

# Translation Research for Chronic Disease

## The case of diabetes

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**D**iabetes 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  $\geq 20$  years with diabetes who participated in the Third National Health and Nutrition Examination Survey (NHANES III), 44.6% had HbA<sub>1c</sub> levels  $< 7\%$ , 63% had levels  $< 8\%$ , and 85.9% had levels  $< 10\%$  (26). Blood pressure (BP) was  $\leq 160/95$  and  $\leq 140/90$  mmHg in 87 and 62% of the diabetic participants, respectively (CDC, unpublished NHANES III analyses). LDL cholesterol was  $\leq 100$  mg/dl in 11%, 46% had LDL cholesterol  $\leq 130$  mg/dl, and 77% had LDL  $\leq 160$  mg/dl (CDC, unpublished NHANES III analyses). Among U.S. NHANES III participants,  $< 20\%$  of the people with dia-

betes 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)

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**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 <sub>1c</sub> (6,7)	I	HbA <sub>1c</sub> <7% in 44.6%, <8% in 63% (26); annual HbA <sub>1c</sub> 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).

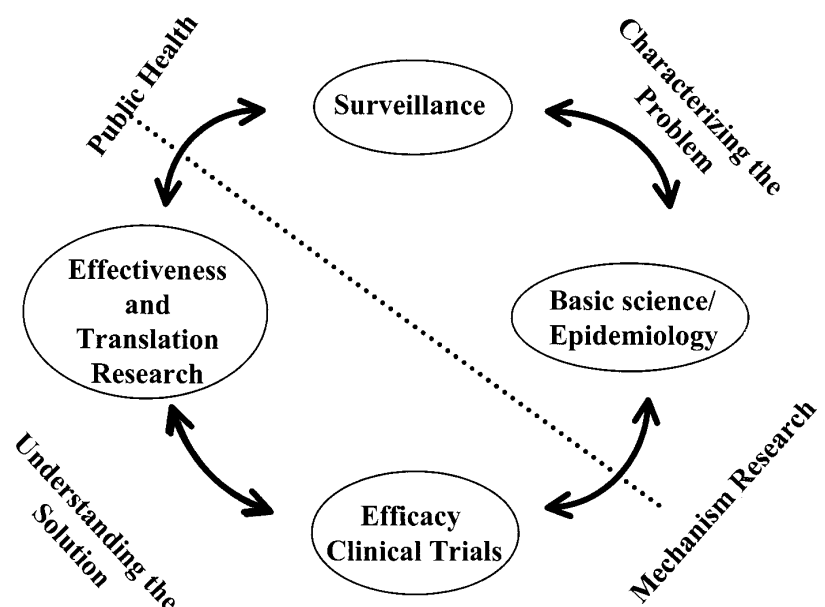
While translation research would encompass many of the attributes of effectiveness research, we consider it to be an extension of effectiveness research and we offer a broader paradigm. Although randomized trials have become increasingly effectiveness-oriented (36), they are still typically limited to 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 dif-

ferences 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 orienta-

tion, 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.**

<u>Mechanism research</u>	→	<u>Translational research</u>
Understanding causal mechanism, Problem-oriented	→	Understanding how to Change practice, Solution-oriented
Technical efficiency; Ideal health for a few	→	Allocative efficiency; Optimal health for many
Efficacy	→	Effectiveness
Biological factors at patient level	→	Multiple factors at patient, provider and system levels
Internal validity	→	Generalizability
May focus on rare	→	Generally focuses on common
Views benefit as relative	→	Views benefit as absolute
Views quality as absolute and unidimensional	→	Views quality as relative and multidimensional

**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  $HbA_{1c} \geq 9.5\%$ , 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.

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