Comparative Effectiveness Research and Formulary Placement: The Case of Diabetes

Michael E. Chernew, PhD; Rick McKellar, BS; Wade Aubry, MD; Roy Beck, MD, PhD; Joshua Benner, PharmD, ScD; Jan E. Berger, MD, MJ; A. Mark Fendrick, MD; Felicia Forma, BSc; Dana Goldman, PhD; Anne Peters, MD; Rebecca Killion, MA; Darius Lakdawalla, PhD; Douglas K. Owens, MD; and Joe Stahl, MA

As the nation transforms its healthcare system—with or without the Affordable Care Act (ACA)—it must face the challenge of how to maintain, or even improve, the quality of care. This requires the system to be more nuanced; to encourage use of those healthcare services that produce greater health and discourage the use of those that produce less. Implementation of this simple idea requires first identifying the clinical benefit associated with different services.

Unfortunately, we cannot always identify when services improve health, as health benefit is dependent on the specific clinical scenario and patient population. In diabetes care, this is often borne out by the existence of complex comorbidities and complications. Understanding the clinical nuances of when and to whom services render the greatest benefit requires more research. The type of research that addresses this issue is commonly labeled comparative effectiveness research (CER)—although CER by other names has been around for years. Recognizing the need for stronger evidence-based practice, the ACA invested in greater CER by establishing the Patient-Centered Outcomes Research Institute (PCORI) which will commission independent CER.[1] Starting in 2011 and moving forward, PCORI will act as a funding source for independent research institutions to conduct CER-related research and will synthesize these findings and make them available to the public.

CER is especially important in diabetes care because of the pervasiveness and multifaceted nature of the disease. Diabetes is one of the nation's most prevalent chronic conditions, with over 8% of the US population living with the disease.[2] In part due to its chronic nature and because of several widely accepted high-value treatments, the management of diabetes has become a widespread benchmark of quality. For example, most standard quality measurement systems, including the Healthcare Effectiveness Data and Information Set and most pay-for-performance systems, include a series of diabetes-related measures. These include clinical services (ie, eye and foot exams) as well as drug management for hyperglycemia, hypertension, and hypercholesterolemia. Due in part to the effectiveness of treatment and disease management as compared with non-treatment, the US Preventive Services Task Force recommended diabetes screening as a high-value preventive service and in turn the ACA has mandated payers to provide diabetes screening without patient cost-sharing. While there is broad consensus that several treatments are clinically effective, there is still great opportunity for CER to elucidate the optimal combination of treatments for each patient population.

There is also an opportunity to gain much more value for the money we spend on the treatment of diabetes. The American Diabetes Association estimated around $116 billion in medical expenditures associated with treating diabetes in 2007, and perhaps as much as $58 billion in reduced worker productivity.[3] Pharmaceuticals represent about 12% of total health expenditure, but could potentially have a sizable spillover effect on inpatient and emergency department visits, as well as substantially reduce the risk of costly complications such as cardiovascular complications, amputation, and end-stage renal disease.[4,5] In addition, despite the proven value of early and aggressive treatment, diabetes-related medications generally share the same problematic adherence patterns seen in prescription use. While the drivers of adherence are many and complex, benefit design (and, specifically, member cost-sharing levels) has been tied to significant changes in patient behavior regardless of the clinical value of the medication.[6] Thus payers, and especially pharmacy benefit managers (PBMs) who play a pivotal role in managing formularies, have an opportunity to use CER to improve the value of spending on patients with diabetes.

The promise of CER will be realized only if patients, providers, insurers, and other stakeholders act on the findings. This can be done in several ways including supply side initiatives (Value Based Purchasing [VBP]) and demand side initiatives (Value Based Insurance Design [VBID]). In the case of pharmaceuticals, VBID entails using CER to guide formulary

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Take-Away Points

- Formularies of the future should use evidence founded on findings from comparative effectiveness research (CER) to better target, not limit, diabetes care.
- In the case of diabetes, partially due to the fact that many cases require more than 1 medication, suboptimal management (ie, lack of adherence due to cost-related issues) may lead to expensive complications.
- CER can provide the knowledge base for patient-specific formulary design, rather than class-specific design.

placement. Specifically, the alignment of clinical knowledge and financial incentives can promote an efficient delivery system. The status quo generally has failed to align quality improvement and cost containment initiatives. In fact, in some instances, these actually compete with each other, contributing directly to inefficiency.[7] In most situations, formulary placement and patient copayment amounts are based on the cost of a drug within its sub-class of therapeutically similar alternatives (eg, dipeptidyl peptidase-4 [DPP-4] X vs DPP-4 Y), not the value of the drug relative to treatments for other disease areas (eg, a DPP-4 vs an acne therapy), relative to alternative therapies for the same disease (eg, a DPP-4 X vs a thiazolidinedione [TZD] or a glucagon-like peptide-1), or relative to varying uses of the product (eg, a DPP-4 as first-line or fourth-line therapy). As a result, patients face the same out-of-pocket costs for all drugs on a given tier regardless of the relative therapeutic value provided.

A more thoughtful approach would be to use CER to guide and target formulary placement more efficiently and effectively. The idea of using CER to guide formulary placement is an important component of the principles of VBID. The basic VBID premise is to align patients' out-of-pocket costs with the value (defined as benefit relative to cost) of health services. This approach to designing benefit plans recognizes that different health services have different levels of value. By reducing barriers to high-value treatments (through lower costs to patients) and discouraging low-value treatments (through higher costs to patients), these plans can achieve improved health outcomes at any level of healthcare expenditure. This can be incorporated at 3 levels of sophistication—across disease areas (eg, diabetes vs acne), within disease areas (eg, DPP-4s vs TZDs), and within drug (eg, DPP-4 use first vs fourth line, or for patient x vs patient y, etc). The broadest application, and the easiest to implement and communicate, would be the entire class of diabetes medications placed on a tier that incentivizes (or avoids dis-incentivizing) adherence. A more refined approach would reserve preferred tier placement for diabetes treatment sub-classes. Finally, and both most coherent and most difficult, individual medications or services could be tiered according to specific needs or actions of a patient (ie, according to indication, place in therapy, program participation, etc). However, such an alignment of incentives is only possible in the setting of improved clinical evidence. Driven by CER, VBID represents a *clinically sensitive, fiscally responsible* approach that advocates keeping patient out-of-pocket payments low on high-value services and raising them on services of no or marginal clinical value.

Such an alignment of clinical and economic incentives facilitates patients making appropriate choices both because evidence suggests that formulary positioning can influence patient decisions on what product to use (ie, formulary positioning can drive positive change to more high-value use and not just lower-cost use), and to mitigate against the unintended consequence of increasingly higher cost sharing. When faced with higher costs, patients often make poor clinical decisions, which in fact could, in some cases, lead to greater overall costs.[8-10] By using incentives to encourage the use of high-value services and discourage the use of low-value ones, VBID has the potential to achieve marked increases in the efficiency of the healthcare system. More health can be achieved at any level of spending.

In the case of diabetes, VBID has already been implemented in several large corporations. Recognizing the clinical and potentially cost-saving value of diabetes medication, both Pitney Bowes and Marriott International, Inc, implemented a VBID program that reduced the copayments for diabetes treatment and a handful of other chronic conditions.[11] The University of Michigan took a related approach that focused solely on diabetes treatment, lowering copayments and coinsurance for diabetes-related office visits and medication.[12] These initiatives all identified the clinical and potential economic benefit of incentives disease management among diabetics and lowered out-of-pocket expenses across the board. This broad-stroke approach is a first, blunt step to aligning copayments with value. Refining the approach by adjusting formularies between classes of diabetes-related therapies to incentivize high-value use may prove effective at guiding patients to more efficient treatments. Going yet another step, there is potential for incorporating clinical nuance that differentiates the value of individual medications based on the profile or behavior of a specific patient.

Regardless of sophistication in application—across disease, within disease, across drug (the current formulary focus), or within drug—more coherent formulary development will also need to address the consequences of some CER-influenced decisions. From one extreme to the other—whether all diabe-

tes products are placed in a low tier because they are categorically considered to be of high value or whether only specific high-value uses of diabetes products are in a low tier—removing the primary role of formularies today (ie, tier differentiation based on cost for products with similar profiles) will greatly increase healthcare costs. This does not imply that the application of greater CER-facilitated sophisticated tier differentiation will come at the expense of cost management. For example, a low-cost diabetes product with high CER-defined health benefit could be placed in a low copay tier, while a high-cost product with a similar CER health benefit could be placed in a high copay tier despite high clinical utility. In these scenarios, however, it is crucial to recognize that incentives must balance the role of cost-sharing in unit cost control and behavior change with the potential to discourage the high-value treatment. Patients facing higher copays for drugs they are currently using may opt to take no medications instead of switching drugs. Payers and PBMs will need to evaluate the value of cost containment across products, with the potential trade-offs in high value product use—particularly as cost sharing rises over time.

In incorporating CER into formularies a few basic principles should be considered. First, CER should take a broad perspective. Notably, many CER studies will not compare one drug against another, but instead will compare one broad treatment strategy (eg, drug treatment) against another broad strategy (eg, surgery). In fact the Institute of Medicine CER priority list generally focused on these broad strategies as opposed to drug versus drug studies.[13] Formulary placement should not be based only on drug versus drug information. For example, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial demonstrated that outcomes from stents were no better than those with medical management.[14] Yet, use of drugs did not change with these findings, suggesting the need for improvement in the transition from research to implementation.

Second, CER should incorporate all outcomes, not just those directly related to the service. This includes the possible reduction in use of other services associated with greater medication adherence or disease management. While CER may not include economic outcomes (existing rules prohibit PCORI-funded CER from examining cost), assessment of value, and thus formulary placement, does require some attention to cost. Previous work has demonstrated that the spending offset associated with better drug adherence may be significant. For instance, a Medicare policy change in California in 2002 that raised office visit and drug copayments by $5 to $20 was associated with a 6% greater likelihood of being hospitalized.[5] This greater expenditure on inpatient hospitalization offset around 20% of the savings associated with increased patient cost sharing. Similar research on the impact of Medicare Part D shows that increased medication coverage was associated with fewer hospitalizations,[15] and that for groups with the greatest change in benefit generosity, the increased expenditure on drugs was totally offset by a reduction in medical expenditure.[16] While these studies provide useful analysis for several types of medical expenditure, offsets should be even broader to include non-medical components such as productivity in the workplace. Better chronic care management may reduce disability and absenteeism. Currently, data limitations often prevent such analysis. Advocating greater investment in building such data is crucial to the next stages of CER and cost containment.

A third principle to guide CER-related formulary placement is recognition that the goal of the healthcare system is not to save money, but to improve health. Similarly, CER-guided formulary placement should aim to encourage high-value uses, which will often increase drug and even total expenditures. That said, the system must be fiscally sustainable, which is a far cry from today's reality. CER can help achieve financial sustainability by allowing targeting of populations that will benefit from specific products and by identifying low-value services. Strategies that finance favorable formulary placement of high value by spreading the cost across other services can improve the efficiency of the system.

Formulary design traditionally has focused on saving money through cost-sharing tiers that differentiate medications with therapeutically similar effects. Over time, the number of tiers and associated cost-sharing amounts have increased, and there is reason for concern that these growing costs may increasingly impact patient adherence and adversely affect health outcomes. Historically, the decisions have been made largely on the basis of the cost of medications across a range of therapeutically similar alternatives, without much consideration of the clinical benefit achieved in one disease area versus another, one disease sub-class versus another, or even in one patient type versus another. Without a strong investment in CER that enables greater sophistication in formulary structure, patients are more likely to face "across the board" increases in cost sharing. That trend makes it increasingly likely that the unintended consequences of discouraging appropriate management of chronic disease will grow. In the case of diabetes—partially due to the fact that, in many cases, the management of hyperglycemia, hypertension, and hypercholesterolemia require more than 1 medication—suboptimal management (ie, lack of adherence due to cost-related issues) may lead to expensive complications. CER can provide the knowledge base necessary to add clinical nuance to formularies—possibly by distinguishing across disease states (eg, insulin vs

acne), within disease drug classes (eg, insulin vs DPP-4s), and within drug uses (eg, Januvia first vs fourth line)—in addition to distinguishing across a class of similar products (eg, generic vs brand vs non-preferred brand), which has been the main focus of formulary management to date. Cost-containment efforts that rely on an improved evidence base are probably preferable to current efforts to drive all practice toward those of the lowest cost. Thus, formularies of the future can use findings from CER is to better target, not limit, care.

Author Affiliations: From Department of Health Care Policy, Harvard Medical School (MEC, RM), Boston, MA; Stanford University School of Medicine (DKO), Stanford, CA; Philip R. Lee Institute for Health Policy Studies (WA), University of California San Francisco, San Francisco, CA; Jaeb Center for Health Research (RB), Tampa, FL; RxAnte Inc (JB), McLean, VA; Health Intelligence Partners (JEB), Chicago, IL; Evidence Based Medicine, sanofi (FF), Bridgewater, NJ; University of Michigan (AMF), Ann Arbor, MI; University of Southern California (DG), Los Angeles, CA; McKenna Long and Aldridge (RK), Washington DC; University of Southern California (DL), Los Angeles, CA; Joe Stahl Consulting LLC (JS), Minneapolis, MN; USC Keck School of Medicine (AP), USC Westside Center for Diabetes Los Angeles, CA.

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Address correspondence to: Michael E. Chernew, PhD, Department of Health Care Policy, Harvard Medical School, 180 Longwood Ave, Ste 207, Boston, MA 02115. E-mail: chernew@hcp.med.harvard.edu.

REFERENCES

1. US Congress. Patient Protection and Affordable Care Act. http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf. Published March 23, 2010. Accessed May 2011.

2. Centers for Disease Control and Prevention. 2011 National Diabetes Fact Sheet, 2012.

3. American Diabetes Association. Economic costs of diabetes in the US in 2007. *Diabetes Care*. 2008;31(3):596-615.

4. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141(6):421-431.

5. Chandra, A, Gruber J, McKnight R. Patient cost-sharing and hospitalization offsets in the elderly. *Amer Econ Rev*. 2010;100(1):193-213.

6. Cramer J. A systematic review of adherence with medication for diabetes. *Diabetes Care*. 2004;27(5):1218-1224.

7. Chernew ME, Rosen AB, Fendrick AM. Rising out-of-pocket costs in disease management programs. *Am J Manag Care.* 2006;12(3):150-154.

8. Chernew ME, Shah MR, Wegh A, et al. Impact of decreasing copayments on medication adherence within a disease management environment. *Health Aff (Millwood)*. 2008;27(1):103-112.

9. Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing: associations with medication and medical utilization and spending and health. *JAMA*. 2007;298(1):61-69.

10. Goldman DP, Joyce GF, Karaca-Mandic P. Varying pharmacy benefits with clinical status: the case of cholesterol-lowering therapy. *Am J Manag Care*. 2006;12(1):21-28.

11. Choudhry NK, Fischer MA, Avorn J, et al. At Pitney Bowes, value-based insurance design cut copayments and increased drug adherence. *Health Aff (Millwood)*. 2010;29(11):1995-2001.

12. Spaulding A, Fendrick AM, Herman WH, et al. A controlled trial of value-based insurance design-the MHealthy: Focus on Diabetes (FOD) trial. *Implement Sci*. 2009;4:19.

13. Chernew M, Fendrick M. The business case for comparative effectiveness research. Appendix 7 in Learning What Works Best: The Nation's Need for Evidence on Comparative Effectiveness in Health Care. IOM Roundtable on Evidence-Based Medicine. Institute of Medicine, March 2007.

14. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. *N Engl J Med*. 2008;359(7):677-687.

15. Afendulis CC, He Y, Zaslavsky AM, Chernew ME. The impact of Medicare Part D on hospitalization rates. *Health Serv Res*. 2011;46(4):1022-1038.

16. Zhang Y, Donohue JM, Lave JR, O'Donnell G, Newhouse JP. The effect of Medicare Part D on drug and medical spending. *N Engl J Med*. 2009;361(1):52-61. ■