Final "Perspectives on the News"

American Association of Clinical Endocrinology and American Diabetes Association 2011

ZACHARY T. BLOOMGARDEN, MD

Genomics and diabetes

At a plenary session of the American Association of Clinical Endocrinology (AACE) Annual Meeting in April 2011, Eric Topol, La Jolla, California, discussed the concept that genomics can be used to create "a revolution in medicine" for diabetes prevention and management. Although the decoding of the human genome was greeted with much fanfare in 2000, this information "has failed so far to produce medical miracles." There has, however, been remarkable progress in the use of the human genome to understand the underpinning of many common diseases. We are progressing from genome-wide association studies (GWASs), involving 10^6 single nucleotide polymorphisms (SNPs) and providing insight into common gene variations with population frequency >5%, to whole-exon sequencing of 1.5% of the genome, finding rare and low frequency elements, to whole genome sequencing, allowing an understanding of regulatory as well as coding sequences. More than one thousand GWASs have been carried out, identifying several hundred traits tracking with important diseases. The discovery of a variant of transcription factor 7-like 2 (TCF7L2) associated with diabetes may lead to the greatest understanding of its pathogenesis, and a number of other polymorphisms have been found to be related to diabetes.

A meta-analysis of GWAS data from over 100,00 individuals confirms 38 gene loci (1), and a recent review cites 67 loci for nonautoimmune diabetes (2), suggesting that there are many different genetic pathways to its development. Topol suggested that diabetes risk is associated with "a combination of lower variants below the 5% threshold . . . down to <1%" (3). He reviewed a number of interesting candidates, including regions of the genome that do not appear to code for specific peptides but, rather, regulate transcription of other genes (4). Another potential cause is variation in the melatonin receptor 1b, which, like TCF7L2, is associated with impairment in insulin secretion (5). More precise whole-exon sequencing should allow us to even better understand the "root causes" of diabetes. Topol cautioned that, with our present technology, genetic information is not "any better than traditional risk factors" in identifying individuals who will develop diabetes (6). As more loci are identified, we may be better able to measure risk, and coupling of gene variant analysis with metabolite profiles may even better predict which individuals will develop diabetes (7). "If we did know, precisely, who was destined to become a diabetic," Topol continued, "we have many therapies that would be preventative." Furthermore, genetic analysis may allow an understanding of which medications are most appropriate for a given individual, with TCF7L2 variant analysis predicting greater response to sulfonylureas (8) and other gene variants predicting response to metformin (9). "As we look at this," Topol said, "there are different pathways . . . which could lead to a much more sound, much more precise prevention [and] treatment," allowing understanding of which single agent or combination of agents from the 11 classes of glucose-lowering drugs would be most appropriate for a given person. "We practice medicine on a population basis," Topol explained, asking, "Aren't we better than that? Can't we use the sequence of each individual?"

"We are, of course, just getting started here," Topol concluded, noting that although a gene associated with cystic fibrosis was discovered in 1989 by Frances Collins, only recently has a drug been developed using the understanding of this gene's action. What if we could do this for diabetes? What if we could take a skin biopsy, coax it to form pluripotent stem cells, and then produce β-cells to test specific treatment approaches?

Critical care endocrine treatment strategies

At the AACE meeting, Grette van den Bergh, Leuven, Belgium, discussed patients with protracted critical illness, of whom 30% are in the hospital for >5 days and 10% for >3 weeks. In the prolonged phase, they lose lean tissue with preservation of adipose tissue mass. They have slow recovery from renal and respiratory failure, with reduced protein synthesis and increased proteolysis, leading to the idea that hormonal treatment might improve outcome. Many studies endeavoring to follow such approaches have, however, suffered from design flaws, and van den Bergh warned that appropriate treatments may be lost if we fail to understand the limitations of negative studies.

The endocrine changes of critical illness, all correlating with adverse outcome, are low insulin-like growth factor (IGF)-1 and ternary complex-binding proteins, low thyroxin and triiodothyronine, insufficiently elevated cortisol with decreased response to adrenocorticotrophic hormone (10), and hyperglycemia with insulin resistance. Treatment, however, has not shown benefit. Growth hormone appears to increase mortality, and thyroxin and cortisol have uncertain outcome. The lowest mortality is seen with normal glucose; mortality is somewhat higher in individuals with a history of diabetes, higher with hypoglycemia, and highest with hyperglycemia; and insulin led to benefit in van den Bergh's own studies, but this was not confirmed by a recent multicenter study (11). Why, she asked, are there conflicting results?

Growth hormone is released in a pulsatile fashion, and levels initially increase with critical illness. However, IGF-1 levels

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.
DOI: 10.2337/dc11-1800

decrease, and in the prolonged critical illness phase growth hormone levels are lower, with reduction in pulse amplitude, associated with further reduction in IGF-1, suggesting that acutely there is growth hormone resistance but that subsequently impaired growth hormone release predominates. In a trial of high-dose growth hormone treatment of 552 critically ill patients from the 2nd through the 4th weeks, mortality doubled (12), but van den Bergh argued that the high dose used was unphysiologic, noting that it led to higher glucose levels. Trials to correct thyroid deficiency with T4 and T3 also failed to show benefit but, again, may have used excessive doses. The multicenter study of intensive insulin treatment, van den Bergh said, compared intermediate relatively good control with very tight glucose control but caused a 13-fold increase in hypoglycemia, finding no morbidity difference and an actual increase in mortality. She argued that the feeding status of the intervention and control group was different and, most importantly, that capillary glucose meters are not sufficiently sensitive for reliable use in detecting hypoglycemia, and that, indeed, comparison in this study of meter and laboratory glucose showed "huge bias," with differences between different lots of strips. She asked whether NICE Sugar (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation), which improperly allowed use of capillary glucose testing with reagent strips, failing to reliably detect hypoglycemia, is going to lead us to "reject another excellent hypothesis because we used the wrong test."

Pancreatic islet stem cells

Gordon Weir, Boston, Massachusetts, discussed pancreatic islet stem cells at the AACE meeting, noting that replacement of β-cells with transplantation can reverse both type 1 and type 2 diabetes. The first islet transplants were carried out in 1972, with successful reversal of type 1 diabetes in 1989. A protocol developed with transplantation to the liver via the portal vein in Edmonton, Canada, currently appears optimal. Weir commented, however, that "the treatment is not durable." The major issues are the supply of insulin-producing cells and the development of safe approaches to avoiding rejection.

Human embryonic stem cells (ESCs) have been studied as approaches to producing islets (13,14). At present, full maturation of β-cells from ESCs can only be achieved in an in vivo environment after transplantation of precursor cells; we need to learn how to achieve full ESC maturation in vitro, which will require understanding of the final stages of β-cell maturation. Weir observed that neonatal β-cells require >30 days for glucose-stimulated insulin secretion to develop, with a variety of transcription factors involved (15), as well as a role of thyroid hormone, suggesting that maturation of mitochondrial shuttles may play a role—particularly important because the electron transport chain plays a crucial role in β-cell glucose recognition. Rather than requiring ESCs, one might be able to reprogram a patient's own tissues to generate pluripotent stem cells; in such a study, fibroblasts generated ESC-like cells with expression of specific genes (16). Rather than use of viral vectors, use of modified mRNA to achieve this might be possible. Thus, skin from a patient with diabetes might be used to generate new β-cells. Mesenchymal stem cells are another potential source and also appear to enhance islet regeneration from other cell types (17). Another idea is transdifferentiation of pancreatic exocrine to islet cells, which requires a specific set of growth factors: pancreatic and duodenal homeobox 1 (Pdx1), which is involved in pancreas formation and maintains normal β-cell differentiation, and neurogenin (Ngn)3 and Mafa (18). Autoimmunity would remain an issue in type 1 diabetes, so Weir speculated that, if these technologies can be developed, better results might be achieved with transplantation of islets in type 2 diabetes.

β-Cell mass is increased with insulin resistance, obesity, and inactivity, with hyperplasia and perhaps hypertrophy. Weir noted that adenosine kinase inhibition selectively promotes islet β-cell replication so that it may be possible to develop adenosine kinase inhibitors to promote this process, which appears to prevent methylation reactions that restrain β-cell replication. The gene product menin plays roles in gene transcription, maintenance of genomic integrity, and control of cell division and differentiation and is deficient or inactive in multiple endocrine neoplasia type 1. Menin inhibits β-cell replication, as part of a histone methyltransferase process, and specific menin inhibitors may be useful in developing approaches to increase β-cell mass therapeutically. Neogenesis of β-cells in pancreatic ducts occurs, Weir said, again introducing the issue of how to increase production levels for treating diabetes. Although glucagon-like peptide-1 may increase this process, there is no evidence that incretin-based therapy has such effects.

The current need for immunosuppressive drugs remains problematic, particularly with nephrotoxicity, and efforts to induce tolerance, specific treatments for autoimmunity, and encapsulation are possible approaches. Weir discussed encapsulation, i.e., use of a semipermeable membrane around transplanted islets to prevent rejection, noting that treatment of autoimmunity and safer immunosuppressant treatments may not be possible and reviewing a study that used alginate encapsulation (19). New materials are being developed with rapid screening approaches (20) that make such approaches seem feasible.

Does the β-cell cause insulin resistance?

Barbara Corkey, Boston, Massachusetts, gave the Banting Lecture at the 71st Scientific Sessions of the American Diabetes Association (ADA), San Diego, CA, 24–28 June 2011, in which she asked whether hypersecretion of insulin is the cause or consequence of diabetes. There has, she said, been progressive change in the population prevalence of obesity, in conjunction with changes in dietary patterns, activity levels, toxin exposure, and use of pharmacologic agents such as antidepressants. Food "is different today than it was in the past," she said, and there has not, she suggested, been sufficient evaluation of the relationships between changes in diet, particularly in increased ingestion of processed food, and the likelihood of obesity and diabetes. In addition to the increase in food intake, the average weight of the poultry we eat has increased while the age at which the animals are marketed has decreased, the fruits we eat have decreased mineral composition, and most foods contain preservatives, emulsifiers, flavoring agents, and fillers to which humans have not until recently been exposed.

The pancreatic islets, liver, fat cells, and many other tissues are profoundly affected by nutrient intake. Corkey proposed that environmentally derived β-cell basal hypersecretion causes diabetes. During progression from normal to obesity to prediabetes to diabetes, insulin levels increase ninefold. In a rodent model using an osmotic minipump to increase circulating

insulin levels, she showed evidence that insulin resistance develops; in man, administration of the potassium channel–opening agent diazoxide, which decreases insulin secretion, increases insulin sensitivity, and under certain circumstances improves glycemia. She suggested that metabolic signals change β-cell secretion, adipose tissue fat metabolism, and hepatic glucose production versus uptake.

Recall that oxidation-reduction (redox) reactions involve the transfer of electrons between molecules. The intracellular cytosolic and mitochondrial redox states can be inferred from circulating lactate-to-pyruvate and β-OH-butyrate–to–acetoacetate ratios, respectively. Corkey reviewed free fatty acid infusion studies performed by Gunther Boden, in which hyperinsulinemia develops, with stable glucose levels after a brief initial dip. She suggested that such a finding of increased insulin secretion at "non-stimulatory glucose levels" may reflect a redox change, which might ultimately lead to insulin resistance both in the liver and in adipocytes. Her group has screened a number of substances that have entered the food supply, including monoacylglycerides (MAGs), used as emulsifiers and preservatives; artificial sweeteners; and iron. All of these stimulate basal insulin secretion in vitro and, to some extent, in vivo. Iron consumption has increased, she noted, as the lean content of food animals has increased. The β-cell is unique because its glucose metabolism generates sequential signals, increasing ATP and also malonyl CoA, closing the potassium channel, and leading to increased intracytoplasmic calcium and insulin exocytosis. MAGs did not increase intracellular calcium but rapidly increased the redox state; Corkey speculated that both MAGs and iron increase intramitochondrial generation of reactive oxygen species (ROS). The redox state and ROS may act as signals to basal insulin secretion.

The use of the ROS scavenger *N*-acetyl cysteine decreased MAG-induced insulin secretion. β-OH-butyrate increases ROS and basal insulin secretion in a dose-dependent fashion, suggesting that a variety of fuels and agents that stimulate ROS may modulate β-cell secretion. Other potential signals include long-chain fatty acid CoA, which like calcium can directly increase insulin exocytosis, and long-chain fatty acids, which increase MAG. Diabetes is associated with increased free fatty acids, branched-chain amino acids, and lactate. These metabolite profiles may increase insulin secretion and may be useful in predicting the risk of developing diabetes. Furthermore, the redox state affects adipocytes in a fashion similar to that in β-cells, and redox changes with nutritional state may influence hepatic metabolism as well, leading Corkey to conclude that dietary interventions based on the relationship between dietary constituents and redox state might prevent β-cell hypersecretion, improving insulin sensitivity.

Is the Food and Drug Administration hindering diabetes treatment?

Two perspectives presented in a symposium at the ADA meeting discussed the complex role of the U.S. Food and Drug Administration (FDA) in the regulation of monitoring, drugs, and devices for diabetes. Aaron Kowalski, New York, New York, from the Juvenile Diabetes Research Foundation, noted that FDA decisions have broad effects affecting the time line of device and drug development but that FDA requirements for end points for novel therapies are not well-defined. He suggested this to be particularly relevant for devices for type 1 diabetes, stating, "Patients have a unique voice in this ... [because they are] self-managing their disease." Patients do want safe treatments, he said, but consider delays in access to novel approaches unacceptable, given the risks of living with diabetes. He used as an example the artificial pancreas, which combines the insulin pump, continuous glucose monitor, and a software algorithm connecting the two, aiming for the avoidance of hypoglycemia and achievement of glucose targets. Part of the effort of the Juvenile Diabetes Research Foundation led to FDA approval of algorithm development simulation rather than requiring animal studies. Such "smart algorithms" do appear to prevent nocturnal hypoglycemia (21), suggesting that "this is a treatment we could use right now ... [with] very low risk and very high potential benefit ... [that] could eliminate 80% of hypoglycemia overnight." Furthermore, closed-loop controller systems have been shown to reduce variability and hypoglycemia risk overnight (22). Studies are being carried out with dual insulin and glucagon infusion to further minimize hypoglycemia (23). The FDA has, Kowalski said, promised a guidance document giving its expectations, but he indicated his frustration at the more rapid approval of such products in Europe along with his concern that companies might "abandon the U.S." A Medtronic product suspending insulin delivery during hyperglycemia has been approved outside the U.S. for nearly 3 years.

Mark Fineman, San Diego, California, from Elcelyx Therapeutics sympathized with the "underappreciated" difficulty of the FDA task but described what he saw as a regulatory trend in the U.S. to have higher scrutiny of safety in development and postmarketing, leading to longer and unpredictable review times, more review cycles, and late-stage project withdrawals. He asked, "Who will fund these risks?" Venture funding of innovation is declining, he said, with the potential for reduced U.S. competitiveness and for impact on patients. The Prescription Drug User Fee Acts of 2002 and 2007 led to development of a Risk Evaluation and Mitigation Strategy (REMS), producing the 2008 guidance for industry on evaluating cardiovascular risk of new antidiabetes therapies. The upper bound for the two-sided 95% CI of estimated risk ratio must be <1.8, and once a product is marketed, this upper bound must be shown to be <1.3 (24). What Fineman described as the unintended consequence is the moving target for industry that "you can't predict, if you can't predict you can't plan, and if you can't plan you can't run an industry." Benefit-risk evaluation has, he said, gone out of balance, with "possible risk" becoming an overly great concern. As an example, he discussed the lack of clarity of the path to approval for weight loss drugs, which appear to be relevant to slowing the progression and delaying the onset of type 2 diabetes. The Orexigen Therapeutics product Contrave is a combination of slow-release formulations of naltrexone and buproprion. Both of these agents have been marketed for >20 years. Although the latter agent has long been recognized to cause a small increase in heart rate and blood pressure, the FDA in January 2011 informed Orexigen that a cardiovascular outcome trial was required before approval and subsequently gave notice that Orexigen would be obliged to undertake a rather stringent cardiovascular outcome trial, which the manufacturer estimated would require a 100,000 person-years study. "This just gets to the point of uncertainty," Fineman said. As a second example, he cited the once-weekly form of exenatide, whose "results fell within the guidance." Because of the suspicion that a linear relationship might be present between blood level of exenatide and the corrected electrocardiographic QT interval, the FDA required a new study, leading to

a 12- to 18-month delay in U.S. approval while the drug was approved in Europe. "It's pretty clear that innovation is declining," Fineman continued. "Given the time required to move a therapy from concept to patient, stalled innovation today will have an impact for at least a decade to come." He pointed out that diabetes treatment–related investment peaked in 2007 and has subsequently declined both for new drugs and for new devices, although "All of this is in the face of a diabetes and obesity epidemic that's breaking the bank."

Approaches to care

At a symposium on health care access and cost, Marshall H. Chin, Chicago, Illinois, began by commenting that, although we would want access to care, quality of care, and low cost, we can only have two of the three, leading to the dilemma of finding a way to maximize all of them. We have the ability to deliver excellent quality in diabetes, he said, but not good access or cost, so we must lead not only in innovation but also in implementation and translation of measures to improve glycemia, blood pressure, lipids, nutrition, cigarette use, and the many other factors involved in the care of patients with diabetes. Many current projections suggest progressively increasing health care costs, raising the likelihood of budget cuts, so that it is important to assess methods of payment for health care services. Fee for service is, Chin said, "the predominant mode. . . . The more patients you see, the higher your reimbursement, [with] procedures . . . much, much better reimbursed than cognition," perhaps because the relative value scale update committee of the American Medical Association is heavily weighted toward procedure-oriented specialties. Chin stated that managed-care incentives for providers and patients to use less expensive treatment were demonstrated to decrease inpatient and outpatient costs but were criticized when introduced in the 1980s as reducing care. Pay-for-performance provider- or group-level incentives are controversial, with the potential to cause physicians to avoid treating patients with serious illness, so it is not clear whether these approaches lead to real improvement (25). Global/bundled payments and capitation similarly have issues with appropriate risk adjustment and have the potential of encouraging underuse, leading to adverse health outcome. Another suggested approach is to use "consumer-directed health care" to choose lower-cost providers.

Chin suggested another approach, based on improving health care efficiency. The U.S. Department of Health and Human Services Agency for Healthcare Research and Quality is developing a concept of value-based purchasing, based on the idea that health care buyers should hold providers to standards using contracts, information, quality management, incentives, and consumer education (http://www.ahrq.gov/qual/efficiency/). This has led to the development of "accountable care organizations" (ACOs), perhaps based on extended hospital staffs (26), although it remains unclear how these will affect access to, quality of, and cost of health care; what incentives are needed to institute such approaches; and whether there is the potential for unintended consequences.

Robert Reid, Seattle, Washington, discussed another approach to improving health care. There is, he said, evidence that primary care improves outcome, improves efficiency, and increases access to care (27). The approach promotes ongoing relationships independent of disease and allows coordination of care. Access to primary care is, however, difficult, particularly for the economically disadvantaged; quality may be mediocre; and the payment system is antiquated, with many valuable functions unrewarded, leading primary care to become an unattractive career choice. "Patient Centered Medical Homes" have many features of primary care but support treatment of chronic illness, relying on innovative information technology approaches and revised mechanisms of reimbursement (28). Pilot projects are underway in many states to study this approach. His organization, Group Health, is an integrated health care insurance system in Washington State. Workload pressures on primary care a decade ago led to greater use and cost in emergency departments and hospitalizations, declining quality, and a looming workforce crisis with early retirements, shift to part-time work, and difficulty recruiting. Over the past 5 years, primary care panel size has decreased from 2,300 to 1,800; appointment duration increased from 20 to 30 min, with additional desktop time "where providers could actually do the tasks of reaching out to patients" using e-technology; and more calls have been redirected to the primary care team. With secure e-mail, better use of phone encounters, patient-centered outreach to track emergency and urgent care visits and hospital discharges, and use of daily mandatory "team huddles," the process of care has improved (29). Patients report more shared decision making and better access. Quality-of-care measures have improved, particularly those related to diabetes. Staff "emotional exhaustion" and "depersonalization" have decreased while in-person primary care visits, emergency department use, preventable hospitalizations, and total hospitalizations decreased, so the total cost per patient per month has been constant. Reid acknowledged the dilemma that the move from fee for service to other payment systems is not straightforward and that, overall, "it is a hard, hard process. . . . You have to be very patient."

Ateev Mehrotra, Pittsburgh, Pennsylvania, discussed "retail clinics," a growing aspect of health care. These are located in retail stores, typically adjacent to pharmacies, staffed by nurse practitioners, not requiring an appointment, and offering care using evidence-based algorithms. The clinic gives consumers a specific "menu" of conditions, such as conjunctivitis, upper-respiratory infection, and wellness and prevention (30). There are 1,200 such clinics, most operated by a large store, usually a pharmacy chain, partnering with a health system such as that of the Cleveland Clinic. CVS Therapeutics has trademarked "Monitoring Made Easy for Diabetes" for its MinuteClinics in 25 states, which advertise that they measure A1C, cholesterol, and kidney function; measure blood pressure and BMI; perform a foot exam; and "provide immediate results, answer your questions, and educate you on what everything means" at a cost of $79 (http://www.minuteclinic.com/diabetes/). Mehrotra noted that the care of diabetes is "relatively well-suited" to nurse-led clinics and nurse case management and pointed out that although "physicians haven't been very excited about this trend," politicians have touted its benefits. Do these clinics improve access or undermine the patient-doctor relationship? Do they follow guidelines and, hence, have high quality or, because of the limited "menu," do they deliver poor quality, with incentive to overprescribe because of their relationship to pharmacies? Do they decrease emergency department visits and, hence, overall costs or increase cost by prompting unnecessary health care follow-up? The close travel distance, short wait, and low cost for uninsured individuals have made these clinics attractive to younger individuals with acute infections (31). Quality appears similar to that in physicians' offices and

emergency departments, patient satisfaction is high, and cost is approximately one-third lower than in physicians' offices and two-thirds lower than in emergency departments. Mehrotra brought up the concept of "disruptive innovation" (http://www.claytonchristensen.com/disruptive_innovation.html), with novel approaches typically coming from outsiders, providing less costly services, and eventually supplanting existing businesses. He wondered whether this might be occurring in medical care, particularly in diabetes, for which care can be delivered via protocol, particularly with increasing use of information technology.

Richard Swanson, Los Angeles, California, from the California Association of Physician Groups, further discussed ACOs, noting that nearly two-thirds of patients in his state are enrolled in managed-care organizations, which he compared favorably to fee for service, and suggesting that if providers have control over services the costs can be reduced, with profit achieved by providing the most appropriate care. Indeed, he said, this model has been successful in giving California a very low average hospital length of stay. Because the health-maintenance organization model appears to allow insurance executives to make medical decisions and does not allow patients to have a choice of physician, capitation systems are not politically desirable. ACOs are different forms of managed-care organization, with physicians in control and with beneficiaries unaware that they have been enrolled in the program. Indeed, assignment to an ACO will be retrospective, and, of concern, the exact rules for patient assignment have not been made clear. ACOs can be based on medical groups or on networks of physicians but also can be hospital-physician joint ventures. There are a number of complex rules for ACOs that have recently been modified (for current information, see http://www.cms.gov/ACO/). ACOs will, in theory, provide higher quality at reduced costs, but the shared savings will be based on a series of complicated formulas and benchmarks and the ACO will need to share in losses as well as gains; this model has been extolled by some commentators (32), although it may discourage some potential participants. ACOs are scheduled to begin operation in 2012.

Final "Perspectives on the News"

As part of the International Diabetes Federation Blue Light Campaign, on 14 November 2010, a strong rally of several thousand participants at the Great Wall of China marked World Diabetes Day (Fig. 1). Mao Zedong's epigram不到长城非好汉 means, "Not reaching the Great Wall, not a good man." The message was not to literally climb a mountain. Rather, we are to an extent defined by our goals and our journey. Each of us should find—and climb—our Great Wall. Extending the metaphor, though, we should realize that the Great Wall has no end point. It is, rather, a series of summits, winding along thousands of miles.

This will be the last article in the 18-year "Perspectives on the News" series. Awareness of the importance of diabetes, the goal of World Diabetes Day, has been basic to the entire series and remains the impetus for my ongoing endeavor to understand and explain the biological and human intricacies of diabetes.

Figure 1—*World Diabetes Day at the Great Wall of China, 14 November 2010. Courtesy of Prof. Linong Ji, Department of Endocrinology, Peking University People's Hospital, Beijing, China.*

Acknowledgments—Z.T.B. has served on speaker's bureaus of Merck, Novo Nordisk, Lilly, Amylin, Daiichi Sankyo, and GlaxoSmithKline; has served on advisory panels for Medtronic, Takeda, Merck, AtheroGenics, CV Therapeutics, Daiichi Sankyo, BMS, and AstraZeneca; holds stock in Abbott, Bard, Medtronic, Merck, Millipore, Novartis, and Roche; and has served as a consultant for Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, and Nastech. No other potential conflicts of interest relevant to this article were reported.

References

1. Voight BF, Scott LJ, Steinthorsdottir V, et al.; MAGIC investigators; GIANT Consortium. Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 2010;42:579–589
2. McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med 2010;363:2339–2350
3. O'Rahilly S. Human genetics illuminates the paths to metabolic disease. Nature 2009;462:307–314
4. Harismendy O, Notani D, Song X, et al. 9p21 DNA variants associated with coronary artery disease impair interferon-γ signalling response. Nature 2011;470:264–268
5. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet 2009;41:89–94
6. Meigs JB, Shrader P, Sullivan LM, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med 2008;359:2208–2219
7. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–453

8. Pearson ER, Donnelly LA, Kimber C, et al. Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study. Diabetes 2007;56:2178–2182
9. Zhou K, Bellenguez C, Spencer CC, et al.; GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group; Wellcome Trust Case Control Consortium 2; MAGIC investigators. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. Nat Genet 2011;43:117–120
10. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 2000;283:1038–1045
11. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
12. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999;341:785–792
13. D'Amour KA, Bang AG, Eliazer S, et al. Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol 2006;24:1392–1401
14. Kroon E, Martinson LA, Kadoya K, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol 2008;26:443–452
15. Aguayo-Mazzucato C, Koh A, El Khattabi I, et al. Mafa expression enhances glucose-responsive insulin secretion in neonatal rat beta cells. Diabetologia 2011;54:583–593
16. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–676
17. Abdi R, Fiorina P, Adra CN, Atkinson M, Sayegh MH. Immunomodulation by mesenchymal stem cells: a potential therapeutic strategy for type 1 diabetes. Diabetes 2008;57:1759–1767
18. Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA. In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. Nature 2008;455:627–632
19. Duvivier-Kali VF, Omer A, Parent RJ, O'Neil JJ, Weir GC. Complete protection of islets against allorejection and autoimmunity by a simple barium-alginate membrane. Diabetes 2001;50:1698–1705
20. Bratlie KM, Dang TT, Lyle S, et al. Rapid biocompatibility analysis of materials via in vivo fluorescence imaging of mouse models. PLoS ONE 2010;5:e10032
21. Buckingham B, Chase HP, Dassau E, et al. Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Care 2010;33:1013–1017
22. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet 2010;375:743–751
23. Russell SJ, El-Khatib FH, Nathan DM, Damiano ER. Efficacy determinants of subcutaneous microdose glucagon during closed-loop control. J Diabetes Sci Tech 2010;4:1288–1304
24. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes [article online]. Available from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf. Accessed 10 September 2011
25. Petersen LA, Woodard LD, Urech T, Daw C, Sookanan S. Does pay-for-performance improve the quality of health care? Ann Intern Med 2006;145:265–272
26. Fisher ES, Staiger DO, Bynum JP, Gottlieb DJ. Creating accountable care organizations: the extended hospital medical staff. Health Aff (Millwood) 2007;26:w44–w57
27. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q 2005;83:457–502
28. Grumbach K, Bodenheimer T. A primary care home for Americans: putting the house in order. JAMA 2002;288:889–893
29. Larson EB, Reid R. The patient-centered medical home movement: why now? JAMA 2010;303:1644–1645
30. Rudavsky R, Pollack CE, Mehrotra A. The geographic distribution, ownership, prices, and scope of practice at retail clinics. Ann Intern Med 2009;151:315–320
31. Mehrotra A, Wang MC, Lave JR, Adams JL, McGlynn EA. Retail clinics, primary care physicians, and emergency departments: a comparison of patients' visits. Health Aff (Millwood) 2008;27:1272–1282
32. Rosenthal MB, Cutler DM, Feder J. The ACO rules—striking the balance between participation and transformative potential. N Engl J Med 2011;365:e6