Translation Research for Chronic Disease

The case of diabetes

K.M. Venkat Narayan, MD
Edward W. Gregg, PHD
Michael M. Engelgau, MD
Bernice Moore, MBA
Theodore J. Thompson, MS
David F. Williamson, PHD
Frank Vinicor, MD

Diabetes is a prototypical chronic disease that imposes a large public health burden (1). Although basic and clinical research has provided efficacious treatments, the quality of care for people with diabetes remains suboptimal (2,3). We wanted to explore the reasons why the existence of efficacious treatments has not reduced the burden of diabetes. In this article, we briefly review the burden of diabetes, the extensive availability of proven treatments, and the inadequate implementation of such treatments. We then argue that efficacy or mechanism research, which is aimed at understanding the causes of disease and the efficacy (proof under ideal conditions) of treatments, cannot ameliorate the burden of chronic disease without more concomitant translation research to change and improve clinical practice at the population level. We then describe translation research and its key elements in the context of other models of research, in particular as an extension of effectiveness research, and contrast translation research with the more widely practiced mechanism research.

A Major Public Health Problem With Several Efficacious Treatments

In the U.S., 16 million people have diabetes, and the age-adjusted prevalence of diagnosed diabetes increased by 16% between 1980 and 1994 (1). The disease is the leading cause of new cases of blindness among working-age adults and of end-stage renal disease and nontraumatic amputation among the general population (1). People with diabetes have two to four times the risk of cardiovascular disease and are at increased risk of neuropathy, dental disease, and complications of pregnancy (1–3). In addition, the total annual costs attributable to diabetes are estimated at $98 billion (5).

As shown in Table 1, high-quality evidence exists for the efficacy of several current treatments in reducing morbidity and mortality in people with diabetes (6–20). Several of these interventions, including glycemic control (21), blood pressure control (22), lipid management (23), and early detection and treatment of retinopathy (24) and nephropathy (25), also appear to be cost-effective.

Inadequate Implementation of Treatments

The levels of implementation of diabetes care in the U.S. (26–30) remain suboptimal (Table 1). Among adults aged ≥20 years with diabetes who participated in the Third National Health and Nutrition Examination Survey (NHANES III), 44.6% had HbA_{1c} levels <7%, 63% had levels <8%, and 85.9% had levels <10% (26). Blood pressure (BP) was ≤160/95 and ≤140/90 mmHg in 87 and 62% of the diabetic participants, respectively (CDC, unpublished NHANES III analyses). LDL cholesterol was ≤100 mg/dl in 11%, 46% had LDL cholesterol ≤130 mg/dl, and 77% had LDL ≤160 mg/dl (CDC, unpublished NHANES III analyses). Among U.S. NHANES III participants, <20% of the people with diabetes used aspirin regularly (27). Analysis of self-report by diabetic participants in the U.S. Behavioral Risk Factor Surveillance System indicated suboptimal receipt of GHb tests, annual eye and foot exams (28), and influenza/pneumococcal vaccinations (29). Several regional and managed care estimates also indicate considerable variation in the implementation of efficacious treatment (30). For example, the proportion of the U.S. managed care population who receives annual foot exams varies from 29 to 79%, eye exams from 23 to 83%, lipid testing from 31 to 61%, and renal screening from 31 to 61% (30).

Many have wondered why the available efficacious treatments have not been implemented more widely. Simple knowledge of the benefits from interventions does not automatically result in uptake. Diabetes is a life-long disease, prolific in its complications and impact on quality of life, complex in its management, and demanding on patients, providers, and health care systems (31). The failure to use efficacious treatments as recommended is often caused by a breakdown at the patient, health care provider, and system levels, and the process of ameliorating these problems is fraught with difficulty (31,32).

Translation Research

Perhaps these challenges indicate a need for more comprehensive applied research that strives to translate the available knowledge and render it operational in clinical and public health practice. We call this translation research. Figure 1 depicts translation research in the context of other types of research and public health assessments. As shown in Fig. 1, basic science/epidemiology and public health surveillance offer means of characterizing a problem, and efficacy clinical trials and translation research are aimed at understanding the solution. Effectiveness and translation research also provide a bridge between efficacy trials and public health translation, and they inform the development of surveillance measures.

Previous reviews have distinguished effectiveness research from classic efficacy trials (4), and the past several years have witnessed considerable progress in effectiveness research using both observational (33)

From the Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia.

Address correspondence and reprint requests to K.M. Venkat Narayan, Mailstop K-68, 4770 Buford Highway NE, Atlanta, GA 30341. E-mail: kav4@cdc.gov.

Received for publication 7 March 2000 and accepted in revised form 28 August 2000.

Abbreviations: BP, blood pressure; NHANES III, Third National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Efficacious treatments for diabetes complications and their levels of implementation in the U.S.*

Strategy	Benefit	Quality of evidence*	Level of implementation in the U.S.
Glycemic control	30% decrease in microvascular disease per 1% decrease in HbA_{1c} (6,7)	I	HbA_{1c} <7% in 44.6%, <8% in 63% (26); annual HbA_{1c} testing in 69% (28)
BP control	35% decrease in macro- and microvascular disease and death per 10-mm decrease in BP (8,9)	I	BP ≤140/90 mmHg in 62% (CDC, unpublished NHANES III data)
Lipid control	25–55% decrease in CHD events; 43% decrease in death (10,11)	II-1	LDL cholesterol ≤100 mg/dl in 11%, ≤130 mg/dl in 46% (CDC, unpublished NHANES III data)
Aspirin use	28% decrease in MI and 18% decrease in CVD (12,13)	I	Regular aspirin use in 20.0% (27)
ACE inhibitor use	42% decrease in nephropathy; 22% decrease in CVD and death (14,15)	I	Not known
Eye exams	60–70% decrease in serious vision loss (16)	I	Annual eye exam in 69.7% (28)
Foot care	50–60% decrease in serious foot disease (17,18)	I	Annual foot exam in 60.8% (28)
Flu/pneumococcal vaccination among elderly	32% decrease in hospitalizations and 64% decrease in respiratory conditions and death (19)	II-2	Influenza vaccination in 52.1% and pneumococcal vaccination in 33.2% (29)

References are indicated in parentheses. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction. *Quality of evidence: I, evidence from at least one randomized controlled trial; II-1, evidence from a well-designed controlled trial without randomization; II-2, evidence from cohort or case-control studies; II-3, evidence from multiple time series; and III, opinions of respected authorities (20).

and experimental (34,35) designs. Whereas efficacy tries to understand causal mechanisms and test associations and interventions under ideal conditions, effectiveness research tries to provide more real-world tests of hypotheses. It does this by encouraging intention-to-treat analysis, testing associations and interventions in real-world settings, recruiting diverse populations, and examining outcomes of practical relevance to the patient, provider, and health care system (e.g., quality of life, health status, patient satisfaction, and resource utilization) as opposed to physiological measures (33–35).

While translation research would encompass many of the attributes of effectiveness research, we consider it to be an extension of effectiveness research and we offer a broader paradigm. Although randomized trials have become increasingly effectiveness-oriented (36), they are still typically limited to specific narrow populations or specific settings. Many of these studies have also lacked tests of sustainability over time, generalizability, and transferability to the majority of people and to diverse settings. The establishment of larger, multicenter, second-generation effectiveness/translation studies better informed by theory and current knowledge will be a move in the right direction (30,32–35).

In making the distinction between traditional mechanism research and translation research (Fig. 2), it is important to note that *1*) the two approaches are complementary and not competing, *2*) the differences are a matter of relative emphasis, and *3*) the differences reside in the research design orientation (e.g., goals, questions posed, populations, contexts, and trade-offs). For example, randomized trials and observational studies may apply equally to both kinds of research, but the nature of study questions and the trade-offs in design may differ.

The overall aim of translation research, consistent with its public health orientation, is to facilitate optimal health care for as many people as possible rather than ideal health care for a few. Thus, translation research takes a perspective that is conducive to developing effective public health policy. Correspondingly, concerns with allocative efficiency, which relates to how care is delivered to a population within constraints of finite resources and equity, are integral to translation research. For example, much of what is paid for to

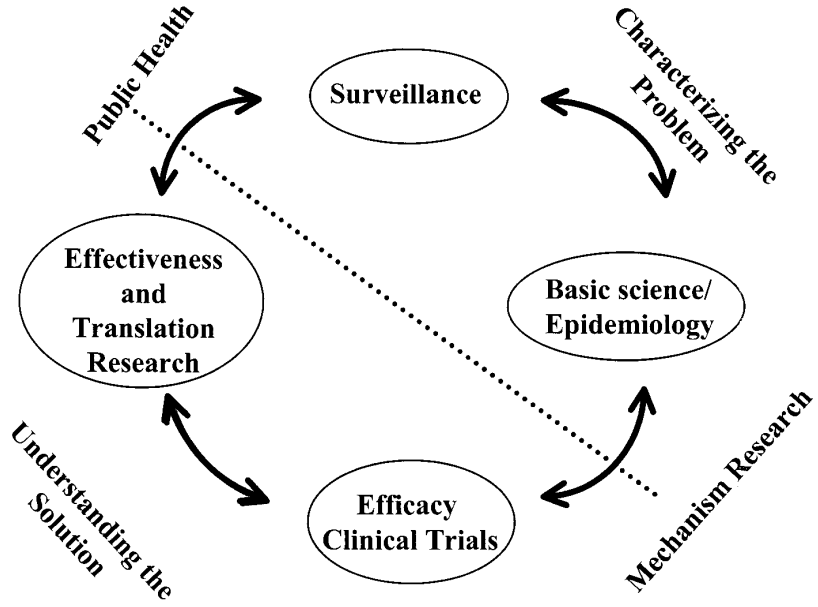

Figure 1—*Translation research in the context of other models of research.*

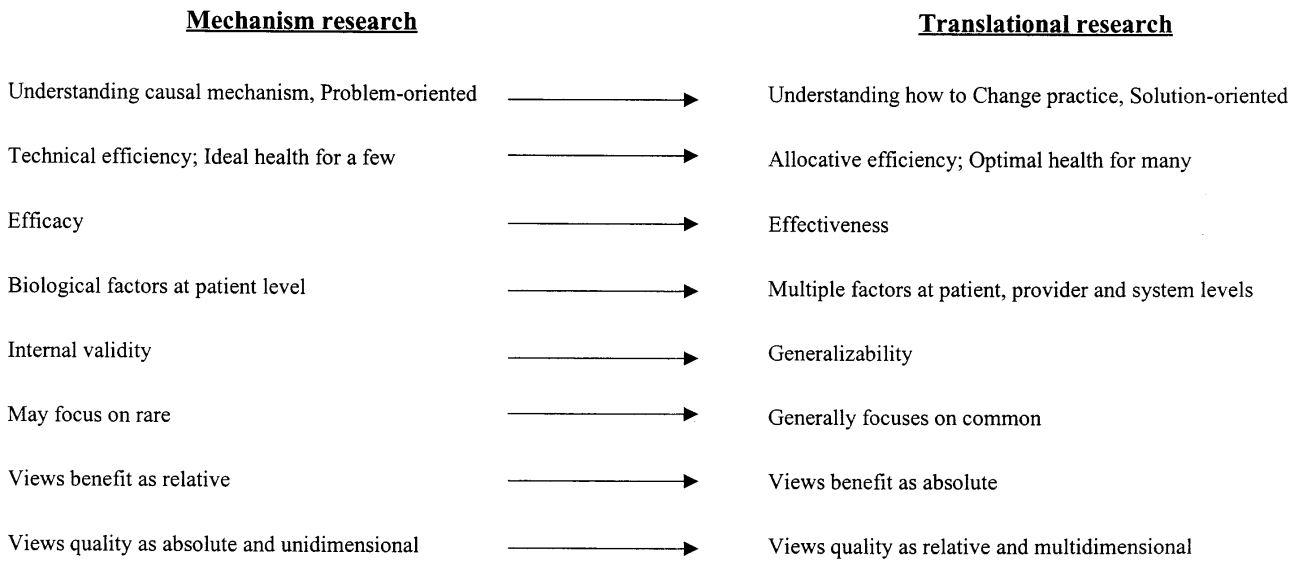

Figure 2—*Main differences between mechanism research and translation research. Note that the differences have more to do with the design orientation and priorities. Furthermore, the differences are not absolute, but are dependent on emphasis.*

implement clinical trial protocols may be impractical in real-world settings. Thus, translation research should aim to work within the context of existing opportunities, resources, and constraints.

Translation research emphasizes effectiveness (i.e., proof under real-life conditions), whereas etiologic research emphasizes efficacy (i.e., proof under idealized conditions). Furthermore, translation research is multifactorial, frequently considering biological, social, cultural, as well as psychological influences on the patient, provider, and health care system. A good example of this multifactorial orientation is the trial reported by Aubert et al. (34), who found that attending to patient-related and organizational issues through the use of a nurse case manager was associated with substantially improved glycemic control.

In terms of generalizability, mechanism research is designed to ensure internal validity with results that apply strictly to people with patient characteristics similar to the study participants. Often, such people may only be a small proportion of the population with the condition (7). Translation research emphasizes application of results to the majority of people with the condition and often focuses on the more common problems.

Mechanism research on therapies usually measures the benefit relative to a placebo or standard treatment group, and effect is measured as the relative risk (i.e., the ratio of incidence in exposed subjects vs. those unexposed), a measure of the strength of the causal association. Translation research may also involve methods of analysis and presentation that serve its mission of understanding the absolute benefit to both the patient and the whole population. For example, there may be a particular emphasis on absolute risk (i.e., the difference in incidence between exposed and unexposed subjects) and the numbers needed to treat, which is the reciprocal of the absolute risk. In addition, translation research will also need population impact measures, which take into account the prevalence of exposure in addition to the excess risk, such as attributable fractions and population attributable fractions.

Mechanism research tends to promote the point of view that quality is absolute and unidimensional, which leads to concepts like the gold standard. Translation research, on the other hand, tends to view quality as relative and multidimensional. Here, the issue of quality for diabetes care is not achieving an ideal level of care (e.g., HbA_{1c} <7%) for all, but is rather moving toward the ideal (e.g., a reduction in the proportion of people with HbA_{1c} ≥9.5%, as suggested by the Diabetes Quality Improvement Project) (37). Translation research includes several dimensions of care within its definition of quality, including technical efficiency, patient satisfaction, and allocative efficiency (i.e., factors such as equitable distribution of resources, opportunity cost, or benefits forgone from alternative uses of resources) (38).

Translation research would also emphasize transferability—the successful application to diverse settings. In terms of barriers, several studies in specific populations (30,33–35) have implicated provider behavior and attitudes, system factors (e.g., organizational models, information systems, guidelines, incentives, and reimbursement policies), and modifiable patient-related factors (e.g., inadequate transportation, limited access, and poor motivation) as affecting implementation of existing treatments (30,33,35). Several small studies in specific populations have also tested a variety of interventions (e.g., provider education, tailored feedback, self-management, case managers, and group visits) to improve quality of care (30,33–35). However, because these studies have been conducted in single sites and in specific populations, it is not possible to generalize their findings across diverse subpopulations and health care systems.

Data to assess overall quality of care or quality of life throughout the range of health care systems, patient populations, and geographic regions are lacking. There is a paucity of data on the relationship between structural factors (e.g., financial barriers, practice structure, provider incentives, and case managers) and both process of care (e.g., quality of care indicators such as HbA_{1c} and BP testing) and such outcomes as quality of life, patient satisfaction, and costs (30).

Conclusion

Chronic diseases like diabetes are major public health problems and will require proactive population-based approaches (39). Wider appreciation of the translation research paradigm and greater availability of suitable research infrastructures are needed to facilitate such approaches (30). Translation research strives to translate science into clinical and public health practices, and it attempts to measure a variety of real-world attributes of interventions shown to be efficacious in idealized settings. These attributes include *1*) public health impact (e.g., the extent of spread and equity), *2*) effectiveness (e.g., the influence on process and outcomes and the sustainability [constraints to long-term implementation]), *3*) efficiency (e.g., relative value under conditions of finite resources), and finally *4*) transferability (e.g., issues concerning application to other diverse settings and situations).

There are some good examples of observational studies (33) and randomized trials (30,34,35,40–42) incorporating aspects of the translation research principles. Many more major translation research initiatives using standardized methods in multiple settings across populations and systems (30,43) are needed to suggest steps toward optimal population care for diseases like diabetes.

Acknowledgments — We thank Drs. Gloria Beckles and Anne Fagot-Campagna of the Division of Diabetes Translation for reviewing the manuscript and the Technical Information and Editorial Services Branch of the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, for their valuable editorial comments.

References

1. Centers for Disease Control and Prevention: *Diabetes Surveillance, 1997*. Atlanta, GA, Department of Health and Human Services, 1997
2. The Carter Center of Emory University: Closing the gap: the problem of diabetes mellitus in the United States (Review). *Diabetes Care* 8:391–406, 1985
3. Vinicor F: Is diabetes a public-health disorder (Review)? *Diabetes Care* 17 (Suppl. 1): 22–27, 1994
4. Greenfield S, Kaplan SH, Silliman RA, Sullivan L, Manning W, D'Agostino R, Singer DE, Nathan DM: The uses of outcomes research for medical effectiveness, quality of care, and reimbursement in type 2 diabetes. *Diabetes Care* 17 (Suppl. 1):32–39, 1994
5. American Diabetes Association: Economic consequences of diabetes mellitus in the U.S. in 1997. *Diabetes Care* 21:296–309, 1998
6. The U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
7. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
8. The U.K. Prospective Diabetes Study (UKPDS) Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 317:703–713, 1998
9. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J: Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension: Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 276:1886–1892, 1996
10. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, the Scandinavian Simvastatin Survival Study (4S) Group: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20: 614–620, 1997
11. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E: Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) Trial: the Care Investigators. *Circulation* 98:2513–2519, 1998
12. ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study Report 14. *JAMA* 268: 1292–1300, 1992
13. Antiplatelet Trialists' Collaboration: Collaborative overview of randomized trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 308:81–106, 1994
14. Ravid M, Lang R, Rachmani R, Lishner M: Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non–insulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med* 156:286–289, 1996
15. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE study. *Lancet* 355:253–259, 2000
16. Early Treatment Diabetic Retinopathy Study Research Group: Early photocoagulation for diabetic retinopathy: ETDRS report number 9. *Ophthalmology* 98 (Suppl. 5):766–785, 1991
17. Littzelman DK, Slemenda CW, Langefeld CD, Hays LM, Welch MA, Bild DE, Ford ES, Vinicor F: Reduction of lower extremity clinical abnormalities in patients with non–insulin-dependent diabetes mellitus: a randomized controlled trial. *Ann Intern Med* 119:36–41, 1993
18. McCabe CJ, Stevenson RC, Dolan AM: Evaluation of a diabetic foot screening and protection programme. *Diabet Med* 15:80–84, 1998
19. Nichol KL, Wuorenma J, von Sternberg T: Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med* 158:1769–1776, 1998
20. U.S. Department of Health and Human Services: *Guide to Clinical Preventive Services: Report of the U.S. Preventive Services Task Force*. 2nd ed. Washington, DC, 1996
21. The Diabetes Control and Complications Trial Research Group: Lifetime benefits and costs of intensive therapy as practices in the Diabetes Control and Complications Trial. *JAMA* 276:1409–1415, 1996
22. The U.K. Prospective Diabetes Study (UKPDS) Group: Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *BMJ* 317:720–726, 1998
23. Schwartz JS, Boccuzzi SJ, Glick H, Cook JR, Kinosian B, Pedersen TR, Kjekshus J: Cost effectiveness of LDL-C reduction in diabetic CHD patients: implications from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 96 (Suppl. 1):1504–1505, 1997
24. Javitt JC, Aiello LP, Chiang Y, Ferris FL III, Canner JK, Greenfield S: Preventive eye care in people with diabetes is cost-saving to the federal government. *Diabetes Care* 17:909–917, 1994
25. Siegel JE, Krolewski AS, Warram JH, Weinstein MC: Cost-effectiveness of screening and early treatment of nephropathy in patients with insulin-dependent diabetes mellitus. *J Am Soc Nephrol* 3 (Suppl. 4): S111–S119, 1992
26. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Racial and ethnic differ-

ences in glycemic control of adults with type 2 diabetes. *Diabetes Care* 22:403–408, 1999
27. Rolka DB, Fagot-Campagna A, Narayan V: Aspirin use among Americans with diabetes: estimates from NHANES III (Abstract). *Diabetes* 48 (Suppl. 1):A41, 1999
28. Beckles GLA, Engelgau MM, Narayan KMV, Herman WH, Aubert RE, Williamson DF: Population-based assessment of the level of care among adults with diabetes in the U.S. *Diabetes Care* 21:1432–1438, 1998
29. Centers for Disease Control and Prevention: Influenza and pneumococcal vaccination rates among persons with diabetes mellitus: United States, 1997. *MMWR* 48: 961–967, 1999
30. The CDC Diabetes in Managed Care Work Group: Exploring and expanding the research agenda for diabetes in managed care: a report of a Centers for Disease Control and Prevention–Managed Care Workshop (Review). *Diabetes Care* 22:1734–1738, 1999
31. Pringle M, Stewart-Evans C, Coupland C, Williams I, Allison S, Sterland J: Influences on control in diabetes mellitus: patient, doctor, practice, or delivery of care. *BMJ* 306:630–634, 1993
32. David RM, Wagner EH, Groves T: Managing chronic disease (Editorial). *BMJ* 318: 1090–1091, 1999
33. Hayward RA, Manning WG, Kaplan SH, Wagner EH, Greenfield S: Starting insulin therapy in patients with type 2 diabetes: effectiveness, complications, and resource utilization. *JAMA* 278:1663–1669, 1997
34. Aubert RE, Herman WH, Waters J, Moore W, Sutton D, Peterson BL, Bailey CM, Koplan JP: Nurse case management to improve glycemic control in diabetic patients in a health maintenance organization. *Ann Intern Med* 129:605–612, 1998
35. Kinmonth AL, Woodcock A, Griffin S, Spiegal N, Campbell J: Randomised controlled trial of patient centered care of diabetes in general practice: impact on current wellbeing and future risk: the Diabetes Care From Diagnosis Research Team. *BMJ* 317: 1202–1208, 1998
36. Narayan KMV, Beckles GLA, Gregg EW, Williamson DF, Saaddine J, Engelgau MM, Vinicor F: Treating type 2 diabetes: study was conducted in exemplary fashion (Letter). *BMJ* 318:666, 1999
37. National Committee on Quality Assurance: Diabetes Quality Improvement Project. Available from http://www.ncqa.org. Accessed 9 October 2000
38. Donabedian A: The definition of quality. In *Explorations in Quality Assessment and Monitoring*. Vol I. Ann Arbor, MI, Health Administration Press, 1985
39. Glasgow RE, Wagner EH, Kaplan RM, Vinicor F, Smith L, Norman J: If diabetes is a public health problem, why not treat it as one? A population-based approach to chronic illness. *Ann Behav Med* 21:159–170, 1999
40. Lobach DF, Hammond WE: Computerized decision support based on a clinical practice guideline improves compliance with care standards. *Am J Med* 102:89–98, 1997
41. Sadur CN, Moline N, Costa M, Michalik D, Mendlowitz D, Roller S, Watson R, Swain BE, Selby JV, Javorski WC: Diabetes management in a health maintenance organization: efficacy of care management using cluster visits. *Diabetes Care* 22:2011–2017, 1999
42. Petitti DB, Contreras R, Ziel FH, Dudl J, Domurat ES, Hyatt JA: Evaluation of the effect of performance monitoring and feedback on care process, utilization, and outcomes. *Diabetes Care* 23:192–196, 2000
43. Narayan KM, Selby JV, Mangione CM, Herman WH, Safford MM, Marrero DG, Curb JD, Cowan DN, Study Group-TRIAD: TRIAD: A multicenter study of managed care and diabetes quality of care, costs, and outcomes (Abstract). *Diabetes* 49 (Suppl. 1):A405, 2000