching for a non-invasive way to detect prostate cancer cells circulating in blood, Duke Cancer Institute researchers have identified some blood markers associated with tumor resistance to two common hormone therapies.

In a study published online this month in the journal *Clinical Cancer Research*, the authors reported that they isolated multiple key gene alterations in the circulating prostate tumor cells of patients who had developed resistance to abiraterone or enzalutamide.

The study, focusing on a small number of patients, used blood analysis technology to demonstrate that circulating tumor cells detected in blood have the potential to reveal important genetic information that could guide treatment selection in the future and suggest targets for new therapies.

“We have developed a method that allows us to examine the whole genome of rare circulating cancer cells in the blood, which is unique in each patient, and which can change over time during treatment,” says senior author Andrew Armstrong, MD, a medical oncologist and co-director of Genitourinary Clinical-Translational Research at the Duke Cancer Institute (DCI).

“Among the genomic changes in the patients’ individual cancers, we were able to find key similarities between the cancer cells of men who have hormone-resistant prostate cancer,” Armstrong says. “Our goal is to develop a ‘liquid biopsy’ that would be non-invasive, yet provide information that could guide clinical decisions.”

Armstrong and colleagues from the DCI and the Duke Molecular Physiology Institute used array-based comparative genomic hybridization to analyze the genome of the circulating tumor cells of 16 men with advanced, treatment-resistant prostate cancer. The technique enabled them to determine which genes had extra copies and which regions were deleted.

Findings: The researchers conclude: Focusing on genes that have previously been implicated in tumor progression, plus other genes important to cancer biology, the researchers found changes in multiple genetic pathways that appear to be in common among the men’s circulating tumor cells. “Our research provides evidence supporting the ability to measure gains and losses of large-scale sections of the circulating tumor cells genome in men with prostate cancer,” says co-author Simon Gregory, PhD, director of the Section of Genomics and Epigenetics at the Duke Molecular Physiology Institute. “We are now evaluating this method combined with higher resolution DNA mutational studies and measurements of RNA splice variants in CTCs to determine their clinical relevance to patients and treatment resistance.”

Nighttime Hot Flashes May Spark Mild Depression

Hypoestrogenic women who perceive a high number of nighttime hot flashes and experience/have sleep disruption are more vulnerable to menopause-associated depressive symptoms, according to a study recently published in *The Journal of Clinical Endocrinology & Metabolism*.

Researchers led by Hadine Joffe, MD, MSc, of Brigham and Women's Hospital and Dana Farber Cancer Institute at Harvard Medical School in Boston, Mass., point out that “[d]epressive symptoms increase when estradiol levels change markedly in association with both natural and surgical menopause” and that hot flashes are the “hallmark” symptom of menopause, occurring in up to 80% of women.

So the authors evaluated 29 healthy, premenopausal women between the ages of 18 and 45 and gave them a GnRH agonist (GnRHa) to simulate the decline in a woman's estrogen levels during menopause. The women took the GnRHa to suppress estrogen production in the ovaries for a four-week period, a treatment that mimics menopause and induces menopausal symptoms to varying degrees of intensity. Before and after the four-week time frame, researchers monitored the participants' sleep with polysomnography and checked their hormone levels. The participants completed mental health interviews at the beginning and end of the study.

“When women were awake long enough to later recall nighttime hot flashes, that perception contributed to mood disturbance in women whose estrogen levels had fallen,” Joffe says. “The association was independent of sleep disruption that the women experienced.”

The study found that women who reported experiencing frequent nighttime hot flashes were more likely to experience mild symptoms of depression than those who reported fewer or no nighttime hot flashes. Although researchers also monitored the women for physiological signs of nighttime hot flashes during the sleep study, they found only the women's perception of hot flash frequency — not the measured number of hot flashes — was linked to changes in mood.

Findings: Women who experienced sleep interruption also were more likely to exhibit symptoms of depression than women who got more sleep. Daytime hot flashes had no effect on the participants' mood. “The results of our research suggest menopausal women who report experiencing nighttime hot flashes and sleep disruption should be screened for mood disturbances,” Joffe says. “Any treatment of mood symptoms in this population also should incorporate efforts to address sleep and nighttime hot flashes.”

Premature or Early-Onset Menopause Linked to CVD Risk, Mortality

Women who experience premature or early-onset menopause may be at a greater risk of coronary heart disease, cardiovascular disease (CVD) mortality, and all-cause mortality, according to a study recently published online in *JAMA Cardiology*.

Researchers led by Taulant Muka, MD, PhD, of Erasmus University Medical Center, Rotterdam, the Netherlands, noted that as many as 10% of women experience natural menopause by the age of 45 years. If confirmed, an increased risk of CVD and all-cause mortality associated with premature and early-onset menopause could be an important factor affecting risk of disease and mortality among middle-aged and older women. To examine this issue, the researchers conducted a systematic review and meta-analysis of 32 studies (310,329 women) that met criteria for inclusion in the study.

Outcomes were compared between women who experienced menopause younger than 45 years and women 45 years or older at onset. The researchers found that overall, women who experienced premature or early-onset menopause appeared to have a greater risk of coronary heart disease (CHD), CVD mortality, and all-cause mortality but no association with stroke risk. Women between 50 and 54 years at onset of menopause had a decreased risk of fatal CHD compared with women younger than 50 years at onset.

Findings: Time since onset of menopause in relation to risk of developing intermediate cardiovascular traits or CVD outcomes was reported in four observational studies with inconsistent results. “The findings of this review indicate a higher risk of CHD, cardiovascular mortality, and overall mortality in women who experience premature or early-onset menopause when younger than 45 years,” the authors write. “However, this review also highlights important gaps in the existing literature and calls for further research to reliably establish whether cardiovascular risk varies in relation to the time since onset of menopause and the mechanisms leading early menopause to cardiovascular outcomes and mortality.”

Diets Avoiding Dry-Cooked Foods Can Protect Against Diabetes



At-risk individuals are encouraged to avoid dry-heat cooking processes such as grilling, in favor of poaching or steaming to reduce insulin resistance.

Simple changes in how we cook could go a long way toward preventing diabetes, say researchers at the Icahn School of Medicine at Mount Sinai. A new randomized controlled trial funded by the National Institutes of Health and by the National Institute of Research Resources, published in *Diabetologia*, found that obese individuals with signs of insulin resistance showed improvement simply by avoiding the intake of advanced glycation endproducts, or AGEs, a byproduct of cooking found most commonly in dry heat-cooked or heat-processed foods.


The study is a follow-up to a 2014 article published in the journal *Proceedings of the National Academy of Sciences*. In the earlier study, the researchers, led by Helen Vlassara, MD, professor emeritus of Geriatrics and Palliative Medicine and Medicine at the Icahn School of Medicine at Mount Sinai, confirmed that high levels of AGEs in the body can cause pre-diabetes characterized by increasing insulin resistance, as well as brain changes similar to Alzheimer's disease. This study focused more on diabetes risk.

"While food AGEs are prevalent, particularly in Western diets, our study showed that avoiding foods high in AGEs could actually reverse the damage that had been done," says Vlassara. "This can provide us with new clinical approaches to pre-diabetes, potentially helping protect certain at-risk individuals from developing full diabetes and its devastating consequences."

The researchers divided the study participants into two groups of obese individuals — one eating a regular diet, which is typically high in AGEs (Reg-AGE) and one with a diet low in AGEs (L-AGE). Members of the L-AGE group were instructed to avoid grilling, frying, or baking their food, in favor of poaching, stewing, or steaming.

At the beginning and end of the trial, blood and urine samples were analyzed to determine insulin resistance. The two groups showed similar levels of insulin resistance at the beginning; at the end, the L-AGE group showed significantly improved insulin resistance, as well as slightly decreased body weight and lowered levels of AGEs in the body. The Reg-AGE group had higher levels of AGEs and more markers of insulin resistance than during the baseline measurements.



Findings: "Elevated serum AGEs in individuals can be used as a marker to diagnose and treat 'at risk' obesity in patients," says Jaime Uribarri, MD, professor of medicine (Nephrology) at the Icahn School of Medicine at Mount Sinai, another investigator in the study. "Even without losing a significant amount of weight, a reduced AGE diet can help prevent diabetes in these patients." The researchers also found a positive effect on six key genes associated with the regulation of oxidant stress and inflammation. Four of these had been found to be suppressed at the baseline blood and urine analysis but were markedly increased at the end, including anti-inflammatory SIRT1 and adiponectin, as well as the receptor for the removal of AGEs, AGER1, and glyoxalase-1. 

“ **Insulin pumps are very beneficial in a patient who wants one.** I would argue that every patient with type 1 diabetes who fits the appropriate criteria for being able to use one — and we discuss those in the guideline — should be offered that as a choice. Providers shouldn’t say, ‘you must go on a pump because your control will get better,’ but rather, ‘a pump is one way to treat diabetes, these are your options.’ It is always the user who makes the device work.”

— ANNE L. PETERS, MD, professor at the Keck School of Medicine at the University of Southern California and chair of the committee that wrote the newly published “Diabetes Technology — Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline” in *Priming the Pump* on p. 30.

FROM THE CENTURY OF ENDOCRINOLOGY TIMELINE

1957:

Enovid Approved by the FDA



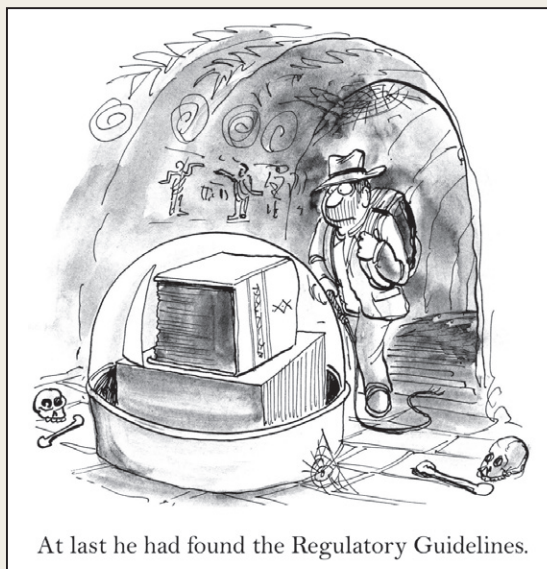
In 1957, Enovid was approved by the U.S. Food and Drug Administration (FDA) as a treatment for menstrual disorders rather than as a contraceptive. Originally, the drug had been developed as an oral contraceptive. The FDA mandated a warning on the label that it would prevent ovulation. It was not until 1960 that the FDA approved the Pill’s use for method of birth control in 1960.

For more about the *Century of Endocrinology*, go to: www.ESCentennial.org/timeline.

192,000

— SOURCE: CONSUMER REPORTS

The number of U.S. physicians that have had at least one malpractice payout since 1990, according to the National Practitioner Data Bank (NPDB), part of the Department of Health and Human Services.



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28

Number of maternal deaths — deaths due to complications from pregnancy or childbirth — per 100,000 births in the U.S. in 2013, up from 23 in 2005.

— SOURCE: INSTITUTE OF HEALTH METRICS AND EVALUATION

53%

Rate of diabetes remission 10 years after gastric bypass surgery (compared to just medical management).

— SOURCE: ANNALS OF SURGERY

An anatomical illustration of a human torso, rendered in a translucent blue color. The internal organs, including the lungs, liver, stomach, and intestines, are visible. The pancreas is highlighted in a bright orange and yellow color, making it stand out from the rest of the body. The background is dark, emphasizing the glowing blue and orange colors of the anatomy.

PANCREAS DONORS: **A KEY TO** a cure?

BY DEREK BAGLEY

If you haven't heard of the JDRF Network for the Pancreatic Organ Donors with Diabetes aka nPOD, you will. nPOD is not just a research lab or a clearing house for pancreas tissue from donors with diabetes, **it's on the front lines to finding a cure.**

Last December, during the International Diabetes Federation World Diabetes Congress in Vancouver, British Columbia, Mark Atkinson, PhD, director of the Diabetes Institute at the University of Florida, Gainesville, presented **results from collaborative studies on viruses' roles in the development of type 1 diabetes.**

The objective of this work, he says, was to seek evidence of viral infections in the etiology of type 1 diabetes, and that investigators had “obtained reproducible data further supporting a potential association of viruses or other environmental agents with type 1 diabetes.” An important finding, to be sure, since that could potentially mean the first step in a cure or vaccine for type 1 diabetes.

But what's also interesting, beyond the finding itself, is the method of obtaining said data — the JDRF Network for the Pancreatic Organ Donors with Diabetes (nPOD), of which Atkinson is the executive director together with Alberto Pugilese, MD. nPOD collects pancreata and other tissues from patients with type 1 diabetes and disseminates those tissues to approved investigators around the world, with one of the main goals being collaborative research using real-time data sharing. Next year will mark nPOD's 10th anniversary, and the group is currently tracking more than 180 projects in 19 countries.

Atkinson explains that about 2.5 million people die in the U.S. each year, and of those, around 100,000 become some sort of tissue donor. Of those, 9,000 become solid organ donors and 5,000 of those donate their organs to research. All of this is overseen by 58 Organ Procurement Organizations (OPOs) around the country. The nPOD staff is on call 24 hours a day, seven days a week, 365 days a year, for obvious reasons. “We at nPOD have relationships with nearly all of these [OPOs] to the point if someone is an organ donor with type 1 diabetes (or diabetes of another form) and is willing to donate their organs to research, we receive a call,” he says.



Micrograph of pancreas tissue, typical pancreatic tissue in the jejunum tissue. The tissue samples are collected from donors and stained for various markers, and then converted to digital slides, and stored in an online database.

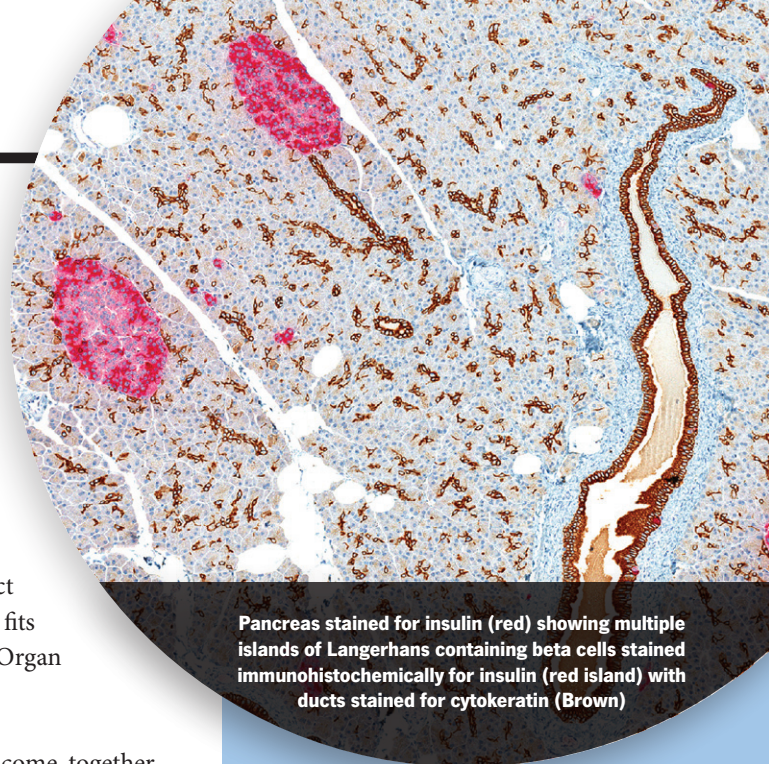
“**The disease is still killing,** and believe me when you get a phone call at three in the morning and they tell you a 12-year-old girl died because of diabetes, it breaks your heart.”

— ALBERTO PUGLIESE, MD, CO-EXECUTIVE DIRECTOR, JDRF NETWORK FOR THE PANCREATIC ORGAN DONOR WITH DIABETES (NPOD)

The University of Florida is the central hub for tissue collection, and the tissues are transplantable quality and are handled as if they are being transplanted into someone. Investigators who want to use these tissues submit an application, are approved by a scientific committee (comprising some of the top diabetes researchers) based on what they want to study, publish papers, and supply their raw data back to nPOD. All tissues are provided free to investigators with, as Atkinson says, “the hope that major lessons will be learned.”

Playing Catch Up

When nPOD started in 2007, one of its missions was to prove that viable, high-quality pancreata could be obtained from organ donors that were suitable for research about type 1 diabetes. Biopsy of the pancreas in living patients is not practiced because it's a surgery with potential for complications, and thus organ donors are the only other possible source of human pancreata with type 1 diabetes. Mouse models and *in vitro* models provide important data, but clinical and translational trials have had limited success; moreover, there are critical questions about the causes and molecular basis of the disease that mouse models cannot answer. Atkinson says that the diabetes-related community had previously elected to deemphasize attempts to study human tissues, especially the pancreas. “I really believe we find ourselves in the current state of diabetes care and research (type 1 and 2) because we have, for decades, ignored what other fields have placed emphasis on, be it psoriasis (autoimmunity) or cancer — that is, on studies of human tissues,” he says. “Pathology is a fundamental basis of medicine, but we, as a community, have seen aversion to such notions and placed them elsewhere. With this, we have fallen behind other diseases.”



Pancreas stained for insulin (red) showing multiple islets of Langerhans containing beta cells stained immunohistochemically for insulin (red islet) with ducts stained for cytokeratin (Brown)

nPOD currently has tissue samples from 406 pancreata, including 141 from donors who had type 1 diabetes, 41 from donors who had type 2 diabetes, and 160 controls. The tissue samples are collected and stained for various markers, and then converted to digital slides, and stored in an online database. Investigators can access the database and see cases based on different demographics, clinical histories, and histopathological features that characterize each particular pancreas. “They can select cases based on all of this information to choose ones that are better fits for their studies,” says Irina Kusmartseva, PhD, director of nPOD’s Organ Processing and Pathology Core (OPPC).

“This is the first time that the type 1 diabetes community has come together to recover and study the tissues directly involved at the site of autoimmune destruction, the pancreas, and the surrounding lymphoid tissue,” says David M. Harlan, MD, chief of the Diabetes Division at the University of Massachusetts School of Medicine.

So nPOD is providing human tissues to investigators with an interest in the pathogenesis of type 1 diabetes, but these human tissue samples are limited, again, for obvious reasons. Collecting samples from a donor around the time of diagnosis is very difficult, because, fortunately, most people no longer die soon after a diagnosis of type 1 diabetes. “Incidentally,” says Alberto Pugliese, MD, co-executive director of nPOD, “that is the pancreas that everybody wants [to study]. We have a few of those, but by necessity, we have a limited supply.”

But this predicament also led to an opportunity for nPOD and the researchers who utilize these tissue samples — collaborative science using the same materials. It’s a different scenario than say, a researcher taking 10 blood samples and 10 controls and publishing the findings, and then another researcher taking 10 different blood samples and 10 different controls and publishing those findings. “When you have studies where multiple people can look at the same patient, at the same samples, I think you can make a lot more sense of what you’re looking at,” Pugliese says.

Atkinson and Pugliese act as managers for the almost 200 ongoing projects around the world. Neither is very hands on with the research projects. Rather, they act as advocates for all nPOD efforts, attracting researchers who may be working on interesting studies, overseeing the application process for the pancreata (“It’s not like going to the supermarket,” Pugliese says), and encouraging investigators to collaborate with one another. Pugliese is very active in promoting collaboration, the formation of working groups, and in helping nPOD investigators obtain funds for the research. For example, he has obtained funds from both the JDRF and the Helmsley Charitable Trust to support collaborative research conducted by nPOD investigators.

AT A GLANCE

- ▶ The JDRF Network for Pancreatic Organ Donors with Diabetes (nPOD) collects pancreata and other tissues from people with type 1 diabetes and distributes them to approved investigators.
- ▶ One of nPOD’s main goals is collaborative research; there are currently 180 projects in 19 countries using tissue samples provided by nPOD.
- ▶ The hope is to find a cure for type 1 diabetes, since the very nature of nPOD is a reminder to all involved that many people still die from complications of type 1 diabetes.



“Moving forward, we see notions of big data, genetics, single cell technologies, and integration of clinical data and new and novel ways to represent the future for nPOD. **We believe this new generation of studies will be vital for efforts for disease prevention/cure.**”

— MARK ATKINSON, PHD, DIRECTOR, DIABETES INSTITUTE,
UNIVERSITY OF FLORIDA, GAINESVILLE

Sorting Cells

In fact, one example of this collaboration comes from Harlan's institution, where he and his colleague Sally Kent, MD, both have ongoing projects with tissues provided by nPOD. Kent has been working with nPOD since the beginning and is currently studying a number of things. One is to look at B lymphocyte phenotype and function, the cells that secrete autoantibodies and also participate in antigen presentation to stimulate T cells. Another is to study the T cells that are the final killers of the insulin-producing cells in the pancreas. Kent pioneered and continues to work on studies of such cells isolated from the spleen and pancreatic draining lymph nodes (PLN) from control donors and from donors with type 1 diabetes. More recently, she and several of her nPOD colleagues have studied T cells that are present in inflammatory lesions of the pancreatic islets in type 1 diabetes.

Harlan says that he and Kent receive aliquots of isolated islets from nPOD that are also shared with multiple other investigators at several institutions. Kent has recovered live islet infiltrating T cells from these islets and has expanded the T cells in culture to then determine the antigen target recognized by those T cells. Harlan's team's work has been focused on the endocrine cells within the isolated islets. They have developed techniques to break the islets up into their individual cellular components, then sort those single cells into their various cell subsets — insulin-producing beta-cells, glucagon-producing alpha-cells, and somatostatin producing delta cells. Then, using next-generation RNA sequencing,

they have been able to determine the gene expression of those individual cell subsets to compare, for instance, the beta-cell transcriptome found in individuals with type 1 diabetes with that found in age-similar control individuals. “These kinds of studies have only been technically possible within the past few years,” Harlan says.

“Looking at the endocrine cells from donors with type 1 diabetes, we are finding that insulin producing beta-cells can be isolated several years after disease diagnosis,” Harlan continues, “and are just beginning to understand how the immune and metabolic stress on those cells influences their gene expression patterns.”

Harlan says that his team is pursuing gene expression patterns found within donor endocrine cells. “The hope is that we'll uncover therapeutic targets to either weaken the T cells that are killing the pancreatic beta-cells or find a gene expression pattern that protects those cells from dysfunction and death,” he says.

Pursuing a Cure

Of course, the main goal of nPOD — and all the researchers the group supports — is finding a cure for type 1 diabetes. No one knows when this breakthrough will come, but nPOD's work may hold the key. For Atkinson, the answer is to stop relying on what was taught decades ago, pointing to what nPOD has accomplished in just 10 years. “Moving forward, we see notions of big data, genetics, single cell technologies,

and integration of clinical data and new and novel ways to represent the future for nPOD,” he says. “We believe this new generation of studies will be vital for efforts for disease prevention/cure.” He invites whoever reads this article to reach out to nPOD in order to identify ways to help them do what they do better. (See “Getting Involved” sidebar).

Kusmartseva says that by being able to look at the entire pancreas, they’re learning that type 1 diabetes is a heterogeneous disease. For example, they’ve learned that a child with type 1 diabetes still has a significant number of insulin-positive islets. They’ve also been able to look at type 1 diabetes-positive pancreata that have some areas totally devoid of beta-cells while other parts of the same pancreas look normal. “The big breakthrough would be finding a cure, and then we’d be out of business,” Kusmartseva says with a laugh. “But I wouldn’t mind.”

And again, it’s the collaborative nature of these projects that give hope to these investigators. “One never knows where the breakthrough to cure type 1 diabetes might come,” Harlan says, “but nPOD is certain to have played a role when that Holy Grail is found.”

Throughout the year, nPOD holds conference calls and webinars with the researchers, during which they discuss findings, what they want to work on next, and so on. So instead of all the researchers who shared the samples waiting for each other to be published, there’s real-time data sharing and peer review. Because of the very nature of nPOD, dealing with human tissues, donations that mean the worst has happened to someone — Pugliese sees this collaboration as a way of accelerating discovery, which means the sooner doctors can start saving lives. He’s one of the nPOD staff on call 24/7, in case a donation is ready to be made. “The disease is still killing,” he says, “and believe me when you get a phone call at three in the morning and they tell you a 12-year-old girl died because of diabetes, it breaks your heart.” ^{EN}

BAGLEY IS THE ASSOCIATE EDITOR OF *ENDOCRINE NEWS*. HE WROTE ABOUT AN ENCAPSULATED FOLLICULAR VARIANT OF PAPILLARY THYROID CARCINOMA BEING CLASSIFIED AS A NON-CANCEROUS THYROID TUMOR IN THE OCTOBER ISSUE.



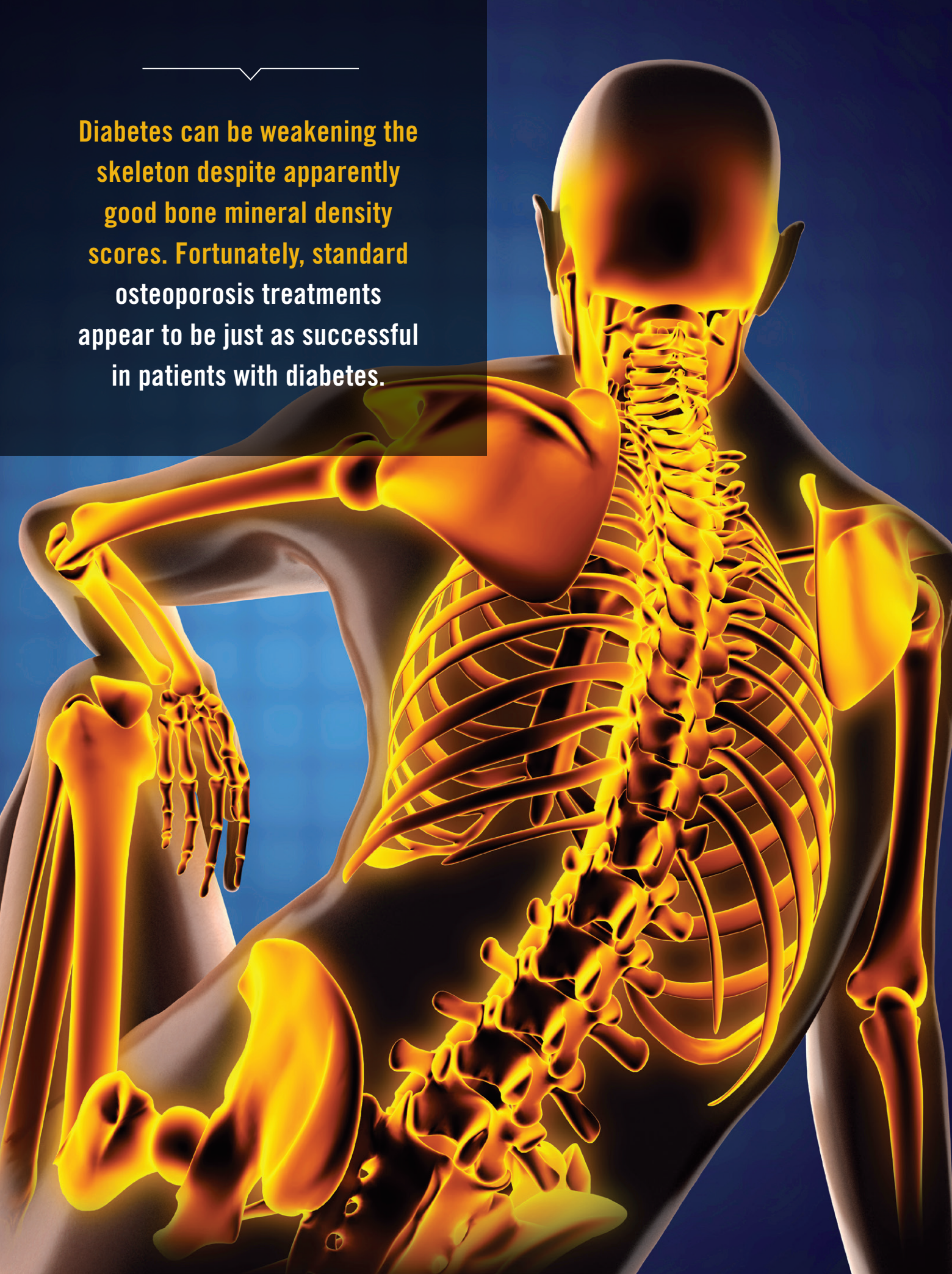
Getting Involved

If you are a medical professional and become aware of the death or impending death of a patient near the time of diagnosis of type 1 diabetes, you could help by involving your local OPO and/or by contacting nPOD, 24/7. The OPO has professionals who can discuss the option of organ donation with the family and work routinely with nPOD. Interested investigators can become part of one of nPOD’s Working Groups:

- ▶ **nPOD-V (Viral)**, formed to investigate the role of viruses in T1D;
- ▶ **nPOD-A (Autoimmunity)**, which studies autoimmune responses through the pancreas and lymphoid tissues;
- ▶ **nPOD-ECM (Extracellular Matrix)**, focused on whether islet and lymph node extracellular matrix components are involved in T1D;
- ▶ **nPOD-T (Transplantation)**, which studies transplanted human pancreatic tissues;
- ▶ **nPOD-O (Omics)**, which looks at genetic factors with genomics, genetic expression, and epigenetic approaches; and
- ▶ **nPOD Pancreas Slices Group**, which is developing novel methods to conduct ex-vivo manipulation and functional analysis of pancreas slices.

For more information on nPOD, visit jdrfnpod.org. You can also call (352) 273-8277 or email nPOD@pathology.ufl.edu. To refer a potential organ donor, please call 866-731-6585, 24/7.

Diabetes can be weakening the skeleton despite apparently good bone mineral density scores. Fortunately, standard osteoporosis treatments appear to be just as successful in patients with diabetes.



Diabetes

BY ERIC SEABORG

& BONES:

AN UNDERAPPRECIATED COMPLICATION

The damage that diabetes can do to bones is a complication that many endocrinologists do not adequately appreciate, say researchers in the field. The danger is insidious because bone mineral density (BMD) scores cannot be taken at face value — diabetes patients are at much higher risk for fracture compared with patients without diabetes who have the same BMD scores.

Guidelines for diabetes care recommend evaluating patients at least annually for long-term complications, such as heart, eye, kidney, and nerve disease, and skeletal complications should be added to that list, says Vikram V. Shanbhogue, MD, PhD, of the Endocrinology Department at Odense University Hospital in Denmark. He says that several European guidelines don't even mention bone as a complication, and "the American Diabetes Association at least mentions bone fragility or osteoporosis as a comorbid condition in diabetes," but the potential complication deserves a higher profile.

The evaluation of a type 2 diabetes patient's status is difficult because their BMD T-scores are hard to interpret — it appears that the risk point is as much as a half to a full standard deviation higher in type 2 diabetes, Shanbhogue says. So, a diabetic woman with a T-score of -1.5 could have the same risk as a nondiabetic woman of the same age with a T-score of -2.5. "At -1.5, you would probably say it appears fine, but the patient still has an increased fracture risk," he says.

Anne V. Schwartz, PhD, MPH, of the University of California, San Francisco, School of Medicine, estimates that although "a nondiabetic woman with a T-score of -2.5 would be at a clinical threshold where you'd start considering pharmacological treatment, [perhaps we] should start thinking about this at a -1.9 or -2 threshold for a diabetic woman."

Evidence of Weakness

The source of this apparent bone weakness is not known for certain, but researchers are finding important differences between the bones of diabetes patients and people without diabetes. High-resolution peripheral quantitative computed tomography has shown "subtle differences in microscopic architecture [of the cortical bone] in diabetes patients," according to Mishaela R. Rubin, MD, associate professor of medicine at Columbia University Medical Center, New York. The tests show that there is an increase in the volume of the pores in the cortical compartment.

"This increase in porosity could actually weaken the bone, rendering it to be easily fractured," says Shanbhogue. "And the porosity is not picked up by our routine dual energy X-ray absorptiometry measurements."



This increase in porosity could actually weaken the bone, rendering it to be easily fractured.

“ I think it is important to emphasize the point that **skeletal deterioration is another diabetic complication.** We understand that patients who have poorly controlled diabetes are going to have worse bone quality, and that will predispose them to an increased fracture risk.”

— MISHAELA R. RUBIN, MD, ASSOCIATE PROFESSOR OF MEDICINE, COLUMBIA UNIVERSITY MEDICAL CENTER, NEW YORK

Another technique called reference point indentation tests the material quality of bone by measuring how far a tiny needle penetrates into the tibia. Deeper penetration reflects weaker bone quality, this time of the collagenous part of the skeleton. Rubin says that studies found a noticeable difference in this “organic matrix part of the bone,” with bone quality significantly lower in diabetes patients than in people without diabetes who have similar BMD scores.

A Familiar Culprit?

The possible culprit in the decrease in bone quality could be a familiar one — the accumulation of advanced glycation end-products (AGEs) that underlies many complications, such as retinopathy and peripheral neuropathy. Rubin and her colleagues wondered whether the increase in glycation in diabetes patients with the “proteins in the collagen becoming encrusted in sugar” could be related to the lower strength of the bones. “We used a skin test to see what the accumulation of these sugar glycation products was in the skin. We found that the more they were present in skin, the weaker the bone material quality was in the diabetes patients. But in the healthy patients, that relationship didn’t exist at all,” Rubin says.

How to Treat?

Another bone-related difference in diabetes patients is a slowing in the bone remodeling cycle — which raises the question of whether treatments for osteoporosis, particularly anti-resorptive drugs that suppress bone turnover, are effective in diabetes patients. Schwartz recently published a review of clinical trials and observational studies of the effects of anti-resorptive and anabolic therapies in diabetes patients. “Post hoc analyses of randomized trials indicate that raloxifene has similar efficacy for prevention of vertebral fractures in diabetic compared with non-diabetic patients,” she says. “Evidence from randomized clinical trials is lacking for anti-fracture efficacy of other osteoporosis therapies in diabetes. However, observational studies suggest that bisphosphonates are effective in preventing fractures in diabetes patients.”

In a separate analysis, “we found similar anti-fracture efficacy in diabetics and nondiabetics in trials of alendronate and zoledronic acid,” Schwartz says. She adds the caveat that there is only evidence for the use of drugs in type 2 patients, with virtually no data on type 1 patients. And the drugs have not been tested for efficacy in patients with better T-scores.

Whom to Treat?

But the issues of which patients to treat and when to begin treatment are open questions with no clear answers. Schwartz believes that question is ripe for a new guideline, and that a literature review could produce enough evidence, if only at the expert opinion level.

Shanbhogue says: “Treatment has to be individualized and probably has to be multifactorial, and include more than just T-scores and the usual considerations for osteoporosis.”



Shanbhogue believes that when a patient begins to have other complications, a clinician should be aware that bone problems could be starting as well: “For example, detecting eye disease is physically very easy, so if a patient has eye disease, I think that you should go ahead and at least screen for bone disease. We have studied patients with type 1 diabetes, and it seems that in these patients, in the absence of the regular long-standing complications of diabetes such as eye, kidney, or nerve disease, their bone structure appears to be normal. But if they have a manifest complication, such as eye disease or the others, then it appears that they have compromises in bone structure. We are following up these patients to see if this compromised structure would actually lead to increased fractures.”

Schwartz says: “The people with type 2 who have higher fracture risk are those with longer duration of diabetes — those with complications and those on insulin therapy.” Insulin is anabolic for bones so is not likely to be implicated in weakening them, but insulin therapy is a marker for longer duration of the condition and more complications.

Because many type 2 patients are overweight or obese — and thus may have acceptable-appearing bone mineral density scores — clinicians should not be lulled into a false sense of security.

“I think it is important to emphasize the point that skeletal deterioration is another diabetes complication,” Rubin says. “We know that these advanced glycation end-products accumulate in other tissues and can harm them. It is possible that the same thing is happening in the skeleton. We understand that patients who have poorly controlled diabetes are going to have worse bone quality and that will predispose them to an increased fracture risk.” ^{EN}

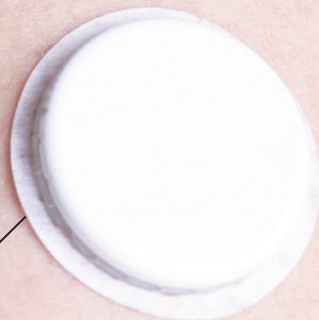
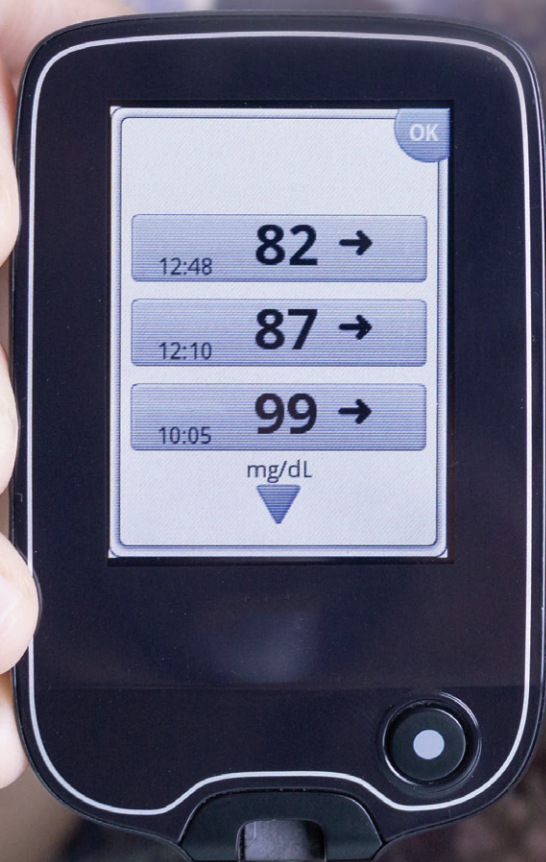
SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA. HE WROTE ABOUT THE ENDOCRINE SOCIETY'S NEW CLINICAL PRACTICE GUIDELINE ON TREATING PRIMARY ALDOSTERONISM IN THE SEPTEMBER ISSUE.

AT A GLANCE

- ▶ The higher risk of bone fracture in diabetes patients is a serious and common complication that merits the attention clinicians devote to better-known complications.
- ▶ The bone mineral density scores of diabetes patients can be misleading because at a given T-score, a type 2 diabetes patient has a higher fracture risk than a patient without diabetes.
- ▶ Standard osteoporosis treatments seem to work as well in diabetes patients as they do in the rest of the population.

PRIMING *the* Pump

BY ERIC SEABORG



Today's continuous glucose monitors provide alarms that indicate when blood glucose levels are above or below various thresholds and record trends in blood glucose levels.



Currently, there are five Food and Drug Administration-approved pumps available in the U.S. providing numerous features to improve accuracy, safety, dosing decisions, convenience, and overall usability.

Insulin pumps and continuous glucose monitors are changing quickly — and their impact is only expected to grow. Details on how these devices should be used with patients are outlined in a new Endocrine Society Clinical Practice Guideline.

New technologies for monitoring and delivering insulin are well-established in the treatment of diabetes, but their use is lagging behind their potential because many endocrinologists hesitate to implement them, according to the lead author of a new Endocrine Society clinical guideline.

The technologies should see greater use, but treatment should be individualized to the patient, says Anne L. Peters, MD, a professor at the Keck School of Medicine at the University of Southern California and chair of the committee that wrote the guideline, “Diabetes Technology — Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline.” The guideline was published in print in the November issue of *The Journal of Clinical Endocrinology & Metabolism* and is available online at www.endocrine.org/CPGDT.

Peters says that it was time for a guideline because technology is changing so quickly that it is difficult for both clinicians and researchers to keep up. “Technology keeps advancing so fast that when you study device A, by the time that paper comes out, device C [is already on the market]. The generations of technology are advancing too fast for the studies to keep up,” Peters says.

Despite its goal of writing an evidence-based guideline, the committee had to rely on clinical experience for some recommendations because of this difficulty in keeping up with the pace of technological change, Peters says. She acknowledges that the new technologies are not for everyone, but because they expand patients’ options, she’d like to see the choice made available to as many patients as possible.



“ Providers shouldn’t say, ‘you must go on a pump because your control will get better,’ but rather, ‘a pump is one way to treat diabetes, these are your options.’ **It is always the user who makes the device work.**”

— ANNE L. PETERS, MD, PROFESSOR, KECK SCHOOL OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES

MEASURING THE BENEFITS

“Insulin pumps are very beneficial in a patient who wants one,” Peters says. “I would argue that every patient with type 1 diabetes who fits the appropriate criteria for being able to use one — and we discuss those in the guideline — should be offered that as a choice,” even though studies show that pumps do not necessarily improve control of hemoglobin A1C compared with injections. “Providers shouldn’t say, ‘you must go on a pump because your control will get better,’ but rather, ‘a pump is one way to treat diabetes, these are your options.’ It is always the user who makes the device work.”

Peters says that studies often cannot measure subjective benefits of the technology. “A lot of the benefits [of technology] that I see have to do with the patient feeling safer or more in control, [or that their] quality of life is better, and those things are not well-measured in studies.”

The guideline stresses that treatment needs to be individualized, and it notes that technology can be difficult to learn to use, hence the caveat about patients being willing and able.

CONTINUOUS GLUCOSE MONITORS

The guideline recommends that adult type 1 diabetes patients consider using real-time continuous glucose monitors whether their A1C levels are well-controlled or above target. It also recommends the devices for short-term, intermittent use in willing adults with type 2 diabetes who have A1C levels greater than or equal to 7%.



The guideline also recommends the devices for short-term, intermittent use in willing adults with type 2 diabetes who have A1C levels greater than or equal to 7%.

The guideline emphasizes the need for education about the devices: “We suggest that adults with T1DM and T2DM who use continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring receive education, training, and ongoing support to help achieve and maintain individualized glycemic goals.”

Peters says that technology can be intimidating because it takes more training time and commitment on the part of the patient. The guideline acknowledges these challenges by recommending that before prescribing an insulin pump, the physician should assess the patient’s mental and psychological status, record of adherence, interest in the device, and availability for follow-up visits.

THE MARCH OF TECHNOLOGY

But it notes that modern pumps have come a long way from the early models, which “were heavy, crude syringe pumps with suboptimal quality control, inadequate battery power, and limited dosing flexibility that used infusion sets with rigid needles. Today, there are five Food and Drug Administration-approved pumps available in the U.S. providing numerous features to improve accuracy, safety, dosing decisions, convenience, and overall usability.”

Similarly, technological advances in monitors mean that patients and clinicians no longer need to rely on standard capillary blood glucose measurements — with their discrete values that supply a limited perspective on the constant daily changes in blood glucose levels. Today’s continuous glucose monitors provide alarms that indicate when blood glucose levels are above or below various thresholds and record trends in blood glucose levels. “Current models measure the glucose concentration in the interstitial fluid, and devices are evolving steadily in terms of accuracy and ease of use,” the guideline notes.

A GOOD TIME TO EVALUATE EVIDENCE

“CSII therapy and continuous glucose monitoring technologies have been among the most widely used technologies for adults with diabetes over the past ten years. Now is an appropriate time to bring together the evidence for using [both these technologies] in the same evidence-based guideline,” says David C. Klonoff, MD, medical director of the Diabetes Research Institute at Mills-Peninsula Health Services in San Mateo, Calif. Klonoff

AT A GLANCE

- ▶ Insulin pumps and continuous glucose monitors can improve diabetes care in many patients but are not being adopted as widely as they could be.
- ▶ As with any diabetes treatment, the use of technology needs to be individualized to the patient’s situation.
- ▶ Technology is changing so fast that it is difficult for both clinicians and researchers to keep up, so the guideline tries to incorporate not only the “why” but the “how” of implementing new options.

GOOD CANDIDATES FOR INSULIN PUMPS



Of course not every diabetes patient is a suitable candidate for an insulin pump. The guideline recommends or suggests continuous subcutaneous insulin infusion (CSII) — insulin pumps — over analog-based basal-bolus multiple daily injections in those patients with type 1 diabetes mellitus who:

- ▶ have not achieved their hemoglobin A1C goal;
- ▶ have achieved their A1C goal but continue to experience severe hypoglycemia or high glucose variability; or
- ▶ require increased insulin delivery flexibility or improved satisfaction.

In all three cases, it adds the caveat that the patient and caregivers must be willing and able to use a device.

In type 2 patients, the guideline suggests patients should consider using insulin pumps if they have poor glycemic control despite intensive insulin therapy, use of oral agents, use of other injectable therapy, and lifestyle modifications.



The guideline emphasizes the need for education about the devices: “We suggest that adults with T1DM and T2DM who use continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring receive education, training, and ongoing support to help achieve and maintain individualized glycemic goals.”

chaired the committee that wrote a 2011 Endocrine Society guideline on continuous glucose monitoring but was not involved in writing this current guideline. “These technologies are continuously improving and indications for their use are expanding — especially in type 2 diabetes. This document provides a thoughtful set of recommendations as well as a framework for organizing future evidence about [their] effectiveness. It will be helpful to diabetes clinicians by presenting a thorough review of the medical literature to establish which technologies and which indications are supported by high-quality evidence.”

“This guideline goes into more detail than has ever been compiled to guide clinicians in terms of understanding the right patient for the technology and how to teach the technology,” Peters says. “We involved a diabetes educator on our committee, who was able to give that whole realm of knowledge about using it.”

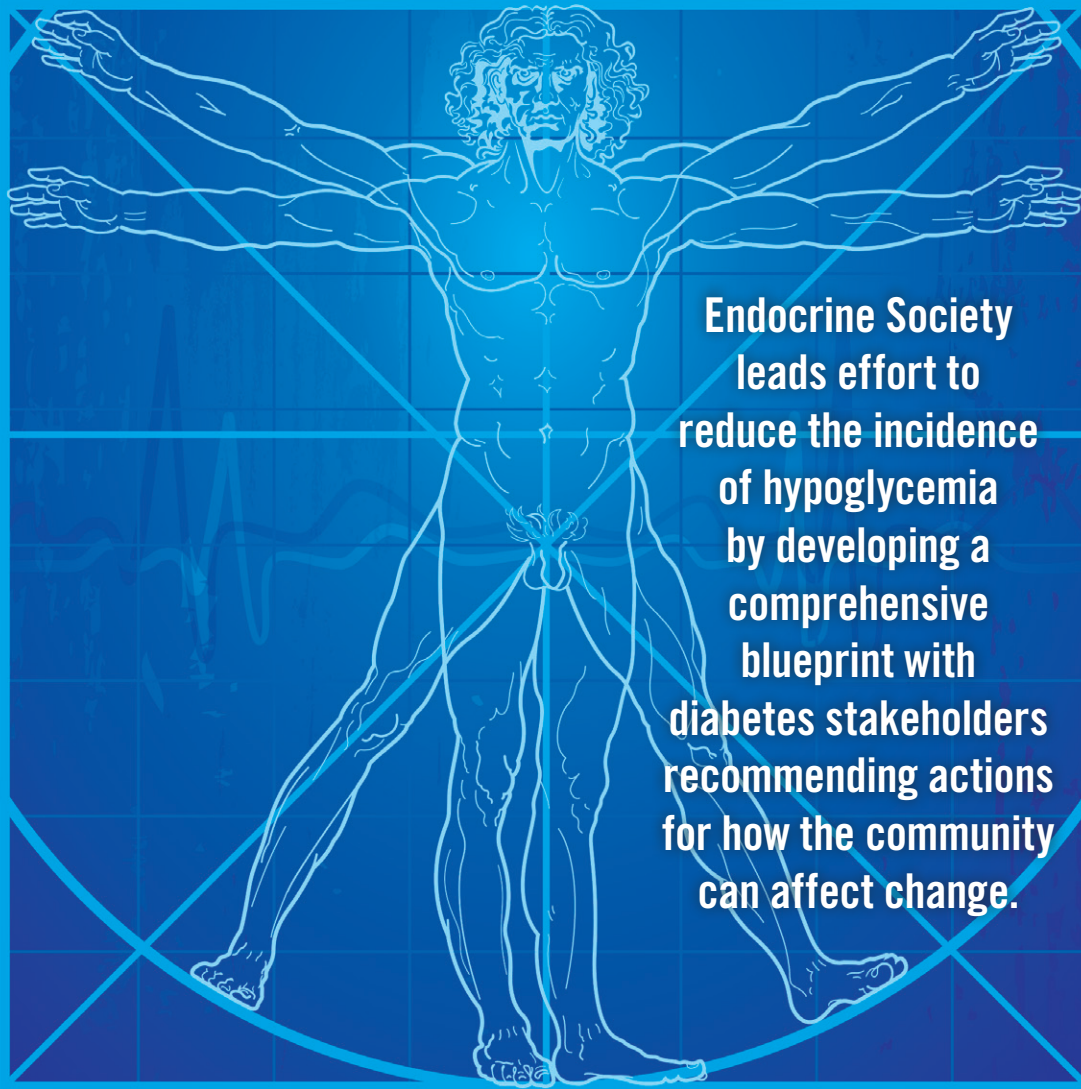
The American Association for Clinical Chemistry, the American Association of Diabetes Educators, and the European Society of Endocrinology co-sponsored the guideline.

Despite the potential benefits of the technology, “we often fail to teach providers how to integrate it in their own practice, so we tried both to summarize the available data and then to help people use it,” Peters says. ^{EN}

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HYPOGLYCEMIA:

A Comprehensive Approach in the U.S.



Endocrine Society leads effort to reduce the incidence of hypoglycemia by developing a comprehensive blueprint with diabetes stakeholders recommending actions for how the community can affect change.

Introducing a Comprehensive Blueprint to Address the Diabetes Complication of Hypoglycemia



HQC Strategic Blueprint to reduce the incidence of hypoglycemia

HIGHLIGHTS

The Endocrine Society created a working group known as the Hypoglycemia Quality Collaborative (HQC) to develop a blueprint.

The Blueprint contains six domains that together create a comprehensive framework for addressing hypoglycemia.

Each of these key domains include three strategic areas which contain specific recommendations for how diabetes stakeholders can contribute to preventing and managing hypoglycemia.

THE NUMBERS ARE INCREASING AND ARE ALARMING: More than 29 million Americans are living with diabetes and an additional 86 million are at risk for developing the disease. The impact to the healthcare system is vast. *The Economic Costs of Diabetes in the U.S. in 2012* estimated that diabetes costs \$245 billion, including \$176 billion in direct medical costs and \$69 billion in reduced productivity. Consequently, the Endocrine Society has prioritized the need to prevent diabetes and effectively manage its complications.

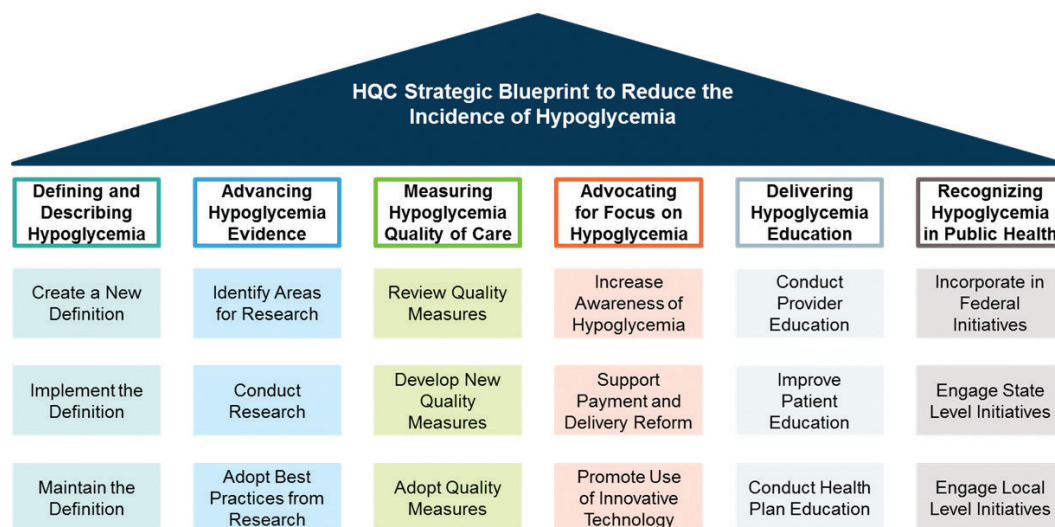
In order to achieve this goal, the Society is well aware that it must work with other diabetes stakeholders to design, implement, and evaluate initiatives that will improve the prevention and management of diabetes, thereby reducing the burden associated with complications such as hypoglycemia. In 2015 the Endocrine Society conducted a roundtable and brought together stakeholders from federal agencies, patient and provider groups, payers, and industry to discuss how the diabetes community can work together to affect change.

The roundtable participants agreed that addressing the burden of hypoglycemia is critical and focused efforts on working together to determine actions needed to increase national awareness and execute tactics that improve its prevention and management in the U.S. To facilitate this

need, the Endocrine Society created a working group known as the Hypoglycemia Quality Collaborative (HQC) to develop a blueprint (Blueprint) that provides a comprehensive approach to reducing the incidence of hypoglycemia and ensuring that patients and providers receive the tools they need to prevent and manage the complication. The resulting Blueprint contains the following six domains that together create a comprehensive framework for addressing hypoglycemia:

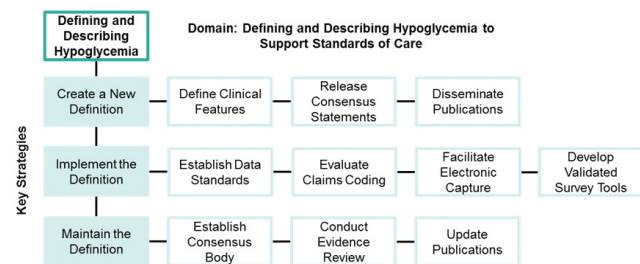
1. Defining and describing hypoglycemia to support standards of care
2. Advancing hypoglycemia evidence to reduce gaps in care
3. Measuring and improving the quality of care for patients who experience hypoglycemia
4. Advocating for an increased focus on hypoglycemia
5. Delivering hypoglycemia prevention and management education
6. Recognizing hypoglycemia as a public health issue

Each of these key domains include three strategic areas which contain specific recommendations for how diabetes stakeholders can contribute to preventing and managing hypoglycemia. Below is a summary of the Blueprint and its recommendations:



Defining and Describing Hypoglycemia to Support Standards of Care

The current definition of hypoglycemia does not support differentiation of hypoglycemic episodes by severity. The foundation for improving the prevention and management of hypoglycemia is an updated definition that accounts for differing hypoglycemia severity. A comprehensive and standardized definition can then be adopted in research, clinical guidance and decision support tools, and reimbursement models that reward quality.



Create a New Definition: A new definition of hypoglycemia must be created through a review of evidence and include both clinical values and descriptions of positive and negative symptoms. The definition should have consensus support and facilitate the recognition, tracking, and treatment of different hypoglycemia severity (Note: JDRC is currently leading efforts to develop a consensus definition for differing hypoglycemia severity).

- ▶ **HQC Recommendation:** A new definition should include both a symptom-complex and a biochemical definition since there are many factors that may affect whether a patient has symptoms.
- ▶ **HQC Recommendation:** To support prevention and management, a new definition should allow for capture of data related to pre- and post-hypoglycemia events in acute, post-acute, and community care settings (e.g., outpatient or home), including patient factors such as fears and beliefs of hypoglycemia.

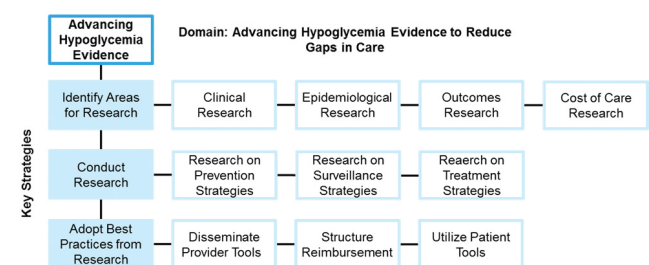
Implement the Definition: The new definition will require a technical expert panel to establish data standards and a set of standardized data elements for consistent electronic capture and transfer of hypoglycemia data by severity. Similarly, diagnostic and procedural coding (e.g., ICD, CPT) must be evaluated to support comprehensive capture of hypoglycemic episodes by severity. These steps provide the foundation for development of survey-based tools and testing of new hypoglycemia quality measures.

- ▶ **HQC Recommendation:** To accelerate the adoption of a new definition, large commercial payers and provider organizations should be engaged to adopt the consensus definition and disseminate it to members within their organizational network such as through the organization's diabetes standards of care.

Maintain the Definition: The definition of hypoglycemia will require a consensus body that periodically monitors and conducts targeted literature reviews to update the evidence base and support definition maintenance.

Advancing Hypoglycemia Evidence to Reduce Gaps in Care

Current research related to glycemic control often focuses on the prevention and management of hyperglycemia. The federal government must increase funding for research at the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to reduce gaps in evidence related to hypoglycemia prevention and management. This research should elucidate the short-term and long-term effects of hypoglycemia on patient outcomes so that standards of care can be updated or newly developed.



Identify Areas for Research: Major gaps in hypoglycemia evidence should be identified so that research may be conducted to design prevention and management strategies that reduce gaps in care for hypoglycemia.

- ▶ **HQC Recommendation:** Major gaps in evidence include:
 - The pre-cursor clinical indicators of severe hypoglycemia such as frequent or protracted non-severe hypoglycemia;
 - The incidence of hypoglycemia by severity level including events in emergency and outpatient settings;
 - The short-term effects of hypoglycemia on outcomes (e.g., arrhythmias, cardiovascular events, and cerebrovascular events);
 - The long-term effects of hypoglycemia (e.g., quality of life, functional status);
 - The patient characteristics that increase hypoglycemia risk such as age, ethnicity, beliefs and fears of hypoglycemia, diabetes self-management education (DSME) status, and therapy choices (e.g., insulin, sulfonylurea, analog insulin, or bolus insulin);
 - The indirect costs of hypoglycemia (e.g., lost productivity/absenteeism);
 - The best practices for using continuous glucose monitor (CGM) data to inform appropriate medication or lifestyle modifications;
 - The best practices for standardized reporting of CGM data.

Conduct Research: Research that is conducted should have the objective of informing prevention, surveillance, and management approaches that account for differing hypoglycemia severity.

- ▶ **HQC Recommendation:** Research on patient beliefs and attitudes impacting behavior is a high priority in order to improve prevention and management strategies, especially for patients at risk for recurrent severe hypoglycemia.

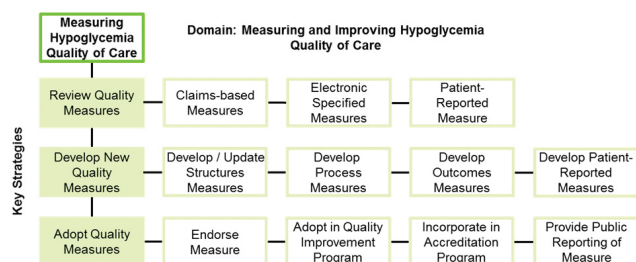
- ▶ **HQC Recommendation:** Research to improve surveillance should focus on elucidating the incidence of hypoglycemia by severity and across settings of care such as the utilization of emergency medical and outpatient services related to hypoglycemia.

Adopt Best Practices from Research: Action by all stakeholders is needed for comprehensive adoption of best practices from research. Medical specialty societies must make timely updates to clinical guidance documents and educational materials; primary care teams must incorporate new surveillance strategies; diabetes educators and patient advocates must update educational materials; commercial and public payers must review and adjust reimbursement and benefit designs; and health information technology vendors and digital health manufacturers must provide tools that support new standards of care.

- ▶ **HQC Recommendation:** To encourage adoption of new best practices for prevention and management of hypoglycemia based on severity, medical specialty societies should develop a communication strategy with key messaging for engagement with regulators and payers.
- ▶ **HQC Recommendation:** Medical specialty societies should engage with primary care providers to identify opportunities to support primary care providers in adopting best practices for hypoglycemia prevention and management.
- ▶ **HQC Recommendation:** Payers and providers should actively consider ways to incorporate CGM data into clinical decision-making for prevention and management of hypoglycemia in high-risk individuals.

Measuring and Improving Hypoglycemia Quality of Care

Quality measures for diabetes that specifically assess prevention and management of hypoglycemia are lacking. Evidence-based quality measures are needed that support coordinated, timely, and safe prevention and management of hypoglycemia. Diabetes stakeholders must coordinate to develop and test hypoglycemia quality measures with appropriate risk adjustment to support improved hypoglycemia outcomes.



Review Current Quality Measures: Current claims, electronic, and patient-reported outcomes measures for diabetes should be reviewed and

updated, if necessary, to improve alignment of the measures with current clinical guidance for preventing and managing severe hypoglycemia.

- ▶ **HQC Recommendation:** Current measures should be reviewed and updated to promote the use of individualized HbA1c target goals and SMBG targets (e.g., fasting, pre-meal, post prandial, and bedtime blood glucose), distinguish differing hypoglycemia severity, and evaluate whether DSME was received/completed.

Develop New Quality Measures: New quality measures are needed that support surveillance of individuals at risk for hypoglycemia across settings of care, use of shared decision-making for medication selection, and evaluation of patient attitudes, fears, and behaviors related to blood glucose management.

- ▶ **HQC Recommendation:** Structural measures should be developed to support timely communication to notify a patient's primary care provider of a hypoglycemia-related emergency room visit or a medication switch following an inpatient admission.
- ▶ **HQC Recommendation:** Process measures should be developed to improve outpatient hypoglycemia risk evaluation, including less severe hypoglycemia, and use of individualized HbA1c targets goals.
- ▶ **HQC Recommendation:** Patient-reported outcomes measures are needed to evaluate fears of hypoglycemia, effect on quality of life, loss of productivity, and confidence with self-management.
- ▶ **HQC Recommendation:** Outcome measures that use clinical endpoints other than HbA1c are needed to better understand glycemetic control. New measures could use multiple metrics including HbA1c, time-in-range, and hypoglycemia as potential endpoints for evaluating glycemetic control.

Adopt Current and New Quality Measures: Evidence-based measures that are closely tied to outcomes and patient-centered interests must be adopted in national quality improvement, provider accreditation, and public reporting programs.

- ▶ **HQC Recommendation:** Physician Consortium for Practice Improvement (PCPI) measures for DSME should be submitted for adoption in Centers for Medicare & Medicaid Services (CMS) inpatient and outpatient quality improvement programs as well as for use by commercial payers.

- These measures can be submitted to CMS for adoption in the Physician Quality Reporting System (PQRS) or future Merit-Based Incentive Payment System (MIPS) using mechanisms such as the Qualified Clinical Data Registry (QCDR) reporting option.

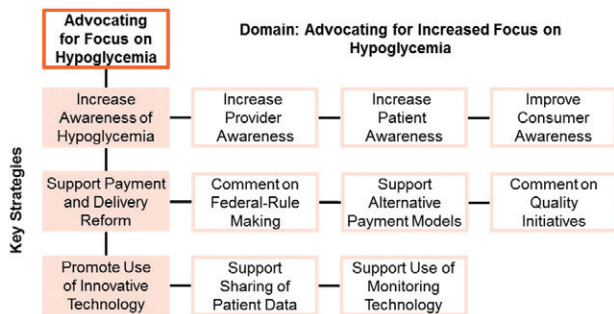
- ▶ **HQC Recommendation:** Quality measures such as NQF 2363: Glycemic Control should be submitted for adoption in the National Committee for Quality Assurance's (NCQA) Diabetes Recognition Program and The Joint Commission (TJC) disease-specific certification programs.



“ The federal government must increase funding for research at the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) to reduce gaps in evidence related to hypoglycemia prevention and management.”

Advocating for Increased Focus on Hypoglycemia

Advocacy is an effective tool to increase national focus on hypoglycemia. Through advocacy, diabetes stakeholders become more aware of the need to devote resources and attention towards preventing and managing hypoglycemia.



Increase Awareness of Hypoglycemia: Advocacy through the development of policy positions, educational events, and engagement with other diabetes stakeholders should improve awareness of the harm of hypoglycemia, describe methods for prevention and management, and promote increased funding of research that supports provider and patient clinical decision-making for hypoglycemia.

- ▶ **HQC Recommendation:** Patients/caregivers should be engaged by diabetes educators, patient advocacy groups, and social workers regarding self-management techniques as well as protective rights in the workplace.
- ▶ **HQC Recommendation:** Primary care providers/organizations and advanced practice providers should be engaged to expand their role in both diabetes management and hypoglycemia prevention by referring patients to certified diabetes educators or patient education programs that are typically covered services.

- ▶ **HQC Recommendation:** Providers should be engaged regarding the impact of hypoglycemia relative to hyperglycemia and the importance of managing hypoglycemia by setting appropriate HbA1c and SMBG targets, using appropriate medications, educating on diet and exercise, and providing blood glucose monitoring education and tools.
- ▶ **HQC Recommendation:** Members of medical specialty societies should be engaged regarding the importance of legislative mechanisms for improving diabetes care such the Diabetes Clinical Care Commission Act.

Support Payment and Delivery Reform: Care models that incentivize coordinated, timely, safe, and accessible care for diabetes should be promoted through engagement with state health officials, federal rule-making, and outreach to commercial payers.

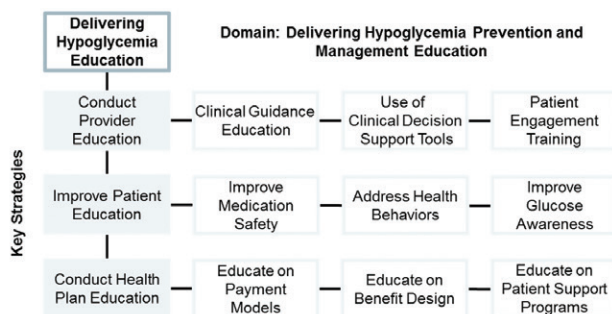
- ▶ **HQC Recommendation:** States with Diabetes Action Plans (Kentucky, Texas, Illinois, Louisiana, New Jersey, North Carolina, North Dakota, Oregon, and Washington) should be engaged to include explicit tactics for preventing and managing hypoglycemia.
 - States without Diabetes Action Plans should be encouraged to develop action plans that specifically include tactics for preventing and managing hypoglycemia.
- ▶ **HQC Recommendation:** Public and commercial payers should be engaged regarding the value of reimbursement strategies that promote evidence-based care for hypoglycemia.
- ▶ **HQC Recommendation:** Policy makers should be engaged regarding the value of reimbursement that promotes evidence-based prevention and management for hypoglycemia to reduce the significant costs and poor outcomes of hypoglycemia.

Promote Use of Innovative Technology: Advocacy to federal regulators, commercial payers, and providers should promote patient access to glucose-monitoring tools (e.g., CGMs, strip meters) and education to support providers to utilize data from these tools to inform prevention and management decisions.

- ▶ **HQC Recommendation:** Public and commercial payers should be engaged regarding the importance of digital health and remote-monitoring technologies for evaluating the burden of hypoglycemia, improving provider care coordination, and promoting shared decision-making.
- ▶ **HQC Recommendation:** Public and commercial payers should be engaged to promote access and use of active surveillance tools such as CGMs for patients at high risk for severe hypoglycemia.
- ▶ **HQC Recommendation:** Electronic medical record vendors should be engaged to integrate clinical decision support tools that allow for capture and transfer of hypoglycemia data by severity.

Delivering Hypoglycemia Prevention and Management Education

Stakeholder education is a significant activity that is necessary to increase the use of evidence-based standards of care for prevention and management of hypoglycemia. Such education is important across settings of care and especially for patients and providers directly involved in the delivery of care.



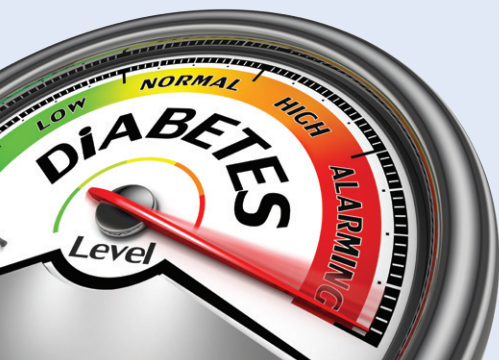
Conduct Provider Education: All primary care healthcare professionals should receive hypoglycemia prevention and management education regardless of care setting. Hypoglycemia-specific education is needed to increase the use of individualized HbA1c and SMBG targets, referral of patients to DSME programs/diabetes educators, shared decision-making for management goals such as medication selections, discussion of barriers to medication adherence such as patient fears, and appropriate use of technology to prevent and manage hypoglycemia.

- ▶ **HQC Recommendation:** Initiatives to educate on new prevention and management approaches for hypoglycemia must be updated to include recommendations by hypoglycemia severity. These initiatives should also consider modifications to the provider's workflow.
- ▶ **HQC Recommendation:** Providers should receive education regarding the interpretation and use of CGM and SMBG tools, including use and definition of multiple basal rates.

Improve Patient Education: Patient education is vital for improving outcomes, however, referral rates to educational programs are too low. Patients should be referred to an accredited or recognized diabetes education program with the overall objective to support self-care behaviors, problem solving, and shared decision-making with the healthcare team.

- ▶ **HQC Recommendation:** Patient education initiatives should meet the National Standards for Diabetes Self-Management Education and Support.
- ▶ **HQC Recommendation:** Hypoglycemia-specific education should be targeted by age and gender, sensitive to the number of hours a patient has available, and ideally include training from behaviorists, nurses, dietitians, pharmacists, and exercise physiologists.
- ▶ **HQC Recommendation:** Hypoglycemia-specific training should include education on glucose pattern recognition and self-management actions, medication safety, fears of hypoglycemia, hypoglycemia unawareness, nutrition and lifestyle strategies, and strategies for appropriate glucose monitoring.
- ▶ **HQC Recommendation:** The use of telephonic/mobile patient education should be expanded with digital education targeted to those who will benefit most.
- ▶ **HQC Recommendation:** Patient-centered perspectives that encompass the experience of hypoglycemia, impact on quality of life, and strategies for self-management should be provided to patients.

Conduct Health Plan Education: Health plans have the ability directly influence provider and patient behavior based on reimbursement and benefit design. Education of both regional and national health plans on reimbursement and benefit design that improves hypoglycemia prevention and management is needed.

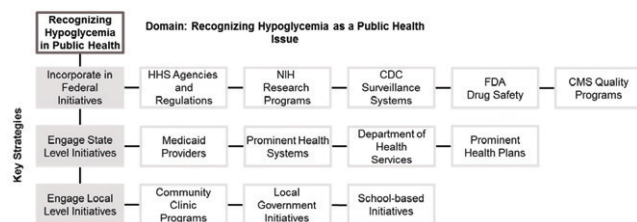


“Quality measures for diabetes that specifically assess prevention and management of hypoglycemia are lacking. Evidence-based quality measures are needed that support coordinated, timely, and safe prevention and management of hypoglycemia.”

- ▶ **HQC Recommendation:** Regional payers and payers should be educated on the importance of reimbursement and benefit design that includes case management for individuals with diabetes from nurses or dietitians as mechanisms to reduce the frequency, impact, and incidence of severe hypoglycemia.

Recognizing Hypoglycemia as a Public Health Issue

Many diabetes public health programs currently exist at federal, state, and local levels. Within these programs, the topic of hypoglycemia must become a point of emphasis. By elevating the topic of hypoglycemia as a public health issue, diabetes stakeholders have a mechanism to significantly improve national awareness of hypoglycemia and reduce its incidence for any severity.



Incorporate in Federal Initiatives: Federal agencies must ensure that hypoglycemia is consistently reflected in research programs, surveillance systems, regulation, drug safety, and quality programs.

- ▶ **HQC Recommendation:** Diabetes stakeholders should engage with the agencies of the Department of Health and Human Services (HHS) to promote focus on hypoglycemia in federal programs and regulations.
- ▶ **HQC Recommendation:** The NIH should increase funding for research to improve prevention and management of hypoglycemia.
- ▶ **HQC Recommendation:** The programs of the CDC should support national hypoglycemia surveillance.
- ▶ **HQC Recommendation:** Important topics such as hypoglycemia in a public health context should be submitted to the Diabetes Mellitus Interagency Coordinating Committee, a workgroup of federal agencies that coordinates government components to work together to address issues in diabetes.

Engage State-Level Initiatives: Medicaid providers and state-level Departments of Health and Human Services (DHHS) should incorporate hypoglycemia awareness and risk reduction into public health initiatives.

- ▶ **HQC Recommendation:** To affect change at the state level, important topics in diabetes such as hypoglycemia awareness and risk reduction should be reflected in state-level Diabetes Action Plan legislation.

- ▶ **HQC Recommendation:** State-level initiatives should be delivered in a culturally sensitive format based upon the state's diabetes population and educate on the use of technology, health literacy, and numeracy.
- ▶ **HQC Recommendation:** State-level DHHS should coordinate with prominent health systems and health plans in the high-priority regions of the state.

Engage Local Level Initiatives: In collaboration with state agencies, local entities can promote hypoglycemia public health awareness and distribute educational resources through clinics, local government, and schools.

- ▶ **HQC Recommendation:** To effectively deliver information and educate communities on pediatric diabetes hypoglycemia prevention and management, programs should be developed in collaboration with school nursing organizations such as National Association of School Nurses.
- ▶ **HQC Recommendation:** Diabetes and hypoglycemia public health resources should be culturally and linguistically appropriate to successfully engage an ethnically diverse diabetes patient population.
- ▶ **HQC Recommendation:** Community and socio-ethnic factors that contribute to hypoglycemia should be identified and targeted strategies must be used to prevent and manage hypoglycemia at a local level.

Moving Forward

The Blueprint has laid out opportunities that can affect change in six domains, offering specific strategies to reduce the incidence of hypoglycemia. It is the hope of the HQC that this Blueprint will elevate the issue of hypoglycemia to national importance, and provide opportunities for stakeholders to work together to improve the prevention and management of hypoglycemia.

For a complete version of the Blueprint, including references, please visit endocrine.org/hypoglycemia. ■

The Hypoglycemia Quality Collaborative Blueprint is an initiative spearheaded by the Endocrine Society in conjunction with: Abbott Diabetes Care Inc., Aetna Inc., American Association of Clinical Endocrinologists, American Association of Diabetes Educators, American College of Physicians, American Diabetes Association, Astrazeneca LP, Close Concerns, Dexcom, Inc., Lilly USA, LLC, JDRF, Johnson & Johnson, Joslin Diabetes Center, Medtronic Diabetes, Merck & Co., Inc., Novo Nordisk Inc., PQA Alliance, and T1D Exchange.

Endocrine Society would like to thank Merck & Co. for their generous support of the Hypoglycemia Quality Collaborative Blueprint.



Diana DeGette

represents Colorado's First District to the U.S. Congress and co-chairs the Congressional Diabetes Caucus

HIGHLIGHTS

One out of every three dollars of Medicare spending goes toward diabetes treatment, and when you combine direct medical expenses and other factors, diabetes costs the U.S. \$245 billion per year.

In September, there was a major breakthrough when the Food and Drug Administration (FDA) approved a first-ever commercial version of an artificial pancreas system to improve the treatment of type 1 diabetes.

There also have been leaps forward under longer-term federal efforts, such as the Special Diabetes Program (SDP), which was enacted as part of the Balanced Budget Act of 1997. Innovations under this program include kidney therapies, eye therapies, immune therapies, and development of the closed-loop insulin pump.

Congressional Perspective on Diabetes

— THE HONORABLE DIANA DEGETTE (D-CO)

Diabetes is having an ever-greater impact on our country, and as a result, more people are becoming alert to its dangers. But we still have a long way to go to ensure that those who might be affected by the disease are alert to it. And there's a strong need for advocacy to ensure that researchers have the resources they need.

There's no better time than Diabetes Awareness Month for that.

As the mother of a daughter with type 1 diabetes, I've been keenly alert to improvements in treatment and outcomes over the years. And as co-chair of the Congressional Diabetes Caucus, I've worked with my colleagues to influence the extent to which federal support speeds along research.

But there's still so much to be done. Nearly 30 million Americans have diabetes, while 86 million have prediabetes — and most of them don't even know it. If current trends continue, one in three Americans will have diabetes by 2050.

Living with diabetes can be very challenging due to the serious health problems involved, along with the higher risk of long-term damage, heart disease, and stroke. The burdens on individuals, on families and on our country's healthcare system are staggering.

Already, one out of every three dollars of Medicare spending goes toward diabetes treatment, and when you combine direct medical expenses and other factors, diabetes costs the U.S. \$245 billion per year.

For all of these reasons, it's important that we in Congress take steps to increase support for diabetes research and treatment. In Congress, as in American society, there's a growing recognition of the critical importance of diabetes prevention and care. And



Support for research and innovation continues to be key in addressing the diabetes epidemic.

that's due, in part, to the work that many of you do every day.

Fortunately, the pace of innovation is encouraging.

In September, there was a major breakthrough when the Food and Drug Administration (FDA) approved a first-ever commercial version of an artificial pancreas system to improve the treatment of type 1 diabetes. This is a huge step forward for medicine, and it will be transformative for countless people with type 1 diabetes. For five years, I and other colleagues had been encouraging the FDA to expedite its review of this technology.

The technology approved by the FDA for patients ages 14 and up is the Medtronic MiniMed 670G hybrid closed-loop system, which consists of insulin pumps, continuous glucose monitors, and software to automate the delivery insulin as needed, as a healthy pancreas does.

Now our work to urge the FDA forward, and to fund the research through the National Institutes of Health (NIH), has paid off. I look forward to providing similar support to the next-generation technologies that are also on the verge of improving outcomes for people with this disease.



NIDDK Perspective on Diabetes

— GRIFFIN P. RODGERS, MD, MACP,
AND JUDITH E. FRADKIN, MD

NIDDK Director Griffin Rodgers and Judith Fradkin, NIDDK's director of the Division of Diabetes, Endocrinology and Metabolic Diseases responded to questions by Endocrine News about future opportunities and challenges in diabetes research.

EN: What are the opportunities and challenges in diabetes research?

The prevalence, costs, and human burden associated with diabetes create both opportunities and challenges for diabetes research. Research is needed to address the particularly troubling emergence of type 2 diabetes and rising rates of both type 2 diabetes and type 1 diabetes in youth. In addition to eye, nerve, kidney, and heart complications, diabetes substantially increases risk for dementia, cancer, and other major concomitants of aging.

NIDDK is collaborating across the National Institutes of Health (NIH) in research to understand and develop therapies to mitigate these risks. Prioritizing across the many unanswered questions about prevention and management of diabetes and its complications is a challenge. Also challenging is translating into practice hugely successful NIDDK-supported research studies such as the Diabetes Prevention Program and Diabetes Control and Complications Trial, and diminishing the disproportionate burden of diabetes in disadvantaged populations. Novel therapies for diabetes and the new Precision Medicine Initiative® create an opportunity to determine which therapy is best for a specific individual. Central to all forms of diabetes are exciting opportunities to regenerate or replace beta cells.

EN: The Special Diabetes Program (SDP) is up for reauthorization next year. How has the SDP helped improve research and treatment over the past two years?

Early SDP funding contributed to the development of the first FDA-approved hybrid closed-loop device, and



Griffin P. Rodgers, MD, MACP, National Institute of Diabetes and Digestive & Kidney Diseases (NIDDK) director



Judith E. Fradkin, MD, director of the NIDDK Division of Diabetes, Endocrinology and Metabolic Diseases

HIGHLIGHTS

Early SDP funding contributed to the development of the first FDA-approved hybrid closed-loop device, and current funding is supporting phase 3 artificial pancreas (AP) trials and development of next generation AP components.

New therapeutic approaches are anticipated through major investments in brain and gut regulation of appetite and metabolism; beta cell biology; brown and beige fat; and tissue crosstalk mediated by hormones, myokines, adipokines, and incretins.

There also have been leaps forward under longer-term federal efforts, such as the Special Diabetes Program (SDP), which was enacted as part of the Balanced Budget Act of 1997. Innovations under this program include kidney therapies, eye therapies, immune therapies, and development of the closed-loop insulin pump.

Congress has appropriated \$2.46 billion to the program since its inception, and I continue to be a leading supporter.

The Special Diabetes Program for Indians (SDPI) has been particularly successful. Native Americans have the highest rate of diabetes among all ethnic groups at 16%. SDPI funds nearly 400 community-directed programs that have led to improvements in diabetes prevention and care among Native Americans.

Nearly 340 members of the U.S. House of Representatives signed on to reauthorize SDP in 2013, and I am urging all to reauthorize it again in 2017.

I'm sure that the Endocrine Society and advocates in the diabetes community will be helping in this effort, as you have for so many years, urging Congress to keep driving diabetes legislation forward — legislation that helps advance research and patient options for care and treatment. Thank you for this important work. ■

“The prevalence, costs, and human burden associated with diabetes create both opportunities and challenges for diabetes research. Research is needed to address the particularly troubling emergence of type 2 diabetes and rising rates of both type 2 diabetes and type 1 diabetes in youth.”



current funding is supporting phase 3 artificial pancreas (AP) trials and development of next generation AP components. The Environmental Determinants of Diabetes in the Young (TEDDY) Study has begun applying ‘omics’ technologies to 2.7 million biosamples from an observational study of over 8,000 newborns at high genetic risk yielding hundreds of children with autoimmunity or type 1 diabetes. This case-control analysis will be the largest study of microbiome development in children and is poised to identify environmental triggers of type 1 diabetes.

In 2015, the Endocrine Society, the American Diabetes Association (ADA), and JDRF adopted a new staging approach for presymptomatic type 1 diabetes based on data from TEDDY, TrialNet, and other SDP-supported studies. TrialNet is near completion of three major randomized trials testing prevention strategies for type 1 diabetes with results expected in 2017 and 2018. The Human Islet Research Network (HIRN) is progressing toward producing and protecting new beta cells; finding markers of silent beta cell loss; identifying beta cell heterogeneity; and creating an “islet on a chip” with multiple islet cell types constituted from human pluripotent stem cells housed in 3-D niches. These tools will help researchers understand how beta cell function is lost in diabetes and test new approaches to slow progression of the disease or replace lost beta cells.

EN: What are some of the exciting diabetes-related research that NIDDK is working on right now?

Major NIDDK clinical trials include: The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), a head-to-head comparison of four commonly used drugs in combination with metformin; Restoring Insulin Secretion study (RISE), testing whether early aggressive

therapy of type 2 diabetes will slow or reverse beta cell loss; Vitamin D and Type 2 Diabetes study (D2d), testing vitamin D’s efficacy in type 2 diabetes prevention; the Diabetes Prevention Program Outcomes Study (DPPOS), phase 3 studying the effect of metformin on cardiovascular disease and cancer; and Preventing Early Renal Function Loss in Diabetes (PERL) trial, which is studying allopurinol for diabetic nephropathy.

New therapeutic approaches are anticipated through major investments in brain and gut regulation of appetite and metabolism; beta cell biology; brown and beige fat; and tissue crosstalk mediated by hormones, myokines, adipokines, and incretins.

EN: What NIDDK-supported resources should scientists be aware of to help advance diabetes research?

The AMP Type 2 Diabetes Knowledge Portal enables browsing, searching, and analysis of human genetic information linked to type 2 diabetes and related traits from more than 100,000 DNA samples. The National Mouse Metabolic Phenotyping Centers (MMPC) provide experimental testing services to scientists studying diabetes, obesity, diabetic complications, and other metabolic diseases in mice. The NIDDK Central Repository provides access to data and biospecimens from NIDDK-funded clinical studies. The NIDDK Information Network (dkNET) enables researchers to search for resources such as mouse strains, antibodies, or data sets. Finally, the Integrated Islet Distribution Program (IIDP) distributes high quality human islets. ■

Links to these and other resources are at www.niddk.nih.gov/research-funding/research-resources. ^{EN}

Heart ON YOUR Sleeve BY MELISSA MAPES



There is a whole new realm of wearables in various stages of development that can detect everything from diabetes and urinary tract infections to UV exposure and concussions. But what role could they play in the future of medicine?

It's not just about counting steps — wearables have played an important role in health and wellness long before the emergence of trendy tech like FitBit. Medical-grade devices like hearing aids, heart monitors, and insulin pumps pioneered the concept of small, portable electronics designed to enhance the lives of users.

Now, the popularity and profitability of consumer-grade wearables is accelerating the development of novel healthcare technologies in this realm, bringing the “quantified self” one step closer to mainstream medicine.

“ We’re doing medicine with 1% of the actual information that’s being generated inside of you. It’s this fallacy that somehow you can guess what’s going on inside of you instead of measuring it.”

— LARRY SMARR, PHD, AN ASTROPHYSICIST AND COMPUTER SCIENTIST



Regulating the Trend

There is serious money to be made from wearables. According to Soreon Research, the market for smart medical wearables will increase from \$2 billion in 2014 to over \$41 billion in 2020. It anticipates the most growth to come from technology focused on diabetes, obesity, sleep disorders, and cardiovascular health.

But like all devices intended for medical uses, the next generation of wearables must obtain approval from the U.S. Food and Drug Administration (FDA) before going to market. The FDA is girding itself for the barrage of applications by expanding its staff of digital health scientists.

While consumer wearables have purposefully evaded the need for FDA approval in the past, companies are now clamoring to demonstrate legitimate clinical benefits. If successful, insurance companies may start covering the price of wearables — a potentially major source of revenue that could eclipse the investment of time and money put into the approval process.

Tech companies have adjusted strategy and are collaborating with the FDA to produce devices that deliver on medical promises. Most wearables, however, still have a ways to go before they can be advertised as having proven clinical benefits.

Going on Trial

Last year, the wearables startup Empatica successfully raised 514% of its crowd-funding goal on Indiegogo for the “Embrace” Alert System, bringing in a total of \$782,666. The Embrace aims to help

patients with epilepsy by sending an alert to caregivers when a seizure occurs. Like other wearables, it monitors physiological activity through a wristband and syncs with an app to analyze a variety of data points.

While thousands of units have already been distributed, Empatica did not receive permission to start a clinical trial for this purpose until May 2016. The company has been upfront about its lack of FDA approval and its efforts to prove clinical benefits. It has still been able to crowd fund, manufacture, and give away the alert system, but not actually sell it to customers for its intended purpose. In fact, regulations prohibit use of the Embrace Alert System outside of its clinical trial.

Empatica hopes to eventually get approval to sell the Embrace for multiple medical purposes. First on the docket is epilepsy, but the company suggests a multitude of additional prospects on its website, ranging from endocrine disorders to depression.

During its crowd-funding campaign, Empatica committed to giving a free Embrace to a child with epilepsy for every system sold. This arrangement is now allowing them to draw upon their community of donors and device recipients as volunteers in the upcoming clinical trial.

Empatica exemplifies the clever strategies that startups are using to clear research hurdles. In partnership with academic institutions, tech companies are combining the traditional approach to medical research and device approval with unconventional methods like crowd funding and partnering with Silicon Valley investors.

Getting to the Data Point

The big question underpinning smart wearables is application. While the technology for gathering all kinds of data is well established, researchers and entrepreneurs are still figuring out how to best analyze and make use of collected information.

Larry Smarr, PhD, an astrophysicist and computer scientist, is a vocal leader of the “quantified self” movement. He tracks over 150 data points on his body and lifestyle — from blood pressure to gut bacteria. Smarr calls this combined information “a dashboard for my body” and aims to optimize his physical state with the goal of longevity and overall wellbeing.

In his TEDMED talk, Smarr claims, “We’re doing medicine with 1% of the actual information that’s being generated inside of you.”

He described how tracking his personal data allowed him to discover that he had 27 times the normal range of C-reactive protein (CRM) in his blood. Upon further investigation, he found that he had disconcertingly high levels of lactoferrin present, an indication of inflammatory bowel disease (IBD). Smarr had experienced issues with his colon for some time but had never received a diagnosis because his symptoms were inconclusive.

“It’s this fallacy that somehow you can guess what’s going on inside of you instead of measuring it,” Smarr continues.

By analyzing his own gut bacteria, Smarr was able to give his physician the necessary information to prescribe a personalized treatment plan with effective and lasting results. As such, he believes that this sort of tracking on an individual level is the inevitable direction of medicine.

Smarr cites the startup uBiome as a way to sequence gut bacteria and add to one’s “quantified self.” Currently, customers have to send swabs for analysis but can then digitally track changes in their microbiomes online.

Smarr was able to close the gap between the quantified self and clinical application, but most smart wearables aren’t there yet. Patients cannot yet walk into their physician’s office, hand over their wearable data — perhaps displayed by an app on their iPhone — and receive a diagnosis.

At this point, smart wearables only empower individuals through information. They do not yet offer treatments or cures, but they do alert users to deviations from normal, healthy activity. The regulatory hurdles facing these devices will likely keep them from entering the clinical world for a couple more years, but scientists and tech investors alike are placing major bets on a bright future for wearables in medicine. ^{EN}

DEVICES ON DECK

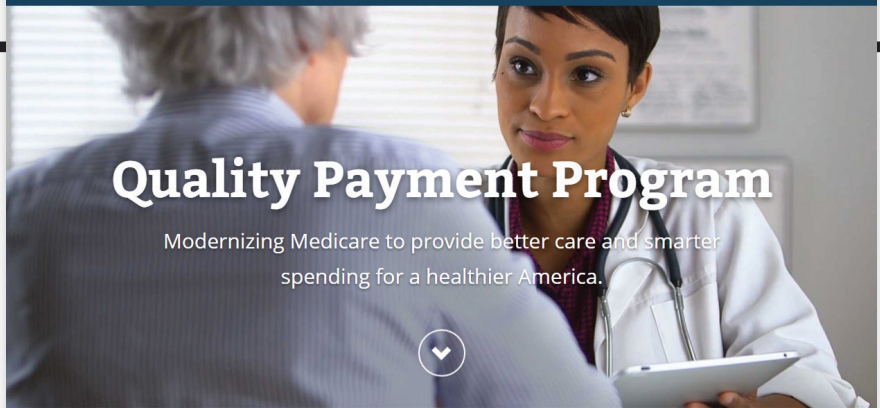
- ▶ **Code4Armour** — A wristband with NFC (near field communication) technology that allows emergency responders to unlock vital personal health records during emergency medical care.
- ▶ **Empatica Embrace Watch** — A wristband that syncs with a mobile app via a Bluetooth connection to alert caregivers when the wearer experiences a seizure.
- ▶ **Quell** — Straps on below the knee and claims to reduce the need for pain medication in 67% of users by tapping into the body’s “natural pain relief system” through electrodes.
- ▶ **Unaliwear Kanega** — Intended for seniors, this device detects falls, reminds users to take meds, and offers audio directions back home to limit wandering off.
- ▶ **TZOA Enviro-Tracker** — Clips to clothing and detects environmental factors like humidity, UV light, and air quality.
- ▶ **Smart Diaper** — Uses chemical markers in children’s urine and detects issues like type 1 diabetes and urinary tract infections.
- ▶ **Netatmo June** — Gathers data on UV exposure and lets users know when they’ve reached their recommended limit.
- ▶ **FitGuard** — A mouth guard that detects head injuries in athletes using an accelerometer, which tracks force of impact.
- ▶ **Duo Fertility** — Continually measures body basal temperature to naturally maximize the chances of pregnancy.

MAPES IS A WASHINGTON D.C.-BASED FREELANCE WRITER AND A REGULAR CONTRIBUTOR TO *ENDOCRINE NEWS*. SHE WROTE ABOUT HOW TO WRITE A SUCCESSFUL RESEARCH GRANT IN THE OCTOBER ISSUE.

ADVOCACY

CMS Releases Final Regulations on New Medicare Payment System

More info can be found at qpp.cms.gov or at the Endocrine Society's www.endocrine.org/macra.



Quality Payment Program

Modernizing Medicare to provide better care and smarter spending for a healthier America.



What's the Quality Payment Program?

The Quality Payment Program improves Medicare by helping you focus on care quality and the one thing that matters most — making patients healthier. The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) ended the Sustainable Growth Rate formula, which threatened clinicians participating in Medicare with potential payment cliffs for 13 years. If you participate in Medicare Part B, you are part of the dedicated team of clinicians who serve more than 55 million of the country's most vulnerable Americans, and the Quality Payment Program's purpose is to provide new tools and resources to help you give your patients the best possible care. You can choose how you want to participate based on your practice size, specialty, location, or patient population.

On October 14, the Centers for Medicare and Medicaid Services (CMS) released its final regulations on how it plans to implement the new payment system called the Medicare Quality Payment Program (QPP). The QPP will begin on January 1, 2017, and is intended to restructure the way in which clinicians are compensated for the services they provide and marks a clear transition to value-based healthcare delivery. In the final rule, CMS has provided flexibility for clinicians who may not be ready to fully transition to the QPP on January 1, which was the primary recommendation in the Society's comments on the Proposed Rule. This "pick your pace" approach will give practices until October 2, 2017, to begin participating in the program. Regardless of when you begin participating, performance data must be submitted to CMS by March 31, 2018.

This performance data will serve as the basis of 2019 payments, which will be increased, decreased, or remain flat depending on the quality, resource use, clinical practice improvement activities, and meaningful use of electronic health record technology that is reported by the practice. Practices must submit at least one quality measure, improvement activity, or other measure of performance in order to avoid a 4% penalty in 2019.

The QPP contains two tracks to provide clinicians with practice-centered options for participation. The first track allows groups who wish to take part in an Advanced Alternative Payment Model (APM) to receive a 5% incentive payment for their participation. Initial analysis of the Final Rule shows that CMS has eased the risk criteria for a model to qualify as an Advanced APM to address concerns that many practices would be ineligible to participate in an existing

Advanced APM. A final list of qualifying Advanced APMs will be released by January 1, 2017.

For those practices that choose not to participate in an Advanced APM, the second track allows practices to earn a performance-based payment adjustment through the Merit-based Incentive Payment System (MIPS). Payment adjustment will be based on data reported in four categories: Quality, Improvement Activities, Advancing Care Information, and Cost. Performance in each category will become part of the composite score for the practice. In a change from the Proposed Rule, CMS has determined that Cost information will not be factored into a practice's composite score for payment adjustment purposes in 2017. Individual or group reporting will continue to be options.

The Society expressed significant concerns about the patient attribution methodology in our Proposed Rule comments as CMS is expected to still be in the process of revising the methodology after the start of the 2017 reporting period. As accurate attribution of costs to a specific clinician will be a challenge, we recommended that this category be down weighted to 0 until an accurate attribution methodology is developed and reviewed.

We also urged CMS to provide support for small and rural practices to ease the transition. There are a number of flexibilities in the Final Rule to help these practices, including exemptions for low-volume practices, allowances for patient-centered medical homes, and increased technical assistance. The Medicare Access and CHIP Reauthorization Act (MACRA) provides \$20 million each year for five years to fund training and education for Medicare clinicians in



Endocrine Society members and staff alike took to Capitol Hill for the Rally for Medical Research Hill Day and surround Rep. Gregory Meeks (D-NY).

Endocrine Society Takes to Capitol Hill on NIH Funding, EDCs

With the presidential election on the horizon and NIH funding hanging in the balance, the Endocrine Society's members have been especially active on Capitol Hill this fall. In September, the Society held a widely attended briefing on Capitol Hill about the public health impacts of endocrine-disrupting chemicals (EDCs), attended a hearing on an important piece of legislation that would regulate known endocrine disruptors in personal care products, and participated in a Hill Day to urge members of Congress to support the NIH in 2017. The advocacy team is now looking forward to building on recent progress following the presidential election.

Endocrine Society Partners with NIEHS to Hold Briefing on EDCs

On September 21, the Endocrine Society collaborated with the National Institute of Environmental Health Sciences (NIEHS) on an educational briefing entitled "From Hormones to Brain Development: 25 Years of Groundbreaking Research on Endocrine-Disrupting Chemicals." Speakers included Linda Birnbaum, PhD, director of the NIEHS, as well as Society members John McLachlan, PhD, Tracey Woodruff, PhD, and Andrea Gore, PhD. The briefing was designed to educate members of Congress and their staff about the tremendous progress made in EDC research over the past 25 years and how new discoveries have helped us understand how exposures to EDCs contribute to critical health problems such as changes in brain development and reproductive health complications.

Senate HELP Committee Conducts Hearing on Personal Care Products Legislation

The Senate Committee on Health, Education, Labor, and Pensions (HELP) held a hearing for bill S. 1014, the Personal Care Products Safety Act, on September 22. The Society has been an avid supporter of this bill, which provides a regulatory mechanism for the Food and Drug Administration to review the ingredients found in everyday personal care products. The scientific evidence for human health impacts due to the presence of EDCs in personal care products is mounting, and Society experts agree that this legislation is a step in the right direction.

Society Members Participate in Rally for Medical Research

On September 22, Society members and staff participated in the third annual Rally for Medical Research. Participants in the Rally highlighted the NIH and scientific achievements made possible through federal funding of biomedical research and urged the federal government to approve a \$35 billion spending package for the NIH and its programs in 2017. Over 300 participants from 38 states attended the event and met with 238 congressional offices in one day. A strong Facebook and Twitter campaign allowed others around the country to show their support.

By Jessica Harris, specialist, Government and Public Affairs, Endocrine Society

individual or small group practices of 15 clinicians or fewer and those working in underserved areas.

The Society is currently reviewing the final regulations and will provide members with a comprehensive overview of how this impacts endocrinology in *Endocrine Insider*. In the meantime, CMS has launched a resource center to help clinicians navigate the new regulations and determine which measures and improvement activities that are most meaningful for their practice at qpp.cms.gov. We have also launched a new web page designed to provide our members with a one-stop shop for resources to help with the transition to the new payment system. The recent Clinical Endocrinology Update meeting included a session that provided attendees with a comprehensive overview of MACRA based on the Proposed Rule; a recording of this session is available on the MACRA web page, which can be accessed at www.endocrine.org/macra.

By Stephanie Kutler, director, Quality Improvement, Endocrine Society, and Meredith Dyer, associate director, Health Policy, Endocrine Society

Congress Faces a Difficult Lame Duck Session in November



Congress was able to agree to and pass a temporary funding bill before October 1 that will avert a federal government shutdown, keep the government running until December 9, and allow representatives and senators to go to their home districts and states to run for re-election. However, Congress faces a very difficult “lame duck” session when it returns to Washington following the November elections.

Congress is scheduled to be in session between November 14 and December 16, and, during that time, it has set the following major legislative decisions on its agenda: a final spending bill, a major package of biomedical measures, emergency aid for floods and Zika, defense authorization, campaign finance fights, a criminal justice overhaul, an energy policy conference, LGBT rights, and confirmation (maybe) of a Supreme Court nominee.

Below is a summary of what the Endocrine Society will be watching when Congress returns:

Omnibus or Minibuses?

Congressional leaders and the White House will have to determine how to wrap up the 11 remaining fiscal 2017 appropriations bills, solve disputes that bogged down negotiations over the continuing resolution (CR), and merge the vastly different spending bills that emerged from the House and Senate committees.

Their first step, however, will not have to do with policy or spending decisions, but with how to package those leftover spending bills. Republican leaders are already staking their support for passing a series of so-called minibuses that would group appropriations bills together, while Democrats are leaning toward an omnibus bill that would include all the bills. From the Society’s perspective, it would be better to have an omnibus spending bill so that the controversial issues surrounding the Labor-HHS-Education bill do not hold up funding for the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and various diabetes-related initiatives.

The second step will be laying out and coming to agreement on the dozens of policy issues that separated the House and the Senate as

well as the political parties throughout this year’s appropriations process. Hopefully, the fact that this will follow the elections and the corresponding partisan politics means the Congress will be able to reach agreement, although the fundamental policy and spending issues that always divide Republicans and Democrats will remain the same. During negotiations on the final spending bill or bills, we will continue to call for Congress to complete its work and pass a funding bill rather than a long-term CR, no sequestration cuts, and no “poison pill” policy riders as we advocate for at least \$34 billion for NIH.

21st-Century Cures

Republican leaders in the House and Senate indicated that they plan to prioritize passing a package of biomedical innovation bills known as 21st Century Cures (H.R. 6) during the lame duck session. 21st Century Cures was passed overwhelmingly by the House last year but has faced a more difficult path in the Senate over disagreements including fights about mandatory funding for the NIH.

Senate Majority Leader Mitch McConnell (R-KY) said that getting the legislation passed would be one of his main goals in the lame-duck session. “My own personal priorities are funding the government and the 21st Century Cures bill, which I think could end up being the most significant piece of legislation we pass in the whole Congress,” he said.

House Speaker Paul D. Ryan (R-WI) made a similar statement. “When we return in November, I look forward to completing work on some very important key initiatives that just haven’t quite gotten over the finish line,” the Wisconsin Republican said, citing the Cures bill. ^{EN}

By Mila Becker, JD, chief policy officer, Endocrine Society

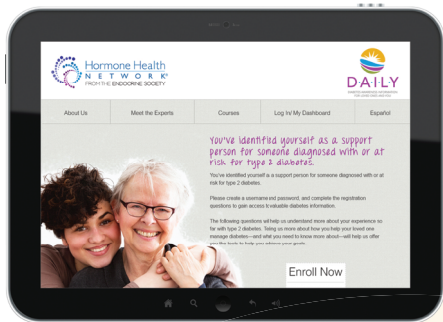
TAKE ACTION: We will keep Endocrine Society members apprised of the discussions in Washington and hope you will join our advocacy campaigns. For more information, please visit our online advocacy center at www.endocrine.org/advocacy.



DAILYDIABETES.ORG

D.A.I.L.Y. (DIABETES AWARENESS INFORMATION FOR LOVED ONES AND YOU) IS A NEW DIGITAL INTERACTIVE DIABETES EDUCATION TOOL FROM THE HORMONE HEALTH NETWORK.

This online platform is a multi-funded initiative to engage, activate and educate people with type 2 diabetes and members of the diabetes community to improve their knowledge, skills and confidence, enabling them to take increasing control of their own condition and integrate effective self-management strategies into their daily lives.

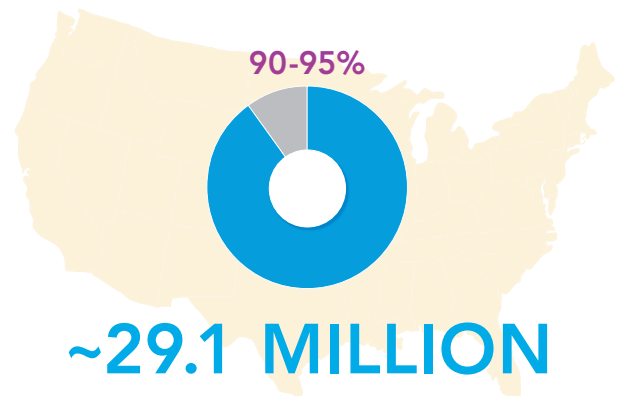


Currently, there is no online support community for type 2 diabetes patients and their families that focuses on how diabetes affects the entire family

and how patients can take an active role in managing their diabetes care. D.A.I.L.Y. will build a community of type 2 diabetes patients by providing access to experts who can address the full spectrum of issues for those newly diagnosed or living with diabetes, and those with diabetes complications.

D.A.I.L.Y. will offer a selection of courses focusing on topics ranging from the emotional components of diabetes; strategies for managing type 2 diabetes; and understanding treatment options (supported by Boehringer Ingelheim and Lilly Diabetes Alliance, and Janssen Pharmaceuticals). Each course will include assessments, videos, fact sheets, and peer-to-peer resources.

D.A.I.L.Y. ADDRESSES A MAJOR HEALTH THREAT IN OUR COUNTRY TODAY:



APPROXIMATELY 29.1 MILLION PEOPLE HAVE DIABETES AND TYPE 2 DIABETES ACCOUNTS FOR 90% TO 95% OF DIAGNOSED CASES OF DIABETES IN ADULTS, ACCORDING TO THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC).¹

7 MILLION

ANOTHER 7 MILLION PEOPLE HAVE TYPE 2 DIABETES AND DON'T EVEN KNOW IT, ACCORDING TO THE ENDOCRINE SOCIETY.²



ONE OUT OF THREE PEOPLE WILL DEVELOP TYPE 2 DIABETES AT SOME POINT IN THEIR LIFETIME.³

D.A.I.L.Y. RESPONDS TO THIS SOCIAL AND HEALTH ISSUE AND FOCUSES ON INSPIRING AMERICANS WITH DIABETES TO TAKE CONTROL OF THEIR CONDITION.



D.A.I.L.Y. ALSO PROVIDES TIPS FOR LOVED ONES TO SUPPORT PEOPLE WITH DIABETES, AND ULTIMATELY, IMPACT THE FUTURE HEALTH OF MILLIONS OF AMERICANS.



D.A.I.L.Y. GOALS

Enroll individuals from diverse patient populations, particularly:

- Patients and caregivers who struggle with managing diabetes
- Individuals who are effective managers seeking additional resources and tips
- Detached patients who don't want to "deal" with their diabetes because they feel "fine" now and may be unaware of how their diabetes can change over time
- Elderly patients whose diabetes is complicated by other comorbidities

Empower patients, through a unique platform, with the day-to-day skills, strategies and resources necessary to live their best life possible with type 2 diabetes.

Increase patient adherence for better outcomes — and the ability to track each patient's journey.

Create an online community for D.A.I.L.Y. members to provide ongoing peer-to-peer support and encouragement and use existing HHN social media to augment the community.

Equip healthcare providers with D.A.I.L.Y. patient resources.

REFERENCES

¹National Diabetes Statistics Report. Centers for Disease Control and Prevention, 2014. <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>

²Endocrine Society. *Endocrine Facts and Figures: Diabetes. First Edition.* 2015.

³Diabetes in the United States. Centers for Disease Control and Prevention. www.cdc.gov/diabetes/prevention.

INTRODUCING OUR D.A.I.L.Y. EXPERT PANEL



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-M. Carol Greenlee, MD, FACE, FACP



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-T. Sean Vasaitis, PhD

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