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COST-EFFECTIVENESS OF IMPLEMENTING THE INTERVENTIONS FOR DIABETES PREVENTION AND CONTROL IN THE COMMUNITY AND MILITARY SETTINGS

by

Shihchen Kuo

BS, Kaohsiung Medical University, Taiwan, 1999

MSCP, National Cheng Kung University, Taiwan, 2002

Submitted to the Graduate Faculty of

the Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2013

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This dissertation was presented

by

Shihchen Kuo

It was defended on

May 22, 2013

and approved by

Thomas J. Songer, PhD, MPH, MSc
Assistant Professor
Department of Epidemiology, Graduate School of Public Health
University of Pittsburgh

Cindy L. Bryce, PhD
Associate Professor
Department of Health Policy & Management, Graduate School of Public Health
University of Pittsburgh

Kenneth J. Smith, MD, MS
Associate Professor
Section of Decision Sciences and Clinical Systems Modeling, School of Medicine
University of Pittsburgh

Kristine M. Ruppert, DrPH
Assistant Professor
Department of Epidemiology, Graduate School of Public Health
University of Pittsburgh

Dissertation Director: Janice C. Zgibor, RPh, PhD
Associate Professor
Department of Epidemiology, Graduate School of Public Health
University of Pittsburgh

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Janice C. Zgibor, RPh, PhD

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ABSTRACT

Diabetes is an increasingly prevalent and costly cause of morbidity and mortality, representing not only a major clinical care concern but an immense public health challenge. In 2010, diabetes affected 25.8 million Americans – 8.3% of the US population and 26.9% of those aged 65 years or older. People with diabetes are disproportionately affected by eye and renal disease, non-traumatic amputations, and cardiovascular disease, which result in significant health-care costs of $245 billion in the US in 2012. Although many interventions can reduce health burden of diabetes, health care resources are limited. Hence, evidence is needed to inform health care practitioners and policymakers of these interventions' costs and benefits to practices, payers, and patients, and thus aid them in prioritizing the interventions for diabetes prevention and control.

Through a decision-analytic approach using computational modeling, this dissertation proposed the cost-effectiveness analysis on implementing the Chronic Care Model (CCM) for diabetes control in the community and military settings and on implementing an Online adaptation of the Diabetes Prevention Program lifestyle intervention (ODPP) for weight management in an overweight/obese primary care population with high cardiovascular risk. Our

analyses showed that from a health care system and a societal perspective, the CCM compared with usual care cost $42,179-$45,495 and $42,051-$113,280 per quality-adjusted life-year (QALY) gained; the CCM compared with provider continuing medical education (PROV) cost $17,186 and $50,718 per QALY gained; and the ODPP compared with usual care cost $7,777-$14,351 and $18,263-$29,331 per QALY gained. Generally, these results were robust in sensitivity analyses. This dissertation provided supporting evidence that compared with usual care or PROV, the CCM for secondary and tertiary diabetes prevention in the community and military settings as well as the ODPP for primary diabetes prevention in the primary care setting appear to be economically reasonable interventions for diabetes management. These findings are of public health significance as the economic evaluation conducted in this dissertation is an important component of evidence-based clinical and public health practices, which is a decision making aid to help assess the relative value of alternative interventions that can enhance clinical care and public health.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

Severn years ago, I decided to leave my loved family and country to study abroad and pursue advanced education training. Over the past seven years, I learned and worked very hard on whatever I was assigned to. Seven years later, although I spent longer time than I was expecting, I greatly appreciated whatever I have experienced and I am very pleased to say that I did it – I can graduate for reaching the main goal that I made to come to the US seven years ago!

In this exciting and thankworthy moment, I really would like to acknowledge many people who have contributed to both this dissertation work and my development as an epidemiologist and a decision-analytic modeler. First, my committee members undoubtedly have been a vital resource throughout the dissertation process. Personally, Dr. Zgibor is not only the advisor and supervisor for my dissertation and staff work, but more like a mother and friend to me. She is an extraordinary mentor to help me persevere over these years, and allowed me to think and work independently while always, always being accessible to discuss the status and issues in my research work and daily life. I have learned a lot and gained many invaluable experiences and skills from her, which have made me a stronger and more capable researcher.

Second, I am grateful to Drs. Songer, Bryce, Smith, and Ruppert for being in the committee to mentor my dissertation work. I would like to thank them for attending many meetings, reviewing all of data and results, and editing and commenting many versions of my drafts. Without their guidance, expertise, dedication, generosity and time, my dissertation projects will never be done.

Lastly, but not least, I would like to thank my whole family members for always being my strongest backup as well as offering me timely and warming support. Especially, I am so

grateful to my parents, parents-in-law, wife, brother, and sisters-in-law for always being thoughtful, supportive, and encouraging whenever I am upset and stressful. The sacrifices they all have made for me, my education and my work have never, ever forgotten. In addition, I would like to beg for forgiveness from my grandma for not being able to attend her funeral last year. I know that she is currently living in a very peaceful place – free of pain, dispute, and tumult. I love her so much, and I can assure her of doing my best to take good care of her sons and daughters. My dear family, I really love them all so very much! I hope that I have made them proud; I truly dedicate this dissertation to my loved family, and I want to say that we did it!

1.0 INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels (1). Diabetes is a chronic illness that can lead to serious complications and premature death (2) and requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (3). Individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are currently considered to have "pre-diabetes" as they are at a relatively high risk of progressing overt diabetes. IFG and IGT should not be regarded as clinical entities in their own right but rather as risk factors for diabetes and/or future cardiovascular disease (CVD) as well as premature mortality (3-5). As is the case for individuals found to have IFG and IGT, individuals with a glycated hemoglobin (A1C) of 5.7-6.4% should also be informed of their increased risk for diabetes as well as CVD and counseled about effective strategies to lower their risks (3). Pre-diabetes is associated with obesity, dyslipidemia with high triglycerides and/or low high-density lipoprotein cholesterol (HDLc), and hypertension. Structured lifestyle intervention, aimed at increasing physical activity and producing 5-10% loss of body weight, and several pharmacological agents can prevent or delay the development of diabetes in people with pre-diabetes (3).

Diabetes is an increasingly prevalent and costly cause of morbidity and mortality, resulting in one of the globally major public health threats (6-9). The estimated prevalence of diabetes among adults (≥20 years of age) worldwide is 2.8% (or 171 million people) and 6.4%

(or 285 million people) in 2000 and 2010 respectively. The prevalence is expected to increase to 7.7%, affecting 439 million people by 2030 (6,7). Adults with diabetes have an annual mortality of about 5.4% (double the rate for non-diabetic adults), and their life expectancy may be shortened by as much as 15 years, with up to 75% dying of macrovascular complications, e.g. coronary heart disease and stroke (10,11). The total number of excess deaths attributable to diabetes worldwide in 2010 is estimated to be almost 4 million in the age group 20-79 years, 6.8% of global (all ages) all-cause mortality. Specifically, diabetes may account for 6% of all-cause deaths in adults in the African Region and up to 15.7% in the North American Region (8). Diabetes is common, disabling, and deadly; however, diabetes is preventable and controllable, based on a large body of existing evidence that support a range of interventions to improve diabetes outcomes by controlling risk factors (3,12). Recent research shows that improvements in risk factor control in the US would collectively increase life expectancy by 1.0 year for people newly diagnosed with diabetes in 2005 compared to those diagnosed with diabetes 11 years earlier (13).

Diabetes is costly to the health care system and society. Globally, the health expenditure on diabetes is expected to total at least US$376 billion in 2010; 12% of the world's total health expenditure with US$1,330 per person spent on diabetes. The projected health expenditure for diabetes will expectedly increase to total at least US$490 billion in 2030 worldwide (9). In the US, the total estimated annual cost of diabetes in 2007 is US$174 billion, including US$116 billion in excess medical expenditures and US$58 billion in reduced national productivity (14). This is an increase of US$42 billion since 2002 (15). This 32% increase translates to more than US$8 billion per year. The annual cost in 2002 US$ of diabetes could rise to an estimated US$156 billion by 2010 and to US$192 billion by 2020 (15) if current trends

continue. The high economic burden of diabetes is one of the most pressing health policy issues in the US today (16) and highlights the urgency of better understanding about new interventions for diabetes prevention and control and whether they may or may not help reduce costs.

Considering the evolving disease burden of diabetes in the US, efforts exploring new interventions to prevent or delay the complications of diabetes, or, better yet, to prevent or delay the development of diabetes itself are urgently needed (17). However, facing increasing demand for limited resources from the growing number of new interventions available, policy makers and health care providers need to seek guidance on how to prioritize health care resources wisely and efficiently (18). Economic analysis of efficiency can help the decision maker determine how to allocate resources across a defined number of competing needs to maximize health outcomes from a limited budget (19,20). Efficiency can be estimated using cost-benefit, cost-effectiveness or cost-utility analysis. Only the latter two are used in health care since the monetary valuation of health benefits is not acceptable on ethical and on practical grounds (21). The use of economic analysis to inform decision making has increased rapidly in the last two to three decades. Currently, economic analysis plays a limited role in decision making, but may increase in importance as health care costs continue to rise (21,22).

Applying the economic framework to inform and guide policy decisions about resource allocation in diabetes prevention and control is important for at least three reasons (18). First, diabetes is costly. Second, resources that can be devoted to diabetes prevention and control are limited because of the "opportunity cost" of doing so. Opportunity costs are the value that is forgone by using resources for one activity instead of another. Third, the need for resources will continue to increase because of the increasing prevalence of diabetes and demand for comprehensive care and new interventions.

The objective of this dissertation is to apply computational simulation modeling for evaluating long-term cost-effectiveness of implementing the diabetes control and prevention interventions in the community and military settings. The overall summary measure from the cost-effectiveness evaluation is the incremental cost-effectiveness ratio (ICER), representing the incremental cost required to achieve one additional unit of health benefits if an intervention is used instead of another. The ICER is expressed as US$ per quality-adjusted life-expectancy gained. First, data from a cluster-design, randomized controlled trial will be used to estimate cost-effectiveness of implementing the Chronic Care Model for diabetes control in an underserved urban area of Pittsburgh, PA. Second, data from a military population will be used to estimate cost-effectiveness of implementing the Chronic Care Model for diabetes control in a military-based medical center in San Antonio, TX. Finally, data from a clinical trial conducted in an academic general internal medicine practice will be used to estimate cost-effectiveness of implementing an Internet-based lifestyle intervention to reduce risk of type 2 diabetes and cardiovascular disease in the primary care setting in Pittsburgh, PA.

2.0 DIABETES

Classification of Diabetes

First written reference to diabetes by ancient Egyptian physicians appears since at least 1500 BC (23). Diabetes is a complex and heterogeneous disorder with diverse etiologic mechanisms; hence, any given classification is arbitrary. Currently, the classification of diabetes includes four clinical categories (i.e., type 1 diabetes (T1D), type 2 diabetes (T2D), other specific types of diabetes due to other causes, and gestational diabetes mellitus), and the first two categories are the most common forms of diabetes (1,24). The Expert Committee also identifies an intermediate group of individuals whose glucose levels do not meet criteria for diabetes but are too high to be considered normal. These individuals have IFG and/or IGT. "Pre-diabetes" is used for these entities as progression to diabetes is common, particularly when interventions such as lifestyle change or medications are not provided (1,4).

Prevalence, Incidence, Morbidity, and Mortality of Diabetes

Approximately 23.6 million people in the US had diagnosed and undiagnosed diabetes, indicating that the prevalence of diabetes among the whole US population has increased by 24% in 5 years from 6.3% in 2002 to 7.8% in 2007. Specifically, the prevalence of diagnosed and undiagnosed diabetes among US people aged 20 years or older in 2007 was 10.7% (or 23.5 million people), while that of diagnosed diabetes in those younger than 20 years of age in 2007 was 0.2% (or 186,300 people). If the 57 million American adults with IFG were added, about a third of the adult US population had abnormal glucose metabolism in 2007 (2,17). Also, the projected number of people with diagnosed diabetes in the US will increase by 198% from 16.2

million in 2005 to 48.3 million in 2050, with the largest increases occurring in older and minority subpopulations (25).

The incidence of diagnosed diabetes in 2003 was 6.9 per 1,000 adults, or 1,330,000 adults in the US. This was a rapid increase of 41% from 1997 when the incidence was 4.9 per 1,000 adults. Incidence varied by age, race/ethnicity, weight status, and education levels. Obesity was a major factor for the increase of newly diagnosed diabetes; diabetes incidence increased sharply with weight status, ranging from 1.9 per 1,000 among normal-weight people to 17.8 per 1,000 among the obese (26). Recent estimates in the US indicate about 1.6 million new cases of diagnosed diabetes in people aged 20 years or older in 2007 (2). Also, another recent study shows that the average, annual and age-adjusted incidence of diagnosed diabetes among adults aged 18 years or older increased from 4.8 per 1,000 people in 1995-1997 to 9.1 in 2005-2007; that is, the rate of new cases of diagnosed diabetes soared by about 90 percent in the US over the past decade (27).

Diabetes is the leading cause of new cases of blindness among adults aged 20-74 years, and diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year. Diabetes is also the leading cause of end-stage renal disease, accounting for 44% of new cases in 2005. Also, severe forms of diabetic nerve disease are a major contributing cause of lower-extremity amputations; more than 60% of non-traumatic lower-limb amputations occur in people with diabetes. People with diabetes aged 60 years or older are 2-3 times more likely to report an inability to walk one-quarter of a mile, climb stairs, do housework, or use a mobility aid compared to those without diabetes in the same age group (2).

At the inception of the 21st century, it was estimated that 5.2% of all deaths globally were attributable to diabetes, ranking diabetes as the fifth leading cause of death after

communicable disease, CVD, cancer, and injury (28). In the US, diabetes was the seventh leading cause of death listed on death certificates in 2006 (2). Individuals with diabetes have twice the all-cause mortality rate and 2-4 times the CVD mortality rate of those without diabetes (29,30). Specifically, life expectancy of people with diabetes aged 55-74 years is on average 4-8 years shorter than that of those without diabetes (29). Recent data show that heart disease and stroke were respectively noted on 68% and 16% of diabetes-related death certificates among the US people aged 65 years or older in 2004 (2).

The prevalence and incidence of diabetes is increasing worldwide and in the US (31). The long-term impact of this growing burden is evidenced in models that estimate that one in three children born in the US in the year 2000 will develop diabetes in their lifetime (32). With this growing number of people who will develop diabetes, the costs that health care system and society will bear in high medical utilizations/expenditures, decreased quality of life, and more years of life lost will be stupendous. Therefore, although efficiently managing diabetes and preventing its complications are crucial to improve the life of people with diabetes, exploring primary prevention of diabetes through individual and community interventions to support people at risk of obesity and diabetes is also warranted.

2.1 TYPE 1 DIABETES

2.1.1 Definition

Type 1 diabetes (T1D) is the form of the disease primarily due to pancreatic islet β-cell destruction, and is characterized by absolute insulin deficiency and thus dependence on insulin therapy for the preservation of life. Individuals with T1D are metabolically normal before the

disease is clinically manifest, but the process of β-cell destruction can be detected earlier by the presence of certain autoantibodies. T1D usually is characterized by the presence of anti-GAD, anti-islet cells, or anti-insulin antibodies, which reflects the autoimmune processes that lead to β-cell destruction. Individuals who have one or more of these antibodies can be subclassified as having type 1A diabetes, or immune-mediated T1D. Type 1B, or idiopathic, diabetes is characterized by low insulin and C-peptide levels similar to those in type 1A. Such individuals are also prone to ketoacidosis, like those in type 1A, although they have no clinical evidence of autoimmune autobodies. Many of these individuals are of African or Asian origin. They may suffer from episodic ketoacidosis, but the pathogenetic basis for their insulinopenia remains obscure (24,33).

2.1.2 Epidemiology

T1D is one of the most common chronic diseases of childhood, but may be present in all age groups (34,35). In most populations, T1D constitutes about 5-15% of all diagnosed cases of diabetes, although classification can be difficult in older age groups (36). The prevalence of β-cell autoimmunity appears proportional to the incidence of T1D in various populations; for instance, the countries of Sweden, Sardinia, and Finland have the highest prevalence of islet cell antibody (3-4.5%) and are associated with the highest incidence of T1D, varying from 22 to 35 per 100,000 (37). T1D is diagnosed more frequently in the winter months (35). Risk factors for T1D may be autoimmune, genetic, and environmental (2). The major genetic susceptibility to T1D is linked to the HLA complex on chromosome 6. These genetic backgrounds interact with environmental factors (possibly certain viruses, foods, and climate) to initiate the immune-mediated process that leads to β-cell destruction (35).

Prevalence

Several prevalence studies of T1D in the US in years 1961-1992 show that the prevalence of T1D in people with age <20 years ranged from 0.6 per 1,000 to 2.5 per 1,000, with most estimates clustering around 1.7 per 1,000. Also, the estimated prevalence of T1D in the total US population (all age groups) was 1.2 per 1,000 in 1970 (38). T1D onset is believed to occur predominantly in youth, but it can begin at any age. A study based on the 1976-80 Second National Health and Nutrition Examination Survey (NHANES II) estimated the prevalence of adult-onset T1D in the US, which showed that 7.4% of all diabetic people diagnosed at age 30-74 years were adult-onset T1D, representing 0.3% of the US population in this age group (38). In addition, the SEARCH for Diabetes in Youth Study, which aimed to estimate the prevalence and incidence of diabetes in youth with age <20 years in the US, found that the prevalence of T1D was 1.54 cases per 1,000 youth in 2001 and T1D accounted for about 85% of all diagnosed diabetes in this age group (39). Lastly, recent data in 2007 showed that T1D accounted for 5.7% (or 1 million people) of all diagnosed diabetes in the US (40).

Incidence

A previous study, which evaluated T1D trends in Allegheny County, PA, from 1965 to 1989, indicated that the incidence of T1D among people aged <20 years was 18.2 per 100,000 each year (41). Another study showed that T1D incidence in an adult US population (age ≥20 years) in 1945-1969 from Rochester, MN was 9.2 per 100,000 each year (42). Applying these two incidence rates to the whole US population in 1990 revealed that about 29,713 Americans developed T1D each year, including 13,171 new T1D cases in people aged <20 years and 16,542

in people aged ≥20 years (38). Recently, the SEARCH for Diabetes in Youth Study based on 2002-2003 data documented 15,000 youth (age <20 years) with newly diagnosed T1D annually in the US, indicating that the incidence of newly diagnosed diabetes cases among youth was 19.0 per 100,000 each year for T1D. Also, T1D accounted for about 78% of all newly diagnosed T1D and T2D cases annually in this age group (43).

There are several characteristics of variation in incidence of T1D. First, there is geographical variation. One of the most striking issues in T1D is the very wide, over 400-fold difference in incidence of childhood-onset T1D worldwide (36). Scandinavia and the Mediterranean island of Sardinia have the highest incidence rates in the world, while oriental and equatorial populations have the lowest ones. A child in Finland is 400 times more likely to develop diabetes than one in certain regions of China. Even within Scandinavia, with genetically homogenous populations and equally developed societies living at the same latitude, incidence rates vary widely from a high of 45 per 100,000 in Finland (2006) to 28 in Sweden and 20 in Denmark. In addition, the great geographical variation can also be seen within the same country, even in countries with relatively homogenous populations; however, these differences remain unexplained at this time. While incidence rates are much higher in European populations, the absolute number of new cases is almost equal in Asia and Europe since the population base is so much larger in Asia. For instance, it is estimated that of the 400,000 total new T1D cases occurring annually in all children under age 14, about half are in Asia even though the incidence rates in that continent are much lower (34).

Second, incidence is increasing. There is a steady increase in the incidence of T1D in most populations studied. For example, the incidence of T1D in Austria doubled from 7.3/100,000 in 1979-1984 to 14.6/100,000 in 2000-2005. Studies from Croatia, France,

Germany, Finland, Newfoundland, and China all show that the incidence of T1D is increasing at a rate of 2-5% annually (34). In the US, during the first three decades of the 20th century, the incidence rate of T1D in the white population younger than age 15 years was fairly constant; however, during the next three decades, the rate almost tripled (44).

Third, there is an effect of migration. In some populations, migrants tend to take on the incidence rates of the host countries within one or two generations. For example, a UK study found that T1D incidence rates among children of South Asian origin were almost identical with those of local whites and were more than 20-fold higher than those reported from their ancestral homelands in South Asia. This may suggest that children who move from low-incidence areas to high-incidence areas can acquire the higher risk due to environmental factors (34).

Fourth, there is variation with age. T1D incidence peaks at the ages of 4-6 and 10-14 years (45). For example, in Norway during 1978-1982, the incidence tended to decrease from age 15 years and stabilize up to age 20-30 years (36). The age distribution of T1D onset is similar across different European populations, but the average age of presentation tends to be higher in African and Asian (low risk) populations. These peaks may coincide with higher exposure to infectious agents (at entry to school) and higher insulin demand (due to insulin resistance at puberty). About half of all T1D present as adults and new cases continue to present past age 70 years (34).

Fifth, there is racial/ethnic variation. Striking racial differences are observed in T1D risk in multiracial populations, although not of the same magnitude as the geographical differences (34). In the US, non-Hispanic white youth (age <20 years) has the highest rate of new cases of T1D. Non-Hispanic whites between ages 10 and 14 have an incidence rate of 32.9 per 100,000 person-years, which is comparable to Scandinavian populations. At the same age, the incidence

rate (per 100,000 person-years) among African-Americans is 19.2 and that in Hispanics is 17.6. Asian-Americans, with an incidence of 8.3 and American-Indians with that of 7.1, have the lowest incidence rates in the US population (43). Among non-Hispanic white youth aged 10-19 years, the rate of new cases of T1D is higher than for T2D. For Asian-American and American-Indian youth aged 10-19 years, the opposite is true - the rate of new cases of T2D is greater than the rate for T1D. Among African-American and Hispanic youth aged 10-19 years, the rates of new cases of T1D and T2D are similar (43).

Sixth, there is seasonal variation. Pooled data from many different countries show significant seasonality in date of diagnosis for T1D in all age groups. These data show a maximum incidence in the winter period around December to January and a minimum in summer around June to July. Data from Australia and New Zealand show similar seasonality (peak incidence in winter, which in the southern hemisphere is in June and July). The amplitudes of these differences are smallest for the youngest age group and largest for the oldest age group. Detailed records from Denmark also show that this seasonal variation seems to vary by year. On the other hand, in several populations, seasonality is absent. It is possible that some environmental factor (e.g., vitamin D, sunshine, or viral exposure) plays a role in the observed seasonality, but its effect may also be overshadowed in some populations by other genetic and environmental factors (34).

Finally, there is variation by gender. Generally, males and females have similar risk of T1D, with the pubertal peak of incidence in females preceding that in males by 1-2 years. In low-risk populations, such as Japan, there is a female preponderance with females outnumbering males by 1.4:1, while high-risk countries tend to have a male preponderance (34,36).

Mortality

Prior to the introduction of insulin in 1922, the mortality rate in people with T1D was extremely high; it was estimated from the Joslin Clinic in Boston, US, that the annual mortality rate for 1897-1914 to be 824 per 1,000 diabetic children aged <10 years, and 600 per 1,000 diabetic children aged 10-20 years. These rates declined for years 1914-1922, but still remained very high at close to 400 per 1,000 diabetic children (46). The use of insulin therapy led to improved metabolic control, having a significant impact on T1D mortality. Joslin Clinic data revealed an ongoing decline in mortality for both males and females aged 5-24 years between the years 1930 and 1958 (47). In addition, the Pittsburgh Epidemiology of Diabetes Complications Study experience reported that 20-year cumulative mortality decreased from 22% in 1950-1959 to 3.5% in 1975-1980 for people with T1D (48). Moreover, a study, which evaluated the mortality for people diagnosed with T1D at age <18 years from a US population-based registry, reported that people diagnosed during 1975-1979 showed significantly improved survival compared to those diagnosed 10 years earlier (49). Similar mortality trends over the 20th century were also reported in Denmark and Australia. Since the 1980s, mortality rates have stabilized (46).

Despite considerable improvements in survival over the past century, people with T1D still die at a greater rate than people without the disease. Data from US diabetic patients indicate that life expectancy in those with T1D aged <20 years at diagnosis is reduced by at least 15 years, with the probability of survival among those diagnosed with childhood-onset diabetes reducing from 88% at 20 years of disease duration to 83% after having diabetes for 25 years (50). Moreover, the mean reduction in life expectancy appears to be greater for younger children than for older children, and in those diagnosed with T1D at younger age than in those diagnosed at an older age. The estimated relative risks for total mortality vary considerably, with reported

risks being 2- to 15-fold in people with T1D. However, it should be noted that these estimates may actually underestimate the relative risk of mortality, since most studies rely on standardized mortality ratios, which are calculated by comparing the mortality rates observed in T1D people to those in the general population, which also includes people with diabetes (46).

Several studies suggest that mortality rates vary substantially across countries, which may reflect differences in access to health care (46). For example, the Diabetes Epidemiology Research International Mortality Study was conducted to investigate T1D mortality patterns in Finland, Japan, Israel, and the US. People diagnosed between 1965 and 1979 at age <18 years with T1D were included in the study cohort and were followed up until January 1, 1985. This study revealed that Japan and the US had much higher age-specific all-cause mortality rates than did Finland and Israel (51).

In addition, men have higher absolute all-cause mortality rates than women. This is true for people with and without diabetes, and for those with T1D and T2D. However, when comparing men with T1D to men without diabetes, and women with T1D to women without diabetes, many studies (but not all) report higher relative mortality risks for T1D women than men. Overall, T1D appears to diminish the protective effects of female gender observed in populations without diabetes (46).

The cause of death for people with T1D differs by age and disease duration. In general, metabolic disturbances account for a large proportion of deaths in younger people and among those who have had diabetes for a shorter time, whereas deaths in older people or people who have had T1D for longer are more likely a result of renal disease or CVD (46,50). Although few studies investigate whether T1D is associated with an increased risk of non-CVD mortality, data

from large population-based studies suggest that the risk of death from cancer is not significantly higher among people with T1D than that in the general population (52-54).

Although mortality rates for T1D in Western developed nations are significantly lower since the introduction of insulin, similar improvements have not necessarily been achieved in poorer developing ones. While poorer health outcomes and higher mortality rates may be due to a range of factors, it is suggested that the inadequate supply of insulin is the most important factor (55).

2.1.3 Etiological Factors

T1D is a discrete disorder and its pathogenesis involves environmental triggers that may activate autoimmune mechanisms in genetically susceptible individuals, leading to progressive loss of pancreatic islet β-cells. Predisposition is mediated by a number of genes that interact in a complex manner with each other and the environment (56).

Familial Clustering of T1D

Familial clustering of T1D is well established, and the highest risk is seen in monozygotic twin siblings of people with T1D. The absolute risk in first-degree relatives (other than monozygotic twins) of people with T1D seems to be about 4-7%, about 10-15 times the risk in the corresponding general populations. Although part of this could theoretically be due to shared environmental factors, the majority of the familial clustering is likely due to genetic factors (36). For instance, in the US, the prevalence in siblings with T1D familial clustering approached 6%, while the prevalence in the general population was only 0.4%, yielding a relative risk of 15 (6/0.4) (34). In Europe, 4-15% of newly diagnosed cases had a parent or sibling with T1D, with

higher proportions in high-incidence nations (57); overall, 3.6% of cases had a sibling, 1.8% a mother and 3-4% a father with T1D. There is an approximately two-fold higher risk in children of fathers with T1D compared with children of mothers with T1D (57-60). In Finland, when the parents rather than the children were probands, the cumulative risk by age 20 years was 7.8% in children of fathers with T1D, compared to 5.3% among mothers with T1D, which is an approximately 10-fold increased risk compared to the general population (60).

Genetic Contribution of T1D

The etiological contribution of genetic susceptibility to T1D is clearly demonstrated by twin and family studies. It has been suggested that the concordance rate of T1D in monozygotic twin pairs is 25-60%, compared to 7.5-15% in dizygotic twin pairs (61). The heritability, namely the proportion of the total phenotypic variation of the liability to T1D ascribable to genes, is estimated to be 0.75-0.88 (62,63). Family studies show rather consistent estimates of recurrence risks of T1D at about 5-10% among siblings and children of T1D people (64,65). It is noted that these risks are lower than those in dizygotic twin pairs, which may indicate that the environment shared by twins might be etiologically important as well.

Quantitatively most important genetic locus influencing risk of T1D is the HLA class II region, which explains about 40% of the familial clustering of the disease (66). The HLA-DQB1*0602 allele is protective against T1D, while the alleles DQA1*03-DQB1*0302 and DQA1*05-DQB1*0201 are associated with an increased risk (67,68). Another gene consistently found to be associated with T1D is the insulin (INS) gene, where the VNTR class I allele confers increased risk and the class III allele confers reduced risk of T1D (69,70). At least nine non-HLA-linked regions have some evidence of linkage to T1D (71).

The degree of haplotype sharing in siblings from T1D families influences the recurrence risk considerably, with an estimated recurrence risk of about 15-20% for HLA-identical siblings, a risk of about 6% for haplo-identical sibs and close to 0% for non-identical sibs. Notably, the estimated risk for HLA-identical siblings seems to be considerably lower than the concordance rate in monozygotic twins. On the other hand, the risk for HLA-identical siblings is considerably higher than the risk among unrelated individuals that carry high-risk HLA-markers. The non-HLA-linked susceptibility to T1D agrees with the higher concordance rate among monozygotic twins compared with HLA-identical siblings, although a higher degree of sharing of environment in twins also may contribute to this difference (61).

Environmental Determinants of T1D

The most striking evidence of a non-genetic contribution to T1D relates to the fact that the concordance rate in monozygotic twins is far below unity (61). Since monozygotic twins partners share all their segregating genes, this difference can be attributed to the influence of non-genetic exposure or epigenetic phenomena (72). The search for environmental determinants of T1D has been intensified over many years and has focused on viral infection, nutritional factors, stressful life events, socioeconomic status, and the intrauterine environment (61).

The development of T1D may be associated with congenital rubella infection, cytomegalovirus infection, mumps, Coxsackie B infections and enteroviruses. Exposure to nitrosamines in women at the time of conception may increase the risk of T1D in the male offspring. There seems to be some consensus that long breast feeding and supplementation with vitamin D in infancy partially protects against T1D, while early exposure to cow's milk protein, cereals and heavy weight in infancy are thought to be risk factors. Birth weight is also associated

with both the HLA and INS VNTR genes in non-diabetic populations; studies on the putative interaction between these genes, birth weight, and diabetes are so far lacking. In addition, it is possible that stressful life events and psychological dysfunction, through elevated stress hormone levels, increase the demand for endogeneous insulin production and thereby accelerate clinical precipitation of T1D in individuals with ongoing β-cell destruction. Lastly, conflicting results are reported regarding the associations between socioeconomic status and T1D: some found higher incidence of T1D in regions with relatively low average income levels, whereas other found an opposite trend. Such associations are probably explained by unknown events and factors in lifestyle that may influence the risk of developing T1D and socioeconomic status (61).

So far, there are limited publications regarding the gene-environment interaction in T1D. However, given available information, there is strong support for the hypothesis that T1D develops as the consequence of interaction(s) between genetic factors and non-genetic determinants, leading to an immune-mediated process of β-cell destruction which may be ongoing for several years before T1D presents clinically (61). Therefore, future studies of potential etiological determinants, focusing on host and environmental risk factors and gene-environment interactions, will provide more understanding about the causes of T1D and lead to interventions for disease prevention.

2.2 TYPE 2 DIABETES

2.2.1 Definition

Type 2 diabetes (T2D) is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that diabetes

becomes clinically manifest. Although the specific etiology of T2D is not clearly known, autoimmune destruction of the β-cells does not occur (24). People with T2D usually have insulin resistance and relative, rather than absolute, insulin deficiency. At the time of diagnosis of diabetes, and often throughout their lifetimes, these patients do not need insulin treatment to survive, although ultimately many require it for glycemic control. T2D is associated with progressive β-cell failure with increasing duration of diabetes (73). Ketoacidosis seldom occurs spontaneously but can arise with stress associated with another illness such as infection. Most people with T2D are obese when they develop diabetes, and obesity aggravates the insulin resistance. T2D frequently goes undiagnosed for many years since the hyperglycemia develops gradually and T2D in the earlier stages is not severe enough to produce the classic symptoms of diabetes; however, such patients are at increased risk of developing micro- and macrovascular complications. Their circulating insulin levels may be normal, or elevated but insufficient to control blood glucose levels within the normal range because of the insulin resistance. Insulin resistance may improve with weight reduction or pharmacotherapy and results in normalization of glycemia. T2D is seen frequently in women who have a previous history of gestational diabetes and in individuals with other characteristics of the insulin resistance syndrome, such as hypertension or dyslipidemia (24).

2.2.2 Epidemiology

T2D is the predominant form of diabetes worldwide, accounting for over 90% of all cases of diabetes globally (56). T2D is increasingly common in both adults and children, indeed epidemic, mainly because of increases in the prevalence of a sedentary lifestyle and obesity (56,74). T2D accounts for about 90-95% of all diagnosed cases of diabetes (2), and even,

virtually all cases of diabetes in people >45 years are due to T2D (75). Moreover, cases of T2D represent a very large proportion of new cases of diabetes developing in adults (76). Therefore, for epidemiological studies and/or the US national surveys, diabetes that develops in adults may be considered as T2D, although this unquestionably results in some misclassification of the type of diabetes (75,76). Both the prevalence and incidence of T2D increase dramatically with age, while the prevalence of T2D also varies among different ethnic populations (74). The pathogenesis of T2D remains unclear; however, perhaps the most important is the heterogeneity of T2D because of an interplay between a variety of genetic and environmental factors. The syndrome of T2D, simply speaking, is due to deficient insulin action. This results from inadequate insulin secretion and/or diminished tissue response to insulin (aka. insulin resistance) at one or more points in the complex pathways of hormone action. These impairments frequently coexist in the same patient, and it is often unclear which abnormality is the primary cause of the hyperglycemia (77). Many clinical studies have affirmed that several lifestyle and pharmacotherapy interventions can delay or prevent T2D developing in high-risk populations and that good glycemic control and other interventions can slow its devastating complications (74). Hence, broad implementation of guidelines and goals established by the American Diabetes Association and others, as well as progress in efficient processes of care, which could help eliminate health disparities, need to be the national priorities (3,78,79).

Prevalence

T2D affects about 3% of the population worldwide. In the US, T2D is one of the most critical public health issues today, reaching epidemic rates - the prevalence is higher, affecting 6-7% of the population and is increasing at an astounding rate (77). Recent US national surveys showed

that the estimated number of total diabetes (i.e., diagnosed and undiagnosed diabetes) among adult people (age ≥20 years) in 2007 was 23.5 million, representing 10.7% of all people in this age group or 7.8% of the population, while that among people aged 60 years or older was 12.2 million, representing 23.1% of all people in this age group or 4.0% of the population (2). In addition, T2D accounted for 94.3% (or 16.5 million people) of all diagnosed diabetes in the US in 2007 (40). There have been many studies demonstrating an increasing prevalence of diabetes during last century. The most reliable data on the prevalence of diagnosed T2D according to calendar time were obtained for the population of Rochester, MN. The age- and sex-adjusted prevalence of diagnosed T2D in the population aged 45 years or older in the census years 1970, 1980, and 1990 increased from 3.5% to 4.5% and then to 5.1% respectively (80). Recent US national surveys also showed this increasing pattern of prevalence; the prevalence of total diabetes among adult people in years 2002, 2005, and 2007 increased from 9.3%, 9.6%, and to 10.7% respectively (2,81,82).

In 2005-2006 (83), the crude estimated prevalence of total diabetes in adult people (age ≥20 years) was 12.9%, of which ~40% was undiagnosed. The prevalence increased with age and peaked at age 60-74 years (crude 30.0%), falling slightly in older ages (crude 29.1%). Prevalence was similar in men (crude 12.4%) and women (crude 13.3). The prevalence of T2D also differs among ethnic populations. In 2005 (81), relative to non-Hispanic whites, the prevalence of total diabetes among adult people was higher in non-Hispanic blacks (1.8 times), Hispanic/Latino Americans (1.7 times), American Indians and Alaska Natives (2.2 times), and Asian Americans and Pacific Islanders (>2.0 times). Growth in the aging population as well as greater racial/ethnic diversity in the US are causing projected increases in the prevalence of diagnosed diabetes among adult people from 7.7% in 2005 to 16.0% by 2050 (25).

Of even greater concern is the fact that T2D has now emerged as a critical health issue in overweight and obese children, especially within minority overweight African-American, Hispanic American, and Native American adolescents. In addition to an increasing prevalence of adiposity, the increasing proportion of youth with apparent T2D is related to an increase in sedentary lifestyle and an inheritable predisposition (56,84-88). The prevalence of T2D in youth is on the rise in the US. Previous population- and clinic-based studies as well as case series in 1988-1998 (85,86) showed that the highest prevalence of T2D in children and adolescents reached 50.9 per 1,000 Pima Indians aged 15-19 years in Arizona. From 1967-1976 to 1987-1996, the prevalence increased 6-fold for Pima Indians adolescents (85). Recently, the SEARCH for Diabetes in Youth Study, which is the largest surveillance effort on diabetes in youth (age <20 years) conducted in the US to date, found that the prevalence of T2D was estimated at 0.22 cases per 1,000 youth in 2001 and T2D accounted for about 12% of all diagnosed diabetes in this age group (39). The prevalence of T2D was extremely rare (0.01 cases per 1,000 youth) among younger youth aged 0-9 years compared to that (0.42 cases per 1,000 youth) among older youth aged 10-19 years. Moreover, among the older youth, the proportion of diabetes accounted for by T2D varied dramatically across racial/ethnic groups, from just 6% for non-Hispanic whites to 76% for American Indians (39).

Incidence

Prospective population-based T2D incidence studies that perform serial diagnostic examinations for diabetes are sparse and are conducted on the populations that are not nationally representative (76,89). Most incidence studies in the US and Canada, particularly those that are nationally representative, use cross-sectional survey data, medical records, registries, or health care

administrative data to identify newly diagnosed cases of diabetes and are unable to detect new cases of disease that have not been diagnosed (89). Previously, the incidence of diagnosed diabetes in the US increased during the 1960s but changed little between 1968 and 1992 (75). However, from 1997 to 2003, the crude incidence of diagnosed diabetes in the US population aged 18-79 years increased 41%, from 4.9 per 1,000 to 6.9 per 1,000 (26). During this period, the incidence increased in most sociodemographic subgroups in the US. Medicare administrative data indicated that the incidence was also increasing among the aged (90). Between 1994 and 2001, the incidence increased 37% in this high-risk population. In addition, population-based studies in the US conducted in earlier periods also indicate that the incidence of T2D is increasing (89). For instance, between the periods 1970-1974 and 1990-1994, age-adjusted incidence in Rochester, MN, residents aged 30 years or older rose 67% for men and 42% for women (91). Also, incidence increased rapidly (almost tripling) from 1987 to 1996 among Mexican Americans and non-Hispanic whites aged 25-64 years participating in the San Antonio Heart Study (92).

Recently, in 2005 and 2007, an estimated 1.5 and 1.6 million Americans were newly diagnosed with diabetes in people aged 20 years or older (2,81). Each year, the number of newly diagnosed cases of diabetes exceeds the number of deaths among adults with diabetes (90,93), adding to the increasing prevalence of diabetes. This imbalance between the number of deaths among people with diabetes and the number of people entering the prevalent pool is likely to continue to grow (89).

In addition to increased age, increased body mass index (BMI) coincides with the increasing trend in T2D incidence in the US (76,89). Various measures of adiposity are associated with the incidence of diabetes. Diabetes incidence increases sharply with BMI, and

obesity is a major factor in the development of diabetes. Regardless of BMI, weight gain and abdominal fat and waist circumference are also associated with diabetes incidence. In addition, physical inactivity, independent of the effects of obesity, further elevates the risk of diabetes. A number of other lifestyle factors are associated with incidence, including smoking, no or excessive alcohol consumption, and various aspects of diet (89). Lastly, the occurrence of T2D is similar in men and women, but there is large variability in the occurrence of T2D according to racial/ethnic groups. Furthermore, large variability in the occurrence of T2D within the same racial/ethnic group according to geography also exists, which may be accounted for by different frequencies of environmental factors, such physical inactivity and obesity (76).

Although T2D remains rare in the general pediatric population, the incidence of T2D in children and adolescents has increased dramatically in the last decade, especially in minority populations (3). Previous data (94) indicated a 10-fold increase in incidence of T2D in youth aged 10-19 years between 1982 (0.7 per 100,000 annually) and 1994 (7.2 per 100,000 annually). Moreover, in the past, it was believed that the overwhelming majority of children and adolescents with diabetes had T1D, and only 1-2% of them were considered to have T2D or other rare forms of diabetes (84). Later report suggested that as many as 8-45% of newly diagnosed cases of diabetes among children and adolescents in the US had T2D, and the variation in these reported percentages appeared to depend on age group, race/ethnicity, and sampling strategy (84,86). Recently, the SEARCH for Diabetes in Youth Study based on 2002-2003 data documented 3,700 youth (age <20 years) with newly diagnosed T2D annually in the US, indicating that the incidence of newly diagnosed diabetes cases among youth was 5.3 per 100,000 each year for T2D. T2D accounted for about 22% of all newly diagnosed T1D and T2D cases annually in this age group (43). In addition, T2D was extremely rare among youth aged

<10 years. While still infrequent, incidence rates were greater among youth aged 10-19 years compared to younger children, with higher rates among US minority populations compared with non-Hispanic whites (43).

Mortality

The 1986 National Mortality Followback Survey for a national sample of US decedents aged ≥25 years estimated that deaths of people with T2D accounted for 17.2% of all deaths in the US residents in this age group. Age-specific death rates for people with diabetes were 1.0% for those aged 25-44 years, 2.8% for aged 45-64 years, 5.8% for aged 65-74 years, 13.7% for aged ≥75 years, and 5.4% for all diabetic people aged ≥25 years (95). Several studies concluded that age-adjusted mortality for people with T2D was about twice that of people without diabetes (95). A few studies on predominantly Asian populations reported a 3-fold relative risk of all-cause mortality for people with diagnosed diabetes compared to those without diabetes (96-98), suggesting that the risk of all-cause mortality may be greater in these populations. In addition, findings from the US NHANES I study (1971-1993) revealed that, among those with diabetes, non-Hispanic blacks had a 27% higher age-adjusted mortality rate than that observed in non-Hispanic whites (29). The difference between these different ethnic groups living in the US may reflect the overall poorer health experiences of non-Hispanic blacks.

It was estimated that middle-aged people with T2D experienced a reduction of 5-10 years in life expectancy (46). Mortality data from the US NHANES I study suggested that median life expectancy was 8 years shorter for people with self-reported diabetes aged 55-64 years, and 4 years shorter for those aged 65-74 years (29). Although several studies reported that diabetes conferred an excess risk for all-cause mortality among older people, the risk for CVD mortality

tended to attenuate with increasing age (46). The reduction in life expectancy for women with T2D was greater than that observed for men with T2D. The reduction in life expectancy for women was greater at both younger age of disease onset and younger current age, whereas that for men only varied according to current age, not according to the age of disease onset (46). In addition, several studies have shown that a positive relationship existed between increasing diabetes duration and mortality risk, and the excess mortality risk associated with diabetes also increased with earlier age of diagnosis (46).

The leading cause of death in people with T2D is heart disease; ischemic heart disease (40%) is the most common, with other leading causes of death being other heart disease, diabetes, malignant neoplasms, cerebrovascular disease, and pneumonia/influenza (46,95). Prospective cohort studies indicate that people with T2D have a two- to four-fold risk for CVD mortality compared to those without diabetes (46). The excess mortality risk observed in people with diabetes remains significant after controlling for the influence of other risk factors, such as hypertension, dyslipidemia, and smoking. This suggests that the coexistence of other known risk factors does not fully explain the increased mortality risk observed in people with diabetes, and other factors, either directly or indirectly associated with diabetes, must also be contributing to the unfavorable risk profile (46).

2.2.3 Etiological Factors

Currently, T2D is considered to occur in genetically predisposed people who are exposed to a series of environmental influences that precipitate the onset of clinical disease (99). Substantial information is available on the genetic and environmental factors that are responsible for the development of T2D, and these are summarized below in Tables 2.1 (56) and 2.2 (77,100-102).

Table 2.1 Etiological determinants and risk factors of T2D

Genetic factors
Genetic markers, family history, "thrifty gene(s)"
Demographic characteristics
Sex, age, ethnicity
Behavioral- and lifestyle-related risk factors
Obesity (including distribution of obesity and duration)
Physical inactivity, diet, stress
Westernization, urbanization, modernization
Metabolic determinants and intermediate risk categories of T2D
Impaired glucose tolerance, insulin resistance
Pregnancy-related determinants (parity, gestational diabetes, diabetes in offspring of women with diabetes during pregnancy, intra-uterine mal- or over-nutrition)

Table 2.2 Candidate genes associated with T2D

PPAR-gamma	PPARGC1	KCNJ11	TCF7L2
CDKAL1	HHEX	SLC30A8	SLC2A1
Chr11	GYS1	IRS1	INS
KCJN11	ABCC8	CAPN10	IGF2BP2
CDKN2A/2B	FTO	WFS1	HNF1B
JAZF1	CDC123/CAMK1D	TSPAN8	THADA
ADAMTS9	NOTCH2		

Twin studies suggest that genetic makeup accounts for 60-90% of the susceptibility to T2D. The concordance rate in monozygotic twins is 70-90% compared to only 15-25% in dizygotic twins. Due to the age-dependent penetrance of T2D, the concordance rate in the monozygotic twin studies increases with age, approaching 100% with lifelong follow-up. T2D and IGT cluster in families. Thus, most patients have a positive family history, and the lifetime risk for developing T2D is increased up to 40% (more than five times the background rate) by having a first-degree relative with the disease. If both parents have T2D, the risk to the offspring may be as high as 70%. Available evidence supports a polygenic mode of inheritance with a considerable environmental factor input (103) (see Tables 2.1 and 2.2). The striking ethnic variation in T2D prevalence supports the importance of genetic factors: In the US, the prevalence is 2-4% in Caucasians, 4-6% in African Americans, 10-15% in Mexican Americans, and 35% in

the Pima Indians in Arizona. In adult Pimas, over 75% of whom are obese, a positive family history of T2D is a better predictor of the incidence of T2D than the combined effects of obesity, gender, and physical fitness (31,77).

Environmental/behavioral influences interact with genetic factors to determine susceptibility to T2D by affecting insulin action and/or insulin secretion. The prevalence of T2D has increased markedly in populations that have rapidly adopted a Western lifestyle (e.g., American Pima Indians) and in many populations that have migrated to regions with a more affluent lifestyle compared to their native country (56,77). Obesity, physical inactivity, and dietary influences are clearly important factors that may increase the risk of diabetes in a genetically predisposed individual (77,104). Obesity is strong independent risk factor, and the duration of obesity is also highly predictive of T2D (105). Sedentary people are more likely to develop T2D. The antidiabetogenic effect of moderate regular physical activity is likely related to the beneficial effects on insulin action and prevention of obesity: The protective effect appears to be greatest in those at highest risk for T2D, such as obese people and those with a positive family history (77,106). In addition, T2D evolves in stages. Insulin resistance is thought to be an inherited initial defect in most patients and risk factors, such as obesity, sedentary lifestyle, and aging, may be additive. At the early stage, fasting insulin levels and glucose-stimulated insulin responses are increased and sufficient to maintain normal glucose tolerance. People who develop IGT typically have increased fasting and postprandial insulin levels that do not fully compensate for insulin resistance. Eventually, compensation fails in some people because islet β-cell function declines. The etiology of this decline may be due to a number of factors such as genetic abnormalities affecting β-cell function and/or due to acquired defects (e.g., glucotoxicity and lipotoxicity) (77). The proportion of insulin-resistant people who progress to T2D varies

between ethnic groups. In most populations, the conversion rate from IGT to T2D is 2-5% per year over 10 years (107). In this Diabetes Prevention Program Research Group study, the conversion rate was as high as 11% (108). A small percentage of people with IGT may revert to normal glucose tolerance, while others remain with IGT for many years.

2.2.4 Screening for Type 2 Diabetes

Undiagnosed T2D is common, with an estimated lag of 5-7 years between the onset of diabetes and diagnosis (109-111). It is estimated that, in up to 30% of affected people, the disease are undiagnosed (112). People with IGT and undiagnosed T2D are at significantly increased risk for coronary heart disease, stroke, and peripheral vascular disease. Hence, the delay in the diagnosis of T2D causes an increase in micro- and macrovascular diseases. In addition, affected people have a greater likelihood of having dyslipidemia, hypertension, and obesity. Therefore, it is important for the health care provider to screen for T2D in a cost-effective manner in people who demonstrate major risk factors for T2D as summarized below in Table 2.3 (3).

Age, ethnicity, and family history are also important risk factors for T2D as are certain lifestyle behaviors and co-morbid conditions (see Table 2.3). Certain risk factors, such as hypertension, low HDLc, and high triglycerides, are associated risk factors but not necessarily causal (31). Increasing prevalence of obesity is one of the most important factors since it is closely linked to increasing prevalence of T2D. In the US, surveys found that for every 1 kg increase in weight, there is a 4.5-9.0% increase in the risk of incident diabetes (113,114). In addition, several analyses suggest that the relationship between ethnicity and diabetes prevalence is not solely based on genetic predisposition but rather a complex net of social factors, such as

lower income and education level, which are more prevalent in certain ethnic groups. These factors independently confer a higher risk of obesity and diabetes (31).

The American Diabetes Association advises against routine screening for T2D outside the health care setting due to low likelihood of follow-up care and the need of discussion for abnormal results (3). Screening for T2D will also help detect people at increased future risk for diabetes (i.e., pre-diabetes). Either A1C, fasting plasma glucose (FPG), or 2-hour 75-gram oral glucose tolerance test (OGTT) is appropriate to test for diabetes or pre-diabetes (3). The OGTT may be necessary for diagnosing diabetes when the FPG is normal, but the FPG is preferred for screening based on cost and convenience. Adults should be screened at 3-year intervals beginning at age 45 years; testing should be considered at an earlier age or be carried out more frequently if diabetes risk factors are present (see Table 2.3) (3). A recent study further supports this recommendation, suggesting that screening for T2D in the US population is cost-effective when started between the ages of 30 and 45 years, with screening repeated every 3-5 years (115). Asymptomatic children who are age 10 years or who experience the onset of puberty before age 10 should be screened every 3 years for T2D if they are overweight and have two or more risk factors listed in Table 2.3.

Effective management of T2D to ensure immediate improved well-being and for prevention of both micro- and macrovascular complications requires near-normalization of blood glucose levels by diet, lifestyle modifications, and glucose lowering medications, as well as attention to other risk factors, involving control of blood pressure and dyslipidemia, and use of antiplatelet agents (3,77).

Table 2.3 Criteria (risk factors) for testing for T2D in asymptomatic adults and children

Adults	***Children (age <18 years)***
Overweight (BMI ≥25 kg/m^2)[a]	Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
Physical inactivity	
Family history of diabetes (first-degree relative)	Family history of T2D in first- or second-degree relative
Ethnic predisposition[b]	Ethnic predisposition[b]
History of GDM, PCOS, or delivery of a baby weighing >9 lb (4.1 kg)	Maternal history of diabetes or GDM during the child's gestation
Hypertension: SBP/DBP ≥140/90 mmHg or on therapy for hypertension	Conditions associated with insulin resistance (e.g., hypertension, dyslipidemia, PCOS, or small for gestational age birthweight)
Dyslipidemia: HDLc cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l)	
Pre-diabetes: A1C ≥5.7%, IGT, or IFG on previous testing	
Clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)	Signs of insulin resistance (e.g., acanthosis nigricans)
History of CVD	

Abbreviations: T2D, type 2 diabetes; BMI, body mass index; GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDLc, high-density lipoprotein cholesterol; A1C, glycated hemoglobin; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; CVD, cardiovascular disease.
[a]At-risk BMI may be lower in some ethnic groups.
[b]Ethnic predisposition refers to members of a high-risk ethnic population, including African American, Latino American, Native American, Asian American, or Pacific Islander.

2.3 PRE-DIABETES

2.3.1 Definition

In 1997 and 2003, the American Diabetes Association (ADA) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (33,117) recognized an intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group was defined as having impaired fasting glucose (IFG) (i.e., fasting plasma glucose [FPG] levels of 110 mg/dl [6.1 mmol/l] to 125 mg/dl [6.9 mmol/l]),

impaired glucose tolerance (IGT) (i.e., 2-hour plasma glucose [2-h PG] levels of 140 mg/dl [7.8 mmol/l] to 199 mg/dl [11.0 mmol/l] after a standard 75-gram load on the oral glucose tolerance test [OGTT]), or both. In late 2003, the ADA issued a new expert report (116), recommending lowering the threshold for IFG from 110 mg/dl (6.1 mmol/l) to 100 mg/dl (5.6 mmol/l). With these definitions above, there is overlap between the two groups. To study the separate characteristics of IFG and IGT, classifications of isolated IFG and isolated IGT that are mutually exclusive have been created (isolated IFG = FPG of 100-125 mg/dl with the 2-h PG of <140 mg/dl; isolated IGT = 2-h PG of 140-199 mg/dl with the FPG of <100 mg/dl). The combined characteristics of IFG and IGT are studied by identifying populations that fulfill both criteria (FPG = 100-125 mg/dl and 2-h PG = 140-199 mg/dl). Conversely, normal glucose tolerance is defined as FPG <100 mg/dl and 2-h PG <140 mg/dl (see Table 2.4). The isolated classifications indicate that both forms of glucose testing are undertaken and only one of the two tests is abnormal.

Individuals with IFG and/or IGT are referred to as having pre-diabetes, indicating the relatively high risk for the future development of diabetes (3). In addition to IFG and IGT, the ADA in 2010 also recommends considering an A1C range of 5.7-6.4% as identifying individuals with high risk for future diabetes and to whom the term pre-diabetes may be applied (1). It should be noted that the 2003 ADA Expert Committee report (116) reduced the lower FPG cut-off point to define IFG from 110 mg/dl (6.1 mmol/l) to 100 mg/dl (5.6 mmol/l), in part to make the prevalence of IFG more similar to that of IGT. This change in the cut-off point increased the overall prevalence of IFG approximately three- to four-fold, although it is clear that IGT and IFG do not define the same individuals (118). This change was highly criticized by other groups led by the European Diabetes Epidemiology Group (119). Also, the World Health Organization

convened a Technical Guideline Development Group which published its report in 2006, recommending retaining the lower cut-off point for IFG at 110 mg/dl (6.1 mmol/l) (120). This lack of concordance has the potential to confuse researchers and clinicians (121,122). Due to applying different diagnostic criteria, data from studies should be read cautiously and may not longer be directly comparable if "diabetes", "IFG", or "IGT" do not refer to the same thing in different studies.

Table 2.4 Diagnostic thresholds for diabetes and other categories of hyperglycemia

Category	American Diabetes Association 2003 (116-118)			
	Test			
	FPG level		2-h PG on the 75-g OGTT[a]	
	mg/dl	mmol/l	mg/dl	mmol/l
NGT	<100	<5.6	<140	<7.8
IFG	100-125	5.6-6.9	<200	<11.1
Isolated IFG	100-125	5.6-6.9	<140	<7.8
IGT	<126	<7.0	140-199	7.8-11.0
Isolated IGT	<100	<5.6	140-199	7.8-11.0
Combined IFG/IGT	100-125	5.6-6.9	140-199	7.8-11.0
Diabetes[b]	≥126	≥7.0	≥200	≥11.1

Abbreviations: NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FPG, fasting plasma glucose; PG, plasma glucose; OGTT, oral glucose tolerance test.

[a]This refers to the 2-hour plasma glucose concentration after a standard 75-gram glucose load on the oral glucose tolerance test.

[b]When both tests are performed, IFG or IGT should be diagnosed only if diabetes is not diagnosed by the other test. A diagnosis of diabetes needs to be confirmed on a separate day. The American Diabetes Association in 2010 also recommends including the use of glycated hemoglobin (A1C) to diagnose diabetes, with a cut-off point of ≥6.5% (1).

2.3.2 Epidemiology

Worldwide, it is estimated that about 344 million people (or 7.9%) in the age group 20-79 have IGT in 2010, the vast majority of whom live in low- and middle-income countries. By 2030, a projected 472 million people (or 8.4%) in the age group 20-79 will have IGT, suggesting that at least 472 million adults will have pre-diabetes (123). Epidemiologic studies demonstrate that IFG (110-125 mg/dl) has lower prevalence than IGT (124-126), since the majority of these

studies were done prior to the year of 2003 when a FPG level of 110 mg/dl (6.1 mmol/l) was used as the lower cut-off point for defining IFG. However, using 100 mg/dl as the cut-off point for IFG, its prevalence markedly increased (118,127) and exceeded that of IGT (2,81,83,128). In addition to the difference in prevalence of both categories, the overlap between the two is only partial (124,126).

In the US, a cross-sectional sample of adults aged 40-74 years, who were tested during the period 1988-1994, showed that 33.8% had IFG, 15.4% had IGT, and 40.1% had pre-diabetes (IGT or IFG or both) (81). When these percentages were applied to the entire US population in 2000, an estimated 35 million adults aged 40-74 had IFG, 16 million had IGT, and 41 million had pre-diabetes (81). More recent estimates from 2005-2006 NHANES data indicated that 25.7% of US adults aged 20 years or older had IFG and 13.8% had IGT, with almost 30% having either (83).

The 2003-2006 NHANES data (2) indicated that 25.9% of US adults aged 20 years and older had IFG, which was not significantly different from the prevalence in 1988-1994 (24.7%) and 1999-2002 (26.0%) (82). Applying this percentage to the entire US population in 2007 yields an estimated 57 million American people aged 20 years or older with IFG, suggesting that at least 57 million American adults had pre-diabetes in 2007 (2). After adjusting for population age and sex differences, IFG prevalence among US adults aged 20 years or older in 2003-2006 was 26.1% for Mexican Americans, 25.1% for non-Hispanic whites, and. 21.1% for non-Hispanic blacks (2). Prevalence of pre-diabetes is generally stable (31,83), although the prevalence of IFG and IGT varies considerably among different ethnic groups (118). IFG and IGT also differ significantly in their age and gender distribution; the prevalence of both

metabolic disorders increases with advancing age, and IFG is more than two-fold higher in men whereas IGT is more frequent in women (31,118,124).

2.3.3 Pathogenesis

Although IFG and IGT are intermediate states between NGT and overt T2D, the epidemiological differences between them suggest that they represent distinct states of glucose intolerance, which are characterized by different pathophysiologic mechanisms (124,129-133). Both IFG and IGT are insulin-resistant states, but they differ in site of insulin resistance. Individuals with IFG predominantly have hepatic insulin resistance and normal muscle insulin sensitivity, while those with IGT have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance. Subjects with combined glucose tolerance (i.e., both IFG and IGT) manifest both forms of insulin resistance in severe form. The pattern of impaired insulin secretion also differs between the two groups. Subjects with isolated IFG manifest a decrease in first-phase insulin secretory response to intravenous glucose and early-phase insulin response to oral glucose. However, late-phase plasma insulin response during OGTT is less severely impaired in IFG than in IGT; subjects with IGT have severe defects in both early- and late-phase insulin responses to intravenous and oral glucose (130). In addition, there are four main risk factors for IGT: age, obesity, physical inactivity, and family history of T2D (see Table 2.5) (107). The NHANES data in the US showed clearly the rise in IGT prevalence with age, the rates in Caucasians aged 65-74 years being 5-fold higher than in individuals aged 25-34 years. Body weight is also strongly predictive of late development of IGT, with a major increase in risk once body mass index exceeds 27 kg/m^2. Generally, the risk factors for IGT are the same as those for T2D (107).

A clearer understanding of the distinct pathophysiologic abnormalities which characterize IFG and IGT provides insights about interventions to slow/halt the progression to T2D. Subjects with IFG, who manifest predominant liver insulin resistance, are most likely to benefit from agents, e.g., metformin, that reduce hepatic insulin resistance, while those with IGT, who predominantly have muscle insulin resistance plus severely impaired insulin secretion, are more likely to respond to agents that improve skeletal muscle insulin resistance, such as peroxisome proliferator-activated receptor-γ agonists, in combination with an insulin secretagogue, such as glucagon-like peptide-1 analog (130).

Table 2.5 Risk factors for the development of IGT

Advanced age
Elevated body mass index
Elevated triglycerides
Physical inactivity
Central obesity
Family history of type 2 diabetes
Low birth weight
Low weight at age 1 year

2.3.4 Clinical Significance of Pre-Diabetes

IFG and IGT are not clinical entities in their own right, but they are associated with a progressively greater risk for progression to diabetes, as well as for death and morbidity due to micro- and macrovascular complications (1,5,117,118,124,129,134,135). IFG and IGT appear as risk factors for diabetes because of their correlation with moderate to severe insulin resistance in muscle and/or liver as well as impaired β-cell function (124). In contrast, the explanation for why IFG and IGT are also risk factors for CVD is less clear; that is, they may not in themselves be directly involved in the pathogenesis of CVD, but rather may serve as statistical risk factors by association because they correlate with those elements of the insulin resistance syndrome (i.e., metabolic syndrome) that are cardiovascular risk factors (33,117).

The transition from the early metabolic abnormalities to diabetes may take many years; however, several estimates indicate that the majority of individuals (perhaps up to 70%) with the pre-diabetic states eventually develop diabetes. The natural history of both IFG and IGT is variable, with about 25% progressing to diabetes, 50% remaining in their abnormal glycemic states, and 25% reverting to NGT over an observational period of 3-5 years. Individuals who are older, overweight, and have other diabetes risk factors are more likely to progress (118,136). Moreover, low insulin secretion and severe insulin resistance identify individuals more likely to progress to diabetes (137). Several studies report an annual conversion rate to diabetes varying from 1-6% for individuals with IFG, but that varying from 2-14% for those with IGT (5). Individuals with both IFG and IGT may approximately double the rate of developing diabetes compared with those with just one of them (118).

Numerous studies indicate that IFG and/or IGT are associated with a modest increase in the relative risk (~1.10-1.66) for CVD risk factors and CVD events (non-fatal and/or fatal), with IGT being a slightly stronger risk predictor (5,116,118,134,135,138). Many cardiovascular risk factors (e.g., hypertension and dyslipidemia) are prevalent in IFG and IGT; however, after adjustment for known cardiovascular risk factors, both IFG and IGT remain as independent, albeit weak, risk factors for CVD in some studies (118,124). Thus, it is likely that insulin resistance is an important risk factor for atherosclerosis (124). In addition, the relative risk of all-cause mortality ranges from 1.03- to 1.48-fold higher in people with IFG or IGT compared with those with NGT (134,138).

2.3.5 Pre-Diabetes in Pediatric Population

The prevalence of pre-diabetes is rapidly increasing in young adults and children. The 1999-2000 NHANES (139) data showed that the prevalence of IFG in US adolescents aged 12-19 years was 7.0% and was higher in boys than in girls (10.0% vs 4.0%). Prevalence of IFG was higher in overweight adolescents (17.8%) but was similar in those with normal weight and those who were at risk for overweight (5.4% vs 2.8%). The prevalence of IFG was significantly different across ethnic groups (13.0, 7.0, and 4.2% in Mexican Americans, non-Hispanic white individuals, and non-Hispanic black individuals, respectively). A clinic-based study in the US (140) showed that IGT was found in 25% of 55 obese children (age 4-10 years) and 21% of 112 obese adolescents (age 11-18 years). In this study, 51% of those with IGT were non-Hispanic white, 30% were non-Hispanic black, and 19% were Hispanic (compared to 58, 23, and 19%, respectively, in the population studied). Recent studies also reported that as many as 10% of obese children have isolated IFG and 15% have isolated IGT, while similar to adults, only partial overlap between IFG and IGT was reported in children (141). In addition, the most recent NHANES 2005-2006 data (128) estimated that the national population-based prevalence rates of IFG, IGT, and pre-diabetes (IFG and/or IGT) among US adolescents aged 12-19 years were 13.1, 3.4, and 16.1%, respectively. IFG accounted for nearly 80% of adolescents with pre-diabetes. Pre-diabetes risk was positively associated with being male and having hyperinsulinemia, but negatively associated with being a non-Hispanic black individual. Moreover, hyperinsulinemia appeared to account for the association of weight status and clustering of cardiovascular risk factors with pre-diabetes.

The metabolic abnormalities that underlie IFG and IGT in children are similar to those in adults (124,141,142). Insulin resistance in skeletal muscle and liver and impaired β-cell function

both contribute to the development of IFG and IGT in children. The insulin resistance in children with pre-diabetes is also associated with the metabolic abnormalities, which are characteristic of the insulin resistance syndrome (139,143) and which are likely to result in an increased future risk for CVD in this age group, although longitudinal studies have not addressed this concern.

Similar to adults, children with pre-diabetes have an increased risk for T2D. In a longitudinal study involving 102 obese children who were followed for up to 2 years, about one third with pre-diabetes at baseline developed T2D (144). Weight gain seemed to be the most important risk factor of predicting development of T2D in children with IGT; children who gained excessive weight during the follow-up period had a greater risk for progression to T2D compared with those who gained the least amount of weight (144). This observation underscores the importance of encouraging weight loss and increased physical activity in obese children.

Further clarification of population-based prevalence and investigation to improve understanding of the diagnosis, clinical significance, and optimal management of pre-diabetes in childhood is required.

2.3.6 Management of Pre-Diabetes

Early identification and treatment of people with pre-diabetes have the potential to reduce or delay the progression to diabetes, related CVD, and microvascular disease (145). A number of well-designed and executed clinical trials demonstrate the value of lifestyle modification or pharmacological therapy to prevent or delay the onset of diabetes (3). The ADA treatment recommendations for individuals with pre-diabetes are summarized in Table 2.6 (3,118). The completed prevention trials indicate that an intensive lifestyle intervention provides the great

reduction in the occurrence of diabetes, along with a modest reduction in CVD risk factors, and has a favorable safety profile. The lifestyle modification studies are associated with virtually no serious untoward effects. In addition, lifestyle modification is likely to have other beneficial health-related effects (118).

Recently, a consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists (ACE/AACE) (145) recommended that, as pre-diabetes progresses, pharmacotherapy directed at hyperglycemia and the individual coronary heart disease risk factors may be required. Also, strict control of all known risk factors for CVD and microvascular complications in people with T2D by aggressive management of glycemia, hypertension, and dyslipidemia and use of aspirin (as well as smoking cessation) has proved to be highly beneficial. Currently, there are no medications that have been approved in the US for prevention of diabetes in adults, nor are there any approved pharmacological options for use in children and adolescents. However, there is strong evidence from randomized controlled trials that metformin or acarbose reduces the progression of pre-diabetes to diabetes. While both agents are less effective than intensive lifestyle interventions, they do have relatively good safety profile. Therefore, it would not be unreasonable to consider either of them for treatment of selected people with pre-diabetes.

Recognizing the limitations of data in pre-diabetes, the ACE/AACE committee (145) recommended that pre-diabetic people achieve the same target blood pressure currently recommended for people with diabetes - that is, a systolic pressure less than 130 mmHg and a diastolic pressure less than 80 mmHg. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers should be first-line agents, with calcium channel blockers as appropriate second-line treatment approaches. In addition, people with pre-diabetes should also have the

same lipid goals as those with established diabetes. As such, statin therapy is recommended to achieve low-density lipoprotein cholesterol levels of 100 mg/dl or below. Attention should be given to achieving goals for non-high-density lipoprotein cholesterol levels of 130 mg/dl or less (and/or apolipoprotein B ≤90 mg/dl). Additional use of fibrates, bile-acid sequestrants, ezetimibe, and other agents should be considered as appropriate. Bile-acid sequestrants may play a unique role in pre-diabetes because one of these drugs, colesevelam, reduces glucose levels and is approved for treatment of diabetes, addressing both cardiovascular and diabetes risk factors. Moreover, low-dose aspirin is recommended for all people with pre-diabetes for whom there is no identified excess risk for gastrointestinal, intracranial, or other hemorrhagic conditions.

Lastly, the ACE/AACE committee (145) recommended that the management of the children or adolescents at increased risk for the development of T2D in childhood or later in life should use many of the measures recommended to prevent or delay the progression to diabetes in adults at increased risk.

Table 2.6 Treatment recommendations for individuals with pre-diabetes

Population	**Treatment/Follow-up**[a]
IFG or IGT or glycated hemoglobin of 5.7-6.4%	Lifestyle modification (i.e., 5-10% weight loss and moderate intensity physical activity ~30 minutes/day)
Individuals with IFG and IGT and any of the following: ▪ Age <60 years ▪ Body mass index ≥35 kg/m^2 ▪ Family history of diabetes in first-degree relatives ▪ Elevated triglycerides ▪ Reduced high-density lipoprotein cholesterol levels ▪ Hypertension ▪ Glycated hemoglobin >6.0%	Lifestyle modification (as above) and/or metformin[b]

Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
[a]Monitoring for the development of diabetes in those with pre-diabetes should be performed every year.
[b]Metformin will be given at 850 mg twice per day. Other medications may be included if they prove to be effective, have a good safety/tolerance profile, and are of relatively low cost.

2.4 COMPLICATIONS OF DIABETES

The increasing prevalence of diabetes leads to an increase in associated complications that result in morbidity and mortality (146). In the US, recent data show that diabetes complications contribute to 810 deaths, 230 amputations, 120 cases of kidney failure, and 55 cases of blindness daily. Among people with diabetes, CVD is the leading cause of death, while heart disease and stroke account for about 65% of all deaths (81,147). There are two types of complications related to diabetes: (1) acute complications, including diabetic ketoacidosis, hyperosmolar hyperglycemic state, and hypoglycemia; and (2) chronic complications, including micro- and macrovascular complications.

2.4.1 Acute Complications

Hyperglycemic crises, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS), and hypoglycemia are acute and potentially life-threatening complications of diabetes (89,148). However, there are encouraging trends in the rates of these acute complications. In the US diabetic population, rates of hospitalizations for DKA (from years 1985 to 2005) and those of mortality due to hyperglycemic crises (from years 1980 to 2005) declined (149,150); and in the elderly Medicare population, rates of emergency department admissions for metabolic crisis and ketoacidosis declined between 1992 and 2001 (151). Generally, in the US, incidence and death rates due to acute complications related to diabetes are higher among Blacks than among Whites (149,150).

2.4.1.1 Hyperglycemic Crises

DKA and HHS are the two most serious acute metabolic complications of diabetes. Both of these conditions carry significant likelihood of morbidity and mortality, including cerebral edema, permanent neurological injury, and death (148,152). DKA is characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentrations, while HHS is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis. These metabolic disturbances result from the combination of absolute or relative insulin deficiency and an increase in counter-regulatory hormones (e.g., glucagon, catecholamines, cortisol, and growth hormone). Most people with DKA have autoimmune T1D; however, people with T2D are also at risk during the catabolic stress of acute illness such as trauma, surgery, or infections (148,152-154).

Hospitalizations for DKA in the US are increasing; in the decade from 1996 to 2006, there was a 35% increase in the number of cases, with a total of 136,510 cases with a primary diagnosis of DKA in 2006 (152). Most people with DKA were between the ages of 18-44 years (56%) and 45-65 years (24%), with only 18% of people aged <20 years; two-thirds of those with DKA had T1D and 34% had T2D, 50% were female, and 45% were nonwhite (152). HHS incidence appears to be increasing, but it is unclear if this is a real increase or artifact of improved detection. Approximately one-third of adults experiencing acute hyperglycemic crisis have mixed DKA and HHS, but the frequency of isolated HHS varies from 15 to 45% depending on the selection criteria (153). DKA is the most common cause of death in children and adolescents with T1D and accounts for half of all deaths in diabetic people aged <24 years. In adults with DKA, the overall mortality is <1%; however, it is more common (mortality rate >5%) in the elderly and in people with concomitant life-threatening illnesses. Mortality

attributed to HHS is considerably higher than that attributed to DKA, with a mortality rate of 4-25%. The prognosis of both conditions is substantially worsened at the extremes of age in the presence of coma, hypotension, and severe comorbidities. Death in these conditions is rarely due to the metabolic complications of hyperglycemia or ketoacidosis but relates to the underlying precipitating illnesses (152,153). The most common precipitating factor for developing DKA and HHS is infection. Other risk factors include discontinuation of or inadequate insulin therapy, pancreatitis, myocardial infarction, cerebrovascular accident, and medications. In addition, new-onset T1D or discontinuation of insulin in established T1D commonly leads to the development of DKA. In young people with T1D, psychological problems complicated by eating disorders may be a contributing factor in 20% of recurrent ketoacidosis. Underlying medical illness that provokes the release of counter-regulatory hormones or compromises the access to water is likely to result in severe dehydration and HHS. In most people with HHS, restricted water intake is due to the patient being bedridden and is exacerbated by the altered thirst response of the elderly (152).

Direct medical care charges associated with DKA episodes represent 28% of the direct medical care charges for all patients, and 56% for those with recurrent DKAs (155). DKA accounts for an annual average of 135,000 hospitalizations at an estimated annual direct medical expense and indirect cost of more than US$2.4 billion (156). There are no reliable data concerning the cost of HHS because of weakness of the incidence data. However, on an individual basis, cost per event is several times higher than that for uncomplicated DKA (153).

Successful treatments of DKA and HHS require correction of dehydration, hyperglycemia, and electrolyte imbalances; identification of comorbid precipitating events; and above all, frequent patient monitoring. Hypoglycemia and hypokalemia are two common

complications with overzealous treatment of DKA with insulin and bicarbonate, respectively, but these complications occur less often with the low-dose insulin therapy. Frequent blood glucose monitoring (every 1-2 hours) is mandatory to recognize hypoglycemia. Hyperchloremic non-anion gap acidosis, which is seen during the recovery phase of DKA, is self-limited with few clinical consequences (152). In fact, many cases of DKA and HHS in people with known diabetes can be prevented by better access to medical care, proper diabetes management education, adequate treatment and self-monitoring of blood glucose, and effective communication with a health care provider during an intercurrent illness (152,153).

2.4.1.2 Hypoglycemia

Hypoglycemia is the most common life-threatening complication of diabetes treatment, causing a spectrum of acute complications from mild cognitive impairment to coma, seizure, and sudden death (153). The ADA developed five hypoglycemia categories to help investigators report hypoglycemic events in clinical trials, including severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, and relative hypoglycemia (157). The ADA recommends that, at a minimum, hypoglycemic events should be reported in each of the first three categories. Thus, since severe hypoglycemia is infrequent, the vast majority of reported episodes will require a corresponding plasma glucose concentration <70 mg/dl (3.9 mmol/l), with (documented symptomatic hypoglycemia) or without (asymptomatic hypoglycemia) typical symptoms (157). In people with diabetes, hypoglycemia is characterized by the interplay of relative or absolute insulin excess, compromised physiological defenses against falling plasma glucose concentrations, and multiple risk factors (153,158,159).

A meta-analysis of 14 studies in T1D, which included 1,028 patients on intensified insulin therapy and 1,039 patients on conventional insulin therapy, showed that the median incidence of severe hypoglycemia was 7.9 and 4.6 episodes per 100 patient-years, respectively. On the other hand, patients with T2D generally experience less frequent severe hypoglycemia than those with T1D. For example, in patients with T2D on insulin therapy and sulfonylureas therapy, the incidence of severe hypoglycemia is approximately 0.83 and 1.5 episodes per 100 patient-years (160). Hypoglycemia contributes significantly to excess mortality in people with diabetes. Sudden nocturnal death in young people with T1D has been reported, and it appears to be responsible for about 6% of deaths in diabetic people aged <40 years. In these cases, nocturnal hypoglycemia is a likely precipitant consistent with demonstrated impairment of counter-regulatory hormone response during sleep and with high frequency of nocturnal hypoglycemia (153). Risk factors for hypoglycemia include: 1) unmodifiable demographic predictors (i.e., age, male gender, and increased duration of diabetes); 2) endogenous insulin deficiency; 3) a history of hypoglycemia, hypoglycemia unawareness, or both; 4) imperfect insulin replacement; 5) recent moderate or intensive exercise; 6) sleep; 7) alcohol consumption; 8) renal failure; 9) lack of adequate health insurance and access to care; 10) coexisting autoimmune conditions (e.g., thyroid autoimmune disease) (153,157).

Using the incidence rate of reported severe hypoglycemia from Colorado (161) and the average annual cost of severe hypoglycemia estimated at US$174 per person (162), the direct medical cost of severe hypoglycemia in the US children was at least US$26 million per year in the late 1990s (153).

Teaching a patient to recognize and treat hypoglycemia is a key component of diabetes care. When patients detect the symptoms discussed above, they should perform a blood glucose

test. If the reading is <70 mg/dl, they should consume 15-20 g of carbohydrate (163). Hypoglycemia can be preventable by improved insulin delivery, using continuous glucose monitors, patient education, and behavioral interventions (135,163).

2.4.2 Chronic Complications

Diabetes, a group of chronic diseases characterized by hyperglycemia, can lead to serious chronic complications, such as blindness, lower-limb amputations, kidney damage, and CVD (i.e., angina, myocardial infarction, stroke, peripheral artery disease, and congestive heart failure), but people with diabetes can lower the occurrence of these and other diabetes complications by controlling blood glucose, blood pressure, and blood lipids (2,164). The importance of protecting the body from diabetes/hyperglycemia cannot be overstated; the direct and indirect effects on the human vascular tree are the major source of morbidity and mortality in both T1D and T2D. Generally, the major injurious chronic effects of hyperglycemia are separated into microvascular complications (diabetic retinopathy, neuropathy, and nephropathy) and macrovascular complications (coronary heart disease, stroke, and peripheral arterial disease) (10,165).

2.4.2.1 Microvascular Complications

Retinopathy

Diabetic retinopathy (DR) is a retinal vascular disorder characterized by typical microvascular funduscopic changes. These typical funduscopic lesions can be broadly divided into two stages, nonproliferative or proliferative retinopathy, with varying degrees of severity in each subset.

They can either precede or follow alterations in retinal function thereby highlighting the importance of timely examinations to detect incipient changes (166). Although numerous classifications of DR have been developed, principally for use in clinical trials, the American Academy of Ophthalmology has adopted a new and simplified classification for use in routine clinical practice (167). The levels in this system consist of five scales with increasing risks of retinopathy, including no apparent retinopathy, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR) (167-170). The characteristic fundus lesions associated with NPDR include cotton wool spots, microaneurysms, dot and blot hemorrhages, retinal vascular caliber changes, hard exudate formation, retinal capillary closure, and macular edema (166). With further ischemic injury, compensatory chemical mediators, mostly notably vascular endothelial growth factor, induce the growth of fragile new blood vessels at the inner surface of the retina. This stage, called PDR, is characterized by neovascularization of the optic disc and neovascularization elsewhere (170). Two leading causes of diabetes-related vision loss are diabetic macular edema (DME) and complication from retinal neovascularization (abnormal blood vessel growth) (171). DME can occur at any stage of DR, while neovascularization is one of important features in PDR (170,171). The vascular disruptions of DR/DME are characterized by abnormal vascular flow, disruptions in permeability, and/or closure or nonperfusion of capillaries (168).

DR may be not only the most common microvascular complication of diabetes, but the leading cause of new cases of blindness in the work-age population (age 20-74 years), accounting for 12% of all new cases of blindness and leading to 12,000 to 24,000 new cases of blindness each year in the US (2,17,165,170). In people with T1D, clinically significant retinopathy almost never occurs in the first 5 years after diagnosis of diabetes or before puberty,

while a fifth of people with newly discovered T2D have retinopathy at the time of diagnosis (10,171). However, the prevalence of DR will be getting high with longer duration of diabetes; 20 years after diagnosis of diabetes, >95% of people with T1D and >60% of people with T2D will have some degree of retinopathy (10,170,171). The proportion of visual impairment in people with diabetes approximately doubles that in people without diabetes (172). Recent data showed that in 2008, the crude percentage of adults with diabetes who report visual impairment was 20.5%, representing a slight decrease from 26.1% in 1997 (150). Also, the risk of blindness in people with diabetes is 20 times higher than that in those without diabetes (10). In the Pittsburgh Epidemiology of Diabetes Complications Study, the 2-year incidence of DR was 33% in T1D (173), while in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the 10-year incidence of DR was 75% in the younger-onset T1D group, 70% in the older-onset T2D group on insulin treatment, and 50% in those not on insulin treatment (174).

Retinopathy in people with diabetes may be a marker of systemic vascular diseases and is linked with cardiovascular morbid-mortality and all-cause mortality (167,175). The single best predictor of DR is the duration of diabetes, while other risk factors that increase the risk of, or are associated with, DR include severity of hyperglycemia, the presence of nephropathy, hypertension, and dyslipidemia (3,166,167,170,175). Diabetes-related blindness and visual impairment places a significant burden on society. The federal budgetary cost of blindness was estimated to be $4.1 billion in the US for the year 1990, and 97% of these costs were accounted for by the working-age adult group. Health care and economic burdens of DR are further compounded by the resulting decline in quality of life; hence, the true impact on society cannot be estimated on a monetary basis alone (168). However, DR is one of the most prevalent but

preventable blinding diseases in the US; with early detection, DR can be treated with modalities that have been proven to decrease the risk of severe vision loss by >90% (170).

Neuropathy

The diabetic neuropathies are heterogeneous, affecting different parts of the nervous system and may present with diverse clinical manifestations. They may be focal or diffuse, and the most two common among the neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) (176,177). Although DPN is a diagnosis of exclusion, complex investigations to exclude other conditions are rarely needed (3). With immensely varying clinical features of diabetic neuropathy, people with diabetes may present to a wide spectrum of specialties, from dermatology to podiatry, or from urology to cardiology (177). The diabetic polyneuropathies (DPN and DAN) are clearly of multifactorial etiology, and a number of metabolic and vascular defects are now implicated in their pathogenesis (178).

The neuropathies are among the most frequent of the long-term complications of diabetes; about 60-70% of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, erectile dysfunction, or other nerve problems. Almost 30% of people with diabetes aged 40 years or older have impaired sensation in the feet (i.e., at least one area that lacks feeling) (2). More specifically, DPN is by far the most common subgroup of the diabetic neuropathies, accounting for more than 80% of patients with clinical diabetic neuropathies (179). Although the prevalence of DPN varies, it appears that at least one manifestation of DPN is present in at least 20% of adults with diabetes (176). Prevalence data for DAN range from 1.6 to 90% depending on tests used, populations

examined, and type and stage of disease (176). DPN is associated with a number of modifiable and nonmodifiable risk factors, including the degree of hyperglycemia, lipid and blood pressure indexes, diabetes duration, and height, while risk factors for the development of DAN include diabetes duration, age, and long-term poor glycemic control and DAN may cosegregate with factors predisposing to macrovascular events such as raised blood pressure and dyslipidemia (176).

Diabetic neuropathy is one of the major contributing causes of amputation and foot ulceration, which are common and major causes of morbidity/disability in all people with diabetes and may lead to mortality in some people with diabetes (2,3,177). The risk of amputation in people with diabetes is 40 times higher than that in those without diabetes (10). In the US, an estimated 15% of people with diabetes will have a diabetic foot ulcer during their lifetime; of these, 6-43% will ultimately undergo a lower-extremity amputation (17). Among people with diabetes who have had an amputation, as many as 85% may have had a preceding foot ulcer (17). Recent data showed that more than 60% of nontraumatic lower-limb amputations occurred in people with diabetes in the US, and in 2004, about 71,000 nontraumatic lower-limb amputations were performed in people with diabetes (2). The risk of ulcers or amputations is increased in diabetic people who have the following risk factors: previous amputation, past foot ulcer history, peripheral neuropathy, foot deformity, peripheral vascular disease, visual impairment, diabetic nephropathy (especially patients on dialysis), poor glycemic control, and cigarette smoking (3,175).

Recent the US national diabetes surveillance data showed that the crude hospital discharge rates for lower-extremity ulcer/inflammation/infection, neuropathy, and nontraumatic lower-extremity amputation in 2003 were 6.9, 6.8, and 5.2 per 1,000 people with diabetes,

respectively (150). Also, the financial cost of diabetic ulceration and/or amputations is staggering (177). Therefore, the early recognition and appropriate management (i.e., prevention and treatment) of neuropathy as well as ulcers and amputations in people with diabetes is important to reduce the burden of these complications.

Nephropathy

Diabetic nephropathy (DN) is a renal damage caused by microangiopathic affection. DN is a chronic vascular complication exclusive of diabetes characterized by alterations in renal microcirculation, leading to a series of functional and structural damages, mainly in the glomerulus (180). Without therapeutic interventions, serum creatinine levels increase and patients go on to develop end-stage renal disease (ESRD; i.e., kidney failure requiring dialysis or transplantation). Microalbuminuria (or incipient nephropathy) in the range of 30-299 mg/24 h is the earliest stage of DN in T1D and a marker for development of nephropathy in T2D (3,181). Without specific interventions, about 80% of people with T1D who develop persistent microalbuminuria have their urinary albumin excretion increase at a rate of about 10-20% per year to the stage of macroalbuminuria (i.e., clinical albuminuria or overt nephropathy; ≥300 mg/24 h or ≥200 µg/min) over a period of 10-15 years, with hypertension also developing along the way. Once overt nephropathy occurs, without specific interventions, the glomerular filtration rate (GFR) gradually falls over a period of several years at a rate that is highly variable from individual to individual (2-20 ml/min per year). ESRD develops in 50% of type 1 diabetic people with overt nephropathy within 10 years and in >75% by 20 years (181).

A higher proportion of people with T2D are found to have microalbuminuria and overt nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for

many years before the diagnosis is made and also because the presence of albuminuria may be less specific for the presence of diabetic nephropathy, as shown by biopsy studies. Without specific interventions, 20-40% of type 2 diabetic people with microalbuminuria progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only about 20% will have progressed to ESRD. Once the GFR begins to fall, the rates of fall in GFR are again highly variable from one individual to another; however, overall they may not be substantially different between people with T1D and those with T2D (181).

Generally, DN occurs in 20-50% of people with diabetes (3,180). Diabetes is the single leading cause of ESRD in the US, accounting for 44% (48,215/108,928) of new cases of treated ESRD in 2006 (182). The risk of ESRD in people with diabetes is 25 times higher than that in those without diabetes (10). Encouragingly, from 1996 to 2006, the age-adjusted diabetes-related ESRD incidence in the US decreased by 3.9% per year from 343.2 to 197.7 per 100,000 diabetic populations (182), probably because of a reduction in the prevalence of ESRD risk factors, improved treatment and care, and other factors. In addition, several factors can influence the development of DN, including genetic factors, poor glycemic control, hypertension, dyslipidemia, smoking habit, retinopathy, and microalbuminuria or progression to proteinuria (175,180).

Microalbuminuria, in addition to being the earliest manifestation of nephropathy, is a well-established marker of greatly increased cardiovascular morbidity and mortality for people with diabetes (3,181). Diabetic people with microalbuminuria who progress to macroalbuminuria are likely to progress to ESRD (3). ESRD is a costly and disabling condition with a high mortality rate. In 2006, ESRD costs reached nearly $23 billion, >6% of the Medicare budget, and mortality rates were about eight times greater among people aged 20-64 years with

ESRD treated by dialysis than among those in the general population of similar age (182). However, recent studies have now demonstrated that the onset and course of DN can be ameliorated to a very significant degree by several interventions, and these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication (3,181).

2.4.2.2 Macrovascular Complications

Cardiovascular Disease

Macrovascular complications commonly develop in individuals with T1D and T2D. This is of a particular concern as the increasing prevalence of diabetes now also affects adolescents and younger adults, thus promoting the earlier development of long-term complications. Diabetes itself accounts for 75-90% of the excess coronary heart disease (CHD) risk and enhances the effects of other cardiovascular risk factors (183). Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in individuals with diabetes and accounts for the greatest component of health care expenditures for diabetes (3,165,184). The types of CVD that accompany diabetes mainly include CHD (angina or myocardial infarction), stroke, congestive heart failure, and peripheral arterial disease (164).

Cardiovascular diseases are defined as diseases and injuries of the circulatory system: the heart, the blood vessels of the heart, and the system of blood vessels throughout the body and to (and in) the brain (185). Angina is the pain that arises when the blood supply to the heart muscle itself is temporarily insufficient. This is usually due to narrowing of the arteries feeding the heart muscle. When one of these arteries becomes fully blocked, a myocardial infarction occurs,

which kills heart muscle and is often fatal (186). People with diabetes without previous myocardial infarction have as high a risk of myocardial infarction as people without diabetes who had a previous myocardial infarction (187). Stroke occurs when areas of the brain die from arterial blockage or arterial breakage and bleeding. Stroke is sometimes fatal but it also often causes paralysis and loss of speech (186). Heart failure results when the heart cannot pump strongly and fluid backs up in the legs, lungs, and other tissues (186). Peripheral arterial disease results from blockages in arteries that feed the legs; it causes pain while walking and can lead to claudication, major surgery, and the need for amputation (186). Peripheral arterial disease is one of the major contributing causes of amputation and foot ulceration, which are common and major causes of morbidity/disability in all people with diabetes (2,3).

Pathogenesis

A range of hemodynamic and metabolic factors are considered responsible for the development and progression of macrovascular complications in diabetes (188). Specifically, the central pathological mechanism in macrovascular complications is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body (165). Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the coronary or peripheral vascular system. In response to endothelial injury and inflammation, oxidized lipids from low-density lipoprotein particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen

accumulation. The net result of this process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion would lead to acute vascular infarction (165,189).

In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of type 1 plasminogen activator inhibitor may also impair fibrinolysis in people with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in diabetes (165,190). Diabetes increases the risk that an individual will develop a CVD. Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound (165).

Prevalence

Globally, the prevalence of CHD in people with diabetes (both T1D and T2D) ranges from 1.0% to 25.2% in clinic-based populations and from 1.8% to 43.4% in population-based studies, while the prevalence of stroke in those people were from 1.0% to 11.3% and from 2.8% to 12.5%, respectively (186). Recently, the US national diabetes surveillance data showed that the age-adjusted percentage of people with diabetes aged 35 years and older self-reporting any CVD condition (i.e., CHD, stroke, or other heart diseases) declined from 36.6% in 1997 to 31.4% in 2007 (150). More specifically, no major changes were apparent in the age-adjusted percentage of CHD, stroke, or other heart diseases between 1997 and 2007. In 2007, the age-adjusted percentage of people with diabetes aged 35 years and older with self-reported CHD was 20.2%,

almost 2.6 times that of self-reported stroke (7.9%) and 1.2 times that of self-reported other heart diseases (16.2%) (150).

In addition, between 1997 and 2007, the percentage of adults with diabetes aged 35 years and older self-reporting any CVD condition was lower in adults aged 35-64 years than that among those older (i.e., people aged 65-74 or 75 years and older). The percentage declined across the time period for adults aged 35-64 years; however, no consistent trend was observed for those aged 65-74 or 75 years and older. In 2007, the percentage was 26.5% among people aged 35-64, 44.9% among those aged 65-74 years, and 48.4% among those aged 75 years or older (150). Regarding gender differences, between 1997 and 2007, the age-adjusted percentage was higher for men than women, but declined for both men and women. In 2007, the age-adjusted percentage was 32.2% for men and 30.6% for women (150). In terms of racial/ethnic differences, between 1997 and 2007, the age-adjusted percentage was highest among whites and lowest among Hispanics. The age-adjusted percentage declined across the time period for whites; however, no consistent trend was seen among blacks or Hispanics. In 2007, the age-adjusted percentage was 32.4% among whites, 30.3% among blacks, and 21.3% among Hispanics (150).

The prevalence of congestive heart failure in people with diabetes varies in different studies, partly because of differences in the definition of this disease and in the characteristics of study populations. Three US studies, focusing on the role of congestive heart failure in people with diabetes, noted that the prevalence of congestive heart failure varied between 1.9% and 22.3% (191-193). In addition, the true prevalence of peripheral arterial disease in people with diabetes is difficult to determine, since many patients are asymptomatic, they do not report their symptoms, their pain perception is blunted by neuropathy, or different methods are used to

estimate its presence. Both asymptomatic peripheral arterial disease and claudication are more common among people with diabetes. Peripheral arterial disease in people with diabetes is both morphologically and physiologically distinguished from non-diabetic atherosclerosis (194). Studies showed that 15-65% of people with diabetes have peripheral arterial disease, while 2.1-7.5% of those with diabetes have claudication (194,195).

Incidence

The incidence of CVD in people with diabetes varies in different studies, largely because of differences in the definition of the disease and in the characteristics of study populations. According to four occupational/population-based studies comparing the incidence of CVD in adults with and without diabetes in the US, all found an increased risk of incident CVD (fatal and non-fatal combined) among diabetic individuals (196). The Framingham Heart Study found that the age-adjusted CVD incidence rate per 1,000 person-years was 128.8 for diabetic men and 106.5 for diabetic women (197). The Honolulu Heart Study found that the age-adjusted CHD (including non-fatal myocardial infarction and fatal CHD) incidence rate per 1,000 person-years was 11.6 for diabetic men (198). The Nurses' Health Study revealed that the CHD (including non-fatal myocardial infarction and fatal CHD) and stroke (including non-fatal and fatal stroke) incidence rates per 1,000 person-years were 4.2 and 1.5 for diabetic women (199). A community-based study in New Haven, CT showed that, during the 6-year follow-up, the weighted incidence of non-fatal myocardial infarction was 10.2% and 11.8% for diabetic men and women, while that of fatal CHD was 12.3% and 16.1%, respectively (200). Other studies indicated that the incidence of CHD was approximately 1-2% per year among young asymptomatic people with T1D (184,201,202). In addition, the most common cause of death in

people with diabetes is CVD, particularly CHD (186,196). The national incidence data for the US came from a 9-year follow-up of the 1971-75 First National Health and Nutrition Examination Survey, in which the age-adjusted fatal CHD rates per 1,000 person-years for diabetic men and women aged 40-77 years at baseline were 28.4 and 10.5, respectively (196).

The incidence of congestive heart failure in diabetes varied greatly, which was influenced by the time of follow-up, the mean age of patients, the state of metabolic control and the complications of diabetes (203). Generally, studies showed that the congestive heart failure incidence rate per 1,000 person-years in people with diabetes ranged from 2.3 to 126 (191,193,204). More specifically, the Framingham Heart Study revealed that the congestive heart failure incidence rates per 1,000 person-years were 9 for diabetic men and 14 for diabetic women (204). In addition, the incidence of peripheral arterial disease in people with diabetes depends on the usual atherosclerosis risk factors and duration of diabetes (195). A Finnish study examined the 5-year incidence of claudication in a group of 133 middle-aged subjects with newly diagnosed T2D and found that the age-adjusted incidence of claudication was 20.3% for diabetic men and 21.8% for diabetic women (205). The Framingham Heart Study found that male sex and age were associated with an increased risk of claudication. The 4-year risks of intermittent claudication at ages 45-54 years were 0.9% for men and 0.4% for women, whereas at ages 65-74 years the risks were 2.5% for men and 1.5% for women. Among those with intermittent claudication, 20% were diabetic, while among those without claudication, only 6% had diabetes (194). The Cardiovascular Health Study including 5,888 men and women aged 65 years or older found that the overall percentage of subjects with incident peripheral arterial disease was 9.5% over 6-year follow-up. Among the incident cases of peripheral arterial disease, 18.8% had diabetes, compared with the non-cases, 10.5% of whom had diabetes (194).

Individuals with diabetes are at two- to fourfold increased risk of CVD events compared with age- and sex-matched individuals without diabetes (2,206). More specifically, diabetes is associated with a two- to fivefold increased risk of myocardial infarction, and with a two- to fourfold increased risk of stroke (2,10). Also, claudication is twice as common in people with diabetes as those without diabetes (195). Recently, a large collaborative meta-analysis confirmed that diabetes confers about a two-fold excess risk for a wide range of vascular diseases (including CHD, major stroke subtypes, and deaths attributed to other vascular causes), independently from other conventional risk factors (207). Interestingly, several studies showed that diabetes reduces the usual female cardioprotection; that is, the absolute rates of CVD in people with diabetes are higher in men than in women (as in the general population), but the relative risk (comparing those with and without diabetes) is higher in women than in men (relative risk: 2-4 for women and 1.5-2.5 for men) (17,184). This gender difference may be mediated in large part by more adverse cardiovascular risk profiles among women with diabetes, combined with possible disparities in treatment that favor men (208,209).

In addition, the incidence of CVD among diabetic people with prior CVD was higher than that among those without prior CVD. A study by Haffner et al. reported that, among diabetic people, the incidence rates of myocardial infarction (fatal or non-fatal) and stroke (fatal or non-fatal) per 100 person-years in those with prior myocardial infarction were 45.0 and 19.5, while those rates in those people without prior myocardial infarction were 20.2 and 10.3 (187). Another study by Giorda et al. showed that the age-standardized incidence rates of stroke (fatal or non-fatal) per 1,000 person-years in diabetic men and women with a history of CVD were 13.7 and 10.8, while those rates in those men and women with no history of CVD were 5.5 and 6.3 (210). In addition, diabetes is defined as a CHD risk equivalent; that is, the incidence of

myocardial infarction among diabetic people without previous CHD was similar to that among non-diabetic people with preexisting CHD (187). Although this equivalency has not been consistently documented (184), this observation is a useful impact on CVD prevention in diabetes by alerting more of the medical community to the importance of considering treatment targets based on the presence of diabetes and the entire CVD risk factor profile (211).

Morbidity

The high rates of morbidity and mortality associated with diabetes are, most notably, due to CVD. In diabetic individuals, CVD accounts for 75-80% of deaths and hospitalizations, approximately 75% of which are due to CHD, as well as for a heavy burden of disability and expense (212-214). Recent estimates in the US indicated that the age-adjusted hospital discharge rates for major CVD, CHD, heart failure, stroke, and peripheral arterial disease as first-listed diagnosis per 1,000 diabetic populations in 2003 were 56.4, 21.5, 18.5, 8.7, and 3.3, respectively (150). Among these, the age-adjusted hospital discharge rates for major CVD increased from 1980 through 1996, then decreased and leveled off through 2003 (150).

Mortality

Among diabetic patients aged 65 years or older in the US in 2004, 68% of deaths were from CHD and 16% were from stroke (2). For example, people with T2D have a shortened life expectancy, with up to 75% dying of macrovascular complications (11). In the United Kingdom Prospective Diabetes Study, fatal CVD events were 70 times more common than deaths from microvascular complications (10). Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes (2). More specifically, diabetes is associated with a

1.2- to 2.0-fold increase in mortality risk after acute myocardial infarction (212), while diabetic patients with heart failure have three times the mortality risk than non-diabetic patients with heart failure (184). In addition, a recent meta-analysis further revealed that diabetes is about a third more strongly related to fatal than to non-fatal myocardial infarction, perhaps suggestive of more severe forms of coronary lesions in people with diabetes than in those without, differential response of the myocardium to ischemia, or possibly in part, differential coding of deaths from CHD (207).

Risk Factors

The risk of developing new CVD is high in diabetes, in part because of its frequent association with other risk factors for CVD. The most important risk factors for CVD are family history, smoking, dyslipidemia, hypertension, diabetes, obesity, and socioeconomic factors (215). Other markers of CVD risk in people with diabetes include age, sex, diabetic retinopathy, autonomic neuropathy, erectile dysfunction, microalbuminuria, and proteinuria (216). Specifically, predictors of cardiovascular mortality in T1D include microalbuminuria, overt nephropathy, hypertension, smoking, and age, while those in T2D include overt proteinuria, presence of CHD, hypertension, and A1C levels (10).

Several interventions, some of which are relatively inexpensive, can dramatically reduce the risk of CVD, including stopping smoking, general blood pressure control, low-dose daily aspirin, ACE-inhibitor pills, and statin drugs (186). In addition, while T1D and T2D share most risk factors for CHD and stroke, there are notable differences. The traditional cardiovascular risk factors of hyperglycemia, dyslipidemia, elevated blood pressure, smoking, and metabolic syndrome are of importance, but they do not explain the excess risk of CHD in T1D patients

(184). CVD prediction models that are valid in non-diabetic people (Framingham score) or in T2D patients (the UK prospective diabetes study risk engine) poorly predict CVD events in T1D patients (217). This area is currently a subject of intensive investigation (218), and recently, Zgibor et al. first developed and externally validated a CHD risk prediction model specific to T1D (219).

2.5 HEALTH UTILIZATION PATTERNS AND ECONOMIC BURDEN OF DIABETES

Both the resource utilization and the spending, which are associated with the clinical consequences of diabetes (e.g., vascular complications) and the modification of its risk factors (e.g., obesity), are tremendous (147). For example, annual spending on direct costs related to CVD is $432 billion nationwide (220), and the annual cost of CVD may range from $8,200 to $13,100 per person depending on the presence of diabetes (221). Moreover, annual health care spending related to just one of the risk factors for diabetes (i.e., overweight or obesity) has been estimated at $92.6 billion (222).

Health Utilization Patterns of Diabetes

Health seeking and health utilization behaviors are influenced by several individual, provider and system level factors. In the case of diabetes, ill health and morbidity as well as preventative care motives result in incrementally more health service utilization (223). Specifically, a substantial amount of attributed health resource use is for chronic complications of diabetes. In particular, CVD, neurological symptoms, and renal complications are associated with high resource use attributed to diabetes (14). In the US, 24.3 million hospital inpatient days, 64.7 million physician

office visits, and 5.6 million emergency visits are attributed to diabetes annually. The diabetes population aged 65 years or more uses a larger portion of health resources, reflecting the burden of diabetes placed on the Medicare program (14).

Various studies demonstrate that people with diabetes use more hospital inpatient care, outpatient and physician office visits, emergency visits, nursing facility stays, home health visits, visits with other health professionals, and prescription drugs and medical supplies than their peers without diabetes (14,147,223,224). For instance, among men aged 60-64 years, those with diabetes have eight times the number of hospital inpatient days, seven times the number of emergency visits, and six times the number of physician office and outpatient visits for heart failure compared to their peers without diabetes (14). Having diabetes doubles one's risk of hospitalization compared to not having diabetes, and this risk is amplified by the development of diabetes-related complications (14,223). Although studies from most regions of the world report late-stage macrovascular or microvascular complications as the leading cause of diabetes-related hospitalizations, lower income settings such as Ethiopia confront a greater proportion (almost two-thirds) of admissions in the form of acute episodes of dysglycemia (223).

A population-based study was conducted to compare prescription utilization between patients with type 2 diabetes and those who did not have diabetes, which found that the mean number of prescriptions dispensed for all drugs, excluding antidiabetic agents, was higher across all age groups for patients with diabetes. After adjusting for age, patients with type 2 diabetes were 1.7 times more likely to be dispensed a drug than those who did not have diabetes. Cardiovascular drugs accounted for 28.8% of the total prescriptions for patients with type 2 diabetes. The likelihood of being dispensed a prescription was increased across all drug classes, including those not normally considered to be associated with diabetes (225). In addition,

patients with diabetes complications are considered high users; they use a greater number of high-cost services than patients without complications. For example, the Centers for Disease Control and Prevention Diabetes in Managed Care Work Group shows that diabetic individuals with multiple complications or comorbidities use significantly more specialty care services (5.8-6.3 times), make significantly more emergency visits (3.3-5.5 times), and have significantly more hospitalizations (3.3-11.9 times) than do those without complications (226).

Economic Burden of Diabetes

Diabetes imposes a serious economic burden on national health care system worldwide. Quantitative calculations suggest that direct and indirect costs of diabetes worldwide cumulatively total US$376 billion in 2010 (9). Almost half of all global expenditure occurred in the US, which is home to only 8% of those affected by diabetes nationwide (9,223). Several recent studies estimated and projected the cost of diabetes in the US. A study in 2008 sponsored by the ADA reported that the total estimated annual cost of diabetes in 2007 is US$174 billion, accounting for 11% of national health expenditures and including US$116 billion in direct health care costs attributed to diabetes and US$58 billion in reduced national productivity (14). A study in 2010 (227) used this base cost and estimated additional costs contributed by undiagnosed diabetes (228), pre-diabetes (229), and gestational diabetes (230), for a total of $218 billion in 2007. This estimate includes $153 billion in higher medical costs and $65 billion in reduced productivity. The average annual cost per case is $2,864 for undiagnosed diabetes, $9,975 for diagnosed diabetes ($9,677 for type 2 diabetes and $14,856 for type 1 diabetes), and $443 for pre-diabetes (medical costs only). For each American, regardless of diabetes status, this burden represents a cost of approximately $700 annually (227). In 2012, the total estimated cost of

diagnosed diabetes in the US reached $245 billion (231), and the health care expenditures for diabetes in the US are expected to be between $264 and $474 billion in years of 2030-2034 (9,16,232).

In the US, one out of every five health care dollars is spent caring for someone with diagnosed diabetes, while one in ten health care dollars is attributed to diabetes (14). The largest components of direct medical expenditures attributed to diabetes are hospital inpatient care (50% of total cost), diabetes medication and supplies (12%), retail prescriptions to treat complications of diabetes (11%), and physician office visits (9%). General medical condition (40%) and cardiovascular complications (36%) constitute the top 2 largest contributors to the attributed medical cost of diabetes for hospital inpatient care. Together, the general medical conditions and cardiovascular complications are responsible for 91% of US expenditures for inpatient care and 76% of hospital inpatient costs attributed to diabetes (14). Indirect costs include increased absenteeism ($2.6 billion) and reduced productivity while at work ($20.0 billion) for the employed population, reduced productivity for those not in the labor force ($0.8 billion), unemployment from disease-related disability ($7.9 billion), and lost productive capacity due to early mortality ($26.9 billion) (14).

Increased health seeking and utilization in people with diabetes and associated complications result in greater medical costs incurred, compared to the general population without diabetes. In the US, people with diabetes, on average, have medical expenditures that are 2.3 times higher ($11,744 vs. $5,095) than those for this same population without diabetes, suggesting that diabetes is responsible for $6,649 in excess expenditures per year per person with diabetes (14). From an employer perspective, it is determined that workers with diabetes generate an average of $4,410 more in medical and productivity costs annually than do those

without diabetes (233). In addition, lifetime costs associated with diabetes and its complications have been estimated as well. Tao et al. (234) reported that, for a newly diagnosed T1D patient aged between 3 and 45 years, his/her expected rest-of-lifetime medical costs attributable to diabetes was $115,230. Caro et al. (235) estimated that the 30-year cumulative cost of managing complications in a patient with T2D was $47,240. Roughly, one half of these costs were associated with macrovascular complications. Moreover, it was noted that macrovascular disease is a greater determinant of cost in the early years than are microvascular complications; it accounts for 85% of cumulative costs over the first 5 years and 77% over the first 10 years. These findings may suggest that modification of cardiometabolic risk in patients with diabetes can reduce the cost of complications of the disease more than modification of microvascular complications.

The tremendous economic burden of diabetes makes the disease an important clinical and public health problem. Also, this highlights the needs and benefits of prevention and control, as well as informs cost-effective models of diabetes prevention and intervention. Notably, early and aggressive management may delay or even prevent diabetes and many of its complications (e.g., CHD, hypertension, and depression), leading to improved quality of life and reduced health care expenditures in the general population (224,236,237).

3.0 QUALITY IMPROVEMENT STRATEGIES FOR DIABETES PREVENTION AND CONTROL

With increasing prevalence and incidence, there is a pandemic of diabetes that represents a huge public health problem. Of particular concern is the increasing prevalence of diabetes with reports indicating diagnosed diabetes among people aged 20 years or more increased from 6.5% in 1999-2002 to 7.8% in 2003-2006 in the US (238). Moreover, diabetes is accompanied by a multitude of severe, long-term complications, which contributes to excess morbidity and mortality, more health utilization, and higher health care expenditures. Without a suitable population-based health response, the epidemic of obesity coupled with an aging population will relentlessly increase these burdens of diabetes. Breakthroughs in management of diabetes and systematic delivery of effective clinical intervention strategies once diabetes is manifest may ameliorate the enormous human and financial costs of the disease, but that is not the solution. Primary prevention of diabetes and its complications should be the critical public health priority of the current era (32).

Although evidence-based clinical practice recommendations that are known to improve clinical outcome and process measures in diabetes care are trumpeted by ADA, disappointingly most patients with diabetes do not receive care in this manner (239). There is a challenge of managing diabetes effectively once it has developed. Less than 10% of people with diabetes reach the ADA goal of the three combined clinical outcome measures (i.e., A1C <7%, blood pressure <130/80 mmHg, and low-density lipoprotein cholesterol (LDLc) <100 mg/dl) that are important risk factors for diabetes complications (240-243), and process measure performance remains far below the ADA recommendations (239). Recent data indicated that the control for

glycemic (A1C <7%), blood pressure (SBP/DBP <130/80 mmHg), and cholesterol (LDLc <100 mg/dl) [ABC] therapeutic goals in people living with diabetes have improved over time from 1988 to 2010 (244). In 2007-2010, 52.5% of people with diabetes achieved A1C <7.0%, 51.1% achieved BP <130/80 mmHg, 56.2% achieved LDL <100 mg/dL, and 18.8% achieved all three ADA-recommended clinical outcomes; however, this indicates that only about 1 in 5 patients with diabetes reached the recommended therapeutic goals for glycemia, blood pressure, and LDLc at the same time in 2007-2010 (244). Despite significant improvement during the past decade, achieving the ABC goals remains suboptimal among adults with diabetes. In addition, improvements in controlling A1C, blood pressure, cholesterol levels may be projected to increase life expectancy for people with newly diagnosed diabetes in 2005 by 1.0 year (13), but significant opportunity remains for further improvement. Diabetes remains a major health challenge in the US, and thus no effort should be spared to improve quality of diabetes care.

3.1 THE INTERVENTIONS FOR DIABETES PREVENTION

Randomized controlled trials show that individuals at high risk for developing T2D (those with IFG, IGT, or both) can significantly decrease the rate of onset of diabetes with particular interventions (245). These include intensive lifestyle modification programs (29-67% relative risk reduction after 2.5-6 years) and use of the pharmacological agents: metformin, α-glucosidase inhibitors, orlistat, and thiazolidinediones, each of which decreased incident diabetes to various degrees (25-81% relative risk reduction after 2.5-4 years) (3). A meta-analysis to quantify the effectiveness of lifestyle and pharmacological interventions to prevent or delay T2D in people with IGT also provided supporting evidence; pooled hazard ratios were 0.51 (95% CI: 0.44 to

0.60) for lifestyle interventions vs. standard advice; 0.70 (0.62 to 0.79) for oral diabetes drugs vs. control; 0.44 (0.28 to 0.69) for orlistat vs. control; and 0.32 (0.03 to 3.07) for the herbal remedy jiangtang bushen recipe vs. standard diabetes advice (246). Follow-up of all three large studies of lifestyle intervention showed sustained reduction in the rate of conversion to T2D, with 43% reduction at 20 years in the Da Qing study (247), 43% reduction at 7 years in the Finnish Diabetes Prevention Study (248), and 34% reduction at 10 years in the US Diabetes Prevention Program Outcomes Study (DPPOS) (249). In addition, group delivery of the DPP intervention in community settings has the potential to be significantly less expensive while still achieving similar weight loss (250).

Based on the results of clinical trials and the known risks of progression of prediabetes to diabetes, American Diabetes Association recommends that people with an A1C of 5.7-6.4%, IGT, or IFG should be counseled on lifestyle changes with goals similar to those of the DPP (7% weight loss and moderate physical activity of at least 150 min/week). Regarding pharmacotherapy for diabetes prevention, metformin has a strong evidence base and demonstrated long-term safety. Metformin therapy for prevention of T2D may be considered in those with IGT, IFG, or an A1C of 5.7-6.4%, especially for those with BMI >35 kg/m^2, aged <60 years, and women with prior gestational diabetes mellitus (245).

3.2 THE INTERVENTIONS FOR DIABETES CONTROL

Once diabetes is diagnosed, several current treatments have proven efficacy in substantially reducing morbidity and mortality. In fact, the progress in treatment strategies during the past two decades has led to more options and better technology, so they now provide greater efficacy

and fewer or less severe side effects. The following recommended intervention strategies (245;251) are aimed for secondary and tertiary prevention of diabetes, which are management of diabetes and risk factors for complications, screening for and early treatment of complications, and treatment of complications and comorbidities.

1) Improving glycemic control can decrease the risk of microvascular complications by 40%; specifically, there would be a 25% risk reduction in microvascular complications per 1% reduction in A1C. 2) Better controlling blood pressure can reduce diabetes-related micro- (33%) and macrovascular (33-50%) complications and total mortality. 3) Lipid management with statins can reduce the risk of coronary events by 25-55% and total mortality by 43%. 4) Aspirin therapy for diabetic persons at high risk for CVD can reduce the risk of myocardial infarction (28%) and total CVD risk (18%). 5) Angiotensin converter enzyme (ACE) inhibitor therapy can reduce the risk of nephropathy (42%) among those with microalbuminuria and reduce the risk of CVD or death (22%) among all subjects at high risk, including those with diabetes. 6) Detecting and treating diabetic eye disease with laser therapy can reduce the risk for loss of eyesight by about 60-70%. 7) Appropriate foot care can reduce the risk of serious foot disease by 50-60%; specifically, comprehensive foot care programs can reduce amputation rates by 45-85%. 8) Influenza/pneumococcal vaccination for senior citizens with diabetes can reduce hospitalizations (32%) as well as respiratory conditions and death (64%).

In addition, 9) diabetes self-management education (DSME) is associated with improved diabetes knowledge and improved self-care behavior, improved clinical outcomes (e.g., lower A1C, lower self-reported weight, improved quality of life and healthy coping), and lower costs. Better outcomes were reported for DSME interventions that were longer and included follow-up support (DSMS), which were culturally and age appropriate and were tailored to individual

needs and preferences, and which addressed psychosocial issues and incorporated behavioral strategies. Both individual and group approaches are effective, and there is growing evidence for the role of community health workers and peer and lay leaders in delivering DSME and DSMS in conjunction with the core team. Also, DSME is associated with increased use of primary and preventive services, lower use of acute, inpatient hospital services, and lower Medicare and commercial claim costs. 10) Maintaining regular moderate-intensity aerobic physical activity has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. 11) Studies of individuals with diabetes consistently demonstrate that smokers have a heightened risk of CVD, premature death, and increased rate of microvascular complications. Smokers with newly diagnosed T2D found that smoking cessation was associated with amelioration of metabolic parameters and reduced blood pressure and albuminuria in 1 year. 12) Screening for early renal disease (microalbuminuria) followed by appropriate treatment (ACE inhibitor or Angiotensin II receptor blockers) can slow the nephropathy progression and prevent or delay end-stage renal disease. 13) The early recognition and appropriate management of neuropathy in the patient with diabetes is important because a) nondiabetic neuropathies may be present in patients with diabetes and may be treatable; b) a number of treatment options exist for symptomatic diabetic neuropathy; c) up to 50% of DPN may be asymptomatic and patients are at risk for insensate injury to their feet; and d) autonomic neuropathy, and particularly CAN, is associated with substantial morbidity and even mortality.

3.3 QUALITY IMPROVEMENT STRATEGIES FOR DIABETES CARE

Despite evidence showing improved clinical outcomes for patients with diabetes who receive various preventive and therapeutic interventions, many patients with diabetes do not receive them (245). Unfortunately, recent data showed that only 1 in 5 patients with diagnosed diabetes reached all three ADA-recommended therapeutic targets for blood glucose, blood pressure, and LDL cholesterol (244), which are the key intermediate outcomes for diabetes complications. Although numerous strategies to improve adherence to the recommended standards have been implemented, a major barrier to optimal care is a delivery system that too often is fragmented, lacks clinical information capabilities, often duplicates services, and is poorly designed for the coordinated delivery of chronic care (245). Indeed, given the current challenges of treating a complex disease like diabetes, novel methods of delivering diabetes care need to be implemented and tested for effectiveness, since most studies, to date, are efficacy studies with limited generalizability to the vast majority of complex patients.

Two high-quality systematic reviews provide consistent supporting evidence that team changes are the one in the top two quality improvement strategies on diabetes management, which produce largest improvement in intermediate outcomes (i.e., A1C, systolic blood pressure, and LDL cholesterol) (252,253). ADA suggests that collaborative, multidisciplinary teams are best suited to provide such care for people with chronic conditions such as diabetes and to facilitate patients' performance of appropriate self-management (245). Specifically, ADA recommends that diabetes care should be aligned with components of the Chronic Care Model (CCM) to ensure productive interactions between a prepared proactive practice team and an informed activated patient (245). Numerous studies demonstrate that the CCM is an effective

framework for improving the quality of diabetes care (254); moreover, a recent systematic review provides evidence that CCM is effective in improving the health of people who have diabetes and receive care in the US primary care settings (255). The CCM includes six core elements for the provision of optimal care of patients with chronic disease: 1) delivery system design (moving from a reactive to a proactive care delivery system where planned visits are coordinated through a team based approach); 2) self-management support; 3) decision support (basing care on evidence-based, effective care guidelines); 4) clinical information systems (using registries that can provide patient-specific and population-based support to the care team); 5) community resources and policies (identifying or developing resources to support healthy lifestyles); and 6) health systems (to create a quality-oriented culture). Incorporating multiple components of the CCM together in the same intervention can help facilitate better CCM implementation (e.g., using the decision-support component to train providers on guidelines such as the ADA Standards of Care and using the delivery system design component to remodel the care delivery process to provide self-management support through DSME in primary care provider offices) (255). Indeed, redefinition of the roles of the clinic staff and promoting self-management on the part of the patient are fundamental to the successful implementation of the CCM (254).

4.0 COST-EFFECTIVENESS OF IMPLEMENTING THE INTERVENTIONS FOR DIABETES PREVENTION AND CONTROL

4.1 COST-EFFECTIVENESS IN HEALTH AND MEDICINE

The cost of health care in the US has gained national attention. The first legislation to apply formal economic evaluation (i.e., cost-benefit/cost-effectiveness analysis) in the US came in 1902 with the River and Harbor Act, which required the US Army Corps of Engineers to assess the costs and benefits of river and harbor projects (256). In the 1970s and early 1980s, the economic evaluation of health care services became an academic interest. However, inconsistency in the approaches used to perform such evaluations led to confusing and often conflicting results. Because of a lack of uniformity in approach, these early economic analyses were of limited use in aiding decisions about which treatments to fund and for whom (257). Moreover, the major forces driving US health care costs include: (1) aging of the US population; (2) the burden of chronic diseases; (3) the availability of new technologies to improve the diagnosis or treatment of diseases; (4) labor shortages with the result of wage inflation; and (5) consumer's demand for flexible choice in health care plans. These factors result in increased health care spending on the part of health care purchasers (primarily employers and the US government) as well as patient consumers, leading to renewed interest in economic evaluation as a tool to curb expenditures (257).

In 1993, the US Public Health Service (USPHS) recognized the need for consensus on methods for economic evaluation, specifically cost-effectiveness analysis (CEA) which is used to weigh the costs of treatment alternatives with their clinical effectiveness. The USPHS convened

a group of 13 nongovernment scientists and scholars with expertise in economic evaluation, collectively referred to as the Panel on Cost-Effectiveness in Health and Medicine. The panel was charged with assessing the current state-of-the-science in the CEA field and with providing recommendations for conduct of economic studies in order to improve their quality and encourage their comparability. The resulting recommendations were compiled in what many refer to as the Gold Book or officially, Cost-Effectiveness in Health and Medicine (257,258).

Economics is a discipline that studies how people choose to use limited resources to satisfy their unlimited wants so that the gain (or value) from the available resources can be maximized. Indeed, facing limited resources and increases in demand from competing programs, health care providers and policy makers seek guidance from economic studies on how to use health care resources wisely (18). The central purpose of CEA is to compare the relative value of different interventions in creating better health and/or longer life, and it would be considered as one of the guides to resource allocation in health and medicine (258). When the intervention being considered is either more effective but has a higher cost or is less effective but has a lower cost than its comparator, an economic analysis is warranted in order to quantify the difference in the costs and health outcomes between the two alternatives. Because new interventions typically cost more than existing options, the former scenario is frequently the case (257). The results of such evaluations are typically summarized in an incremental cost-effectiveness ratio (ICER), where the denominator reflects the gain in health/effectiveness from a candidate intervention and the numerator reflects the additional cost of obtaining that health/effectiveness gain. A CEA provides information that can help decision makers sort through alternatives and decide which ones best serve their programmatic and financial needs. Decision makers may be federal, state, or local, and they may be in the public sector or in the

private sector. They may control dollars or they may run programs. CEA provides a framework within which decision makers may pose a range of questions (258).

The three primary techniques as a form of full economic evaluation that are used in health are cost-benefit analysis (CBA), CEA, and cost-utility analysis (CUA). In CBA, costs and benefits are converted to monetary units. In contrast, in CEA and CUA, costs are expressed in monetary units but health benefits are expressed in a natural unit (such as cases of disease) or quality-adjusted life-years (QALYs). QALYs are a measure of health outcome in which each period of time is assigned a weight ranging from 0 to 1 that corresponds to health-related quality of life during that period. A weight of 1 corresponds to perfect health, and a weight of 0 corresponds to death, and then the weights are aggregated across time periods (18,259).

CEA promises to inform decisions and enhance population health in an explicit, quantitative, efficient and systematic manner. Yet, various factors have conspired to create resistance to its explicit use for priority-setting in the US: a lack of understanding about the conceptual approach, a mistrust of methods, a mistrust of motives, legal and regulatory constraints, political factors, and ethical objections. The best explanation is that, at its roots, resistance to CEA in the US is grounded, not in methodological or legal barriers, but in Americans' penchant for medical innovation and our distaste for limits – and in our deep-rooted suspicion of governments or corporations that impose them (256).

Apparently, the importance of CEA in decision making should not be overstated. Although estimates derived from CEA can be an important source of advice to inform the judgment of officials making public policy and clinical decisions, it cannot provide definitive answers concerning whether a particular intervention should be adopted. CEA estimate is only one aspect to consider in the multifactorial process of judging whether a particular intervention

should be adopted. CEA does not address treatment preferences and the values (i.e., willingness-to-pay) of patients, society, and other stakeholders; societal and legal aspects; or ethical issues. Judgment about these preferences – acceptability, feasibility and strategic planning – also should contribute substantially to the decision-making process concerning whether an intervention should be adopted (260,261).

4.2 COST-EFFECTIVENESS OF THE INTERVENTIONS FOR DIABETES PREVENTION AND CONTROL

Few researchers have conducted systematic reviews of the cost-effectiveness (CE) of diabetes interventions (18,262-264), and the most recent report published by the investigators in Centers for Disease Control and Prevention in 2010 was to synthesize the CE of interventions recommended by the 2008 American Diabetes Association (ADA) Standards of Medical Care in Diabetes to prevent and control diabetes, its complications, and comorbidities (260). They categorized the strength of evidence about the CE of an intervention as strong, supportive, or uncertain. CE was classified as cost saving (more health benefit at a lower cost), very cost-effective (≤$25,000 per life year gained [LYG] or quality-adjusted life year [QALY]), cost-effective (from $25,001 to $50,000 per LYG or QALY), marginally cost-effective (from $50,001 to $100,000 per LYG or QALY), or not cost-effective (>$100,000 per LYG or QALY). A total of 56 studies from 20 countries were included in the final data synthesis.

Among 26 interventions were classified as supported by “strong” evidence concerning their CE, six interventions were cost saving, eight were very cost-effective, six were cost-effective, two were marginally cost-effective, and four were not cost-effective (260). These

interventions consisted of primary prevention, screening for undiagnosed type 2 diabetes, diabetic risk factor control, early prevention of diabetes complications, and treatment of diabetes complications. First, the six cost-saving interventions with strong evidence were: 1) ACEI therapy for intensive hypertension control, as in the UK Prospective Diabetes Study (UKPDS), in persons with type 2 diabetes (T2D) compared with standard hypertension control; 2) ACEI or ARB therapy to prevent ESRD for T2D compared with no ACEI or ARB therapy; 3) early irbesartan therapy at the stage of microalbuminuria to prevent ESRD in people with T2D compared with treatment at the stage of macroalbuminuria; 4) comprehensive foot care to prevent ulcers in a mixed population with either T1D or T2D compared with usual care; 5) multi-component interventions for diabetic risk factor control and early detection of complications compared with conventional insulin therapy for persons with T1D; and 6) multi-component interventions for diabetic risk factor control and early detection of complications compared with standard glycemic control for persons with T2D. Second, the eight very cost-effective interventions with strong evidence included: 1) primary prevention through intensive lifestyle modification for T2D; 2) universal opportunistic screening for undiagnosed T2D in African Americans between 45 and 54 years old; 3) intensive glycemic control as implemented in UKPDS for T2D; 4) statin therapy for secondary prevention of cardiovascular disease in T2D; 5) counseling and treatment for smoking cessation in T2D; 6) annual screening for diabetic retinopathy and early treatment of it in T2D; 7) annual screening for diabetic retinopathy and treating the positive cases in T1D; and 8) immediate vitrectomy to treat diabetic retinopathy compared with deferral of vitrectomy in a mixed population with either T1D or T2D. Third, the six cost-effective interventions with strong evidence were: 1) one-time opportunistic targeted screening for undiagnosed T2D in hypertensive persons aged 45 years and older compared with

no screening; 2) intensive insulin treatment for persons with T1D compared with conventional glycemic control; 3) UKPDS-like intensive glycemic control applied to the US health care system among adults younger than age 54 years with T2D compared with conventional glycemic control; 4) intensive glycemic control by a Diabetes Prevention Program type of intensive lifestyle intervention in persons with newly diagnosed T2D compared with conventional glycemic control; 5) statin therapy for primary prevention of cardiovascular disease in persons with T2D compared with no statin therapy; and 6) multi-component interventions including insulin therapy, ACEI therapy, and screening for retinopathy in persons with T1D compared with intensive insulin therapy. Fourth, the two marginally cost-effective interventions with strong evidence were: 1) intensive glycemic control for all US residents with T2D diagnosed at age 25 years and older compared with usual care; and 2) screening for diabetic retinopathy every two years compared with screening every three years in persons with T2D. Fifth, the four interventions with strong evidence of not being cost-effective were: 1) one-time universal opportunistic screening for undiagnosed T2D and ensuring treatment among those aged 45 years and older compared with no screening; 2) one-time universal opportunistic screening for T2D compared with targeted screening; 3) intensive glycemic control in the US setting for patients diagnosed with T2D at older ages (55-94 years of age) compared with usual care; and 4) annual screening for retinopathy compared with screening every two years in T2D.

Among 18 interventions were classified as having “supportive” evidence concerning their CE, 10 interventions were cost saving, seven were very cost-effective, one was cost-effective, and none were marginally cost-effective or not cost-effective (250). First, the 10 cost-saving interventions with supportive evidence were: 1) screening using the sequential method (50-g glucose challenge test followed by 100-g glucose tolerance test [GTT]) for gestational diabetes

[GDM] in 30-year-old pregnant women between 24-28 weeks' gestation compared with no screening; 2) screening for GDM using the 100-g GTT method compared with no screening; 3) the sequential method compared with the 75-g GTT screening for GDM; 4) 100-g GTT compared with the 75-g GTT screening for GDM; 5) diabetes self-management education for persons with T1D compared with no education; 6) full reimbursement policy for ACEI for patients with T1D compared with patients paying out-of-pocket; 7) full-reimbursement policy for ACEI for patients with T2D compared with patients paying out-of-pocket; 8) screening using a mobile camera at a remote area and processing data in a reading center compared with a retina-specialist's visit in a mixed population of T1D and T2D; 9) screening for diabetic nephropathy and ensuing ACEI or ARB therapy in persons with T1D compared with no screening; and 10) intensified foot ulcer treatment in a mixed population with T1D and T2D compared with standard treatment. Second, the seven very cost-effective interventions with supportive evidence included: 1) primary prevention of T2D in women with GDM history, currently IGT, through intensive lifestyle intervention compared with usual care; 2) universal opportunistic screening for T2D in African Americans aged 25-44 years compared with no screening; 3) 100-g GTT compared with the sequential screening method for detecting GDM in 30-year-old pregnant women between 24-28 weeks' gestation; 4) diabetes self-management education for persons with T2D compared with no education; 5) disease management programs using specialist nurse-led clinics to treat and control hypertension or hyperlipidemia in patients with T2D in a city in England or a culturally sensitive case-management training program to control diabetes and its risk factors in a Latino population with both T1D and T2D in a US county compared with usual care only; 6) self-monitoring of blood glucose (SMBG) three times per day compared with no SMBG in T2D non-insulin users; and 7) SMBG once per day compared with no SMBG in T2D

non-insulin users. Third, the one cost-effective intervention with supportive evidence was the use of metformin to prevent T2D in obese persons with impaired glucose tolerance compared with standard lifestyle intervention.

Investigators also concluded that the CE of optimal age to start screening for T2D was uncertain (260). Two studies evaluated the CE of screening for undiagnosed T2D; one study reported that incremental CE ratios increased with initial screening age (265) while the other reported that they decreased with screening age (266). However, according to a high-quality CE report using the Archimedes model to compare eight simulated screening strategies for T2D with a no-screening control strategy, screening for T2D in the US population is very cost-effective when started between the ages of 30 years and 45 years, with screening repeated every 3-5 years (115).

Many ADA-recommended interventions intended to prevent/control diabetes are cost saving or very cost-effective and supported by strong evidence. Health care providers and policymakers should use this information in making clinical and policy decisions in order to use resources efficiently. Economic assessment studies should be based on standard research methods and reliable data to ensure validity and comparability of results. Also, economic evaluations of new technologies or programs should continue to ensure that they add value.

5.0 SUMMARY

The prevalence and incidence rates of diabetes and pre-diabetes are increasing rapidly throughout most regions of the developed and developing world. This emerging pandemic is driven by the combined effects of aging of the population, growing levels of obesity and inactivity, and greater longevity among diabetic patients, which is attributable to improved management (267). In the US, CDC estimated that approximately 25.8 million people had diagnosed and undiagnosed diabetes in 2010, indicating that the prevalence of diabetes among the whole US population has increased by 6% in 3 years from 7.8% in 2007 (2) to 8.3% in 2010 (268). More specifically, about 25.6 million or 11.3% of all adult Americans aged 20 years or older had diabetes, and another 79 million people in this age group had pre-diabetes (268). If recent increases in diabetes incidence continue and diabetes mortality is relatively low, as many as 1 in 3 (or 33%) US adults aged 18-79 years could have diabetes by 2050 (269).

The pandemic of diabetes continues at tremendous human and financial cost, leading to one of the globally major public health challenge. Much of the expense that attends diabetes and its care is attributable to the development of long-term complications, such as retinopathy, nephropathy, and neuropathy, which cause more disabled cases of blindness, renal failure, and amputations than any other disease (270). In addition, diabetes is associated with a 2- to 5-fold increase in cardiovascular disease, which contributes to premature mortality (270). Increased health seeking and utilization in people with diabetes and associated complications result in greater medical costs incurred, compared to the general population without diabetes. In 2007, the US national economic burden of pre-diabetes and diabetes was estimated to be $218 billion, including $153 billion in higher medical costs and $65 billion in reduced productivity from

higher levels of absenteeism, presenteeism, disability, and early mortality (227). In 2012, the total estimated cost of diagnosed diabetes reached $245 billion (including $176 billion in direct medical costs and $69 billion in reduced productivity), a 41% increase from the previous estimate of $174 billion in 2007 (231). Fortunately, disability and premature death are not inevitable consequences of diabetes. Working together, people with diabetes, their support network, and their health care providers can reduce the occurrence of disability and premature death by controlling blood glucose, pressure and lipids, and by receiving several preventive care practices in a timely manner (12).

Considering the evolving disease burden of diabetes, efforts exploring new intervention strategies to delay or prevent the complications of diabetes, or, even better, to delay or prevent the development of diabetes itself are urgently needed. Moreover, the heavy economic burden of diabetes is one of the most pressing health policy issues and underscores the urgency to better understand the cost-mitigation potential of prevention and control strategies for diabetes. Demands for new competing strategies for delaying or preventing diabetes case and for comprehensive diabetes management are increasing, but resources that can be devoted to diabetes prevention and control are limited. Hence, health care policy makers and providers need to seek guidance on how to prioritize health care resources wisely and efficiently.

Health care costs for diabetes in the US are increasing unsustainably (227,231,267), and efforts to control high expenditures should focus on the value, in addition to the costs, of health care intervention strategies. Whether an intervention strategy provides high value depends on assessing whether its health benefits justify its costs (271). Economic evaluation or efficiency evaluation, which estimates the incremental cost-effectiveness ratio as the additional cost required to obtain additional health benefits, provides a key measure of the value of a health care

intervention strategy (271). More specifically, economic evaluation can help inform the decision makers how to allocate resources across a defined number of competing intervention strategies to maximize health outcomes from the limited available resources. Three primary techniques of evaluating an intervention strategy in health and medicine are considered a form of full economic evaluation, including cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis, but only the latter two are commonly used in the field of health care as the monetary valuation of health benefits is not acceptable on ethical and on practical grounds (259). The use of economic evaluation to inform decision making in health and medicine has increased rapidly in the last two to three decades, and the literature on the cost-effectiveness of intervention strategies to prevent and control diabetes has been comprehensively reviewed recently (260).

Prevention and control of diabetes involve complex interactions among patients, physicians, health care system, and society as a whole, with translational barriers that may occur at every level. Although many efficacious and economically acceptable prevention and control strategies are currently available to reduce the burden of diabetes and its complications (260), translation of these evidence-based approaches from clinical trials into clinical and public health practice is not easy and remains limited. A major contributor to suboptimal diabetes management is a delivery system that too often is fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the delivery of the prevention and control strategies.

With respect to diabetes prevention, the Diabetes Prevention Program (DPP) study funded by the US National Institutes of Health is one of the pivotal diabetes prevention trials to suggest that the lifestyle modification intervention is effective in providing much greater weight loss and a greater increase in physical activity (108,259), reducing risk factors of cardiovascular

disease (108,249,272) and components of the metabolic syndrome (273), and delaying or preventing the development of diabetes (108,249) in overweight individuals with pre-diabetes. Several delivery approaches of the DPP-based lifestyle intervention are successfully translated into a variety of practice settings to achieve reduction of risk factors for diabetes and cardiovascular disease.

With respect to diabetes control, collaborative multidisciplinary teams are best suited to provide care for people with chronic conditions like diabetes and to facilitate patients' performance of appropriate self-management (274). The Chronic Care Model (CCM) may be well suited to the management of diabetes since it addresses complex issues in diabetes care by including six essential core elements to redefine the roles of the providers and promote self-management on the part of the patient, which are for the provision of optimal care of people with chronic conditions (254,255). The CCM is a multifaceted framework to redesign daily medical practices and enhance health care delivery, and it is used in many practice settings to guide systematic and individual improvements for chronic illness care, including diabetes.

However, knowledge on the economic evaluation in these new strategies delivering diabetes prevention and control interventions is rare. This dissertation conducts cost-effectiveness analysis through a decision-analytic approach using computational modeling, which adds evidence to provide a better understanding of these strategies' costs and benefits to practices, payers, and patients. This evidence would not only inform health care policymakers and providers how to integrate traditional clinical skills with the use of new intervention strategies, but aid them in prioritizing these intervention skills/strategies to prevent or control diabetes and its complications.

6.0 METHODS

6.1 SPECIFIC AIMS

In conditions of limited resources and increasing demand for new competing programs or technologies for diabetes management, health care policymakers and providers seek guidance on how to use health care resources wisely. Hence, the approaches exploring how the intervention for diabetes prevention and control is delivered, not only effectively, but efficiently, are needed to improve both clinical outcomes and process measures at the patient, provider, community, and health systems levels. Cost-effectiveness analysis through a decision-analytic approach using computational modeling can be used to help inform health care policymakers and providers of the decisions about prioritizing intervention programs to be funded from limited available resources.

This dissertation proposes to evaluate long-term cost-effectiveness of implementing interventions to prevent and control diabetes in the community and military settings. The specific aims of this dissertation are:

1. To assess cost-effectiveness of implementing the Chronic Care Model (CCM) intervention for diabetes control relative to a provider continuing medical education (PROV) intervention and to usual care in an underserved urban area of Pittsburgh, PA. We hypothesize that the application of the CCM intervention for diabetes care in underserved communities is cost-effective relative to a PROV intervention and to usual care.

2. To estimate cost-effectiveness of implementing the CCM intervention for diabetes control relative to usual care in a military-based medical center in San Antonio, TX. We hypothesize that the performance of the CCM intervention for diabetes care in a military-based setting is cost-effective relative to usual care.
3. To analyze cost-effectiveness of implementing an Internet-based lifestyle intervention to reduce risk of type 2 diabetes (T2D) and cardiovascular disease (CVD) relative to usual care (or do nothing) in the primary care setting in Pittsburgh, PA. We hypothesize that an Internet-based lifestyle intervention delivered in coordination with primary care medicine to reduce risk of T2D and CVD is cost-effective relative to usual care (or do nothing).

6.2 STUDY DESIGN

6.2.1 Overview

This dissertation is to apply computational modeling, the Markov decision model, for evaluating long-term cost-effectiveness of implementing interventions to control and prevent diabetes in the community and military settings. Model input parameters, including intervention cost and outcomes, disease progression rates, other direct medical/non-medical costs, mortality rate, and utilities, were directly obtained from the clinical trials that have been completed by our research teams, or were drawn from published literature. The overall summary measure from the cost-effectiveness evaluation is the incremental cost-effectiveness ratio (ICER), representing the incremental cost required to achieve one additional unit of health benefits if an intervention is

used instead of another. The ICER can be expressed as US$ per quality-adjusted life-expectancy gained or US$ per clinical outcome/event averted.

6.2.2 Data Sources and Model Parameters

Specific Aim 1

Data for Specific Aim 1 were primarily based on a randomized controlled trial completed by Piatt et al. (275). Piatt et al. conducted the first multifaceted, cluster-design, randomized controlled trial to determine the effectiveness of implementing the comprehensive CCM in a community-based setting. This trial took place in an underserved suburb of Pittsburgh, PA, between 1999 and 2003, and included a one-year follow-up. Participating patients had a confirmed diagnosis of diabetes, based on ICD-9 codes, problem lists, laboratory results, or diabetes medication use. Eleven primary care practices and their patients were randomly assigned to one of three study groups: CCM intervention, PROV intervention, or usual care. The CCM group (three practices; 30 patients) involved implementation of all six CCM elements. The PROV group (three practices; 38 patients) consisted of providers attending one continuing medical education session, an in-person review of chart audit results by a certified diabetes educator, and the availability of a certified diabetes educator for consultation. Providers in the usual care group (five practices; 51 patients) were mailed their practices' chart audit results.

The primary outcomes of this clinical trial included reductions in glycated hemoglobin (A1C), blood pressure, and lipid levels. Secondary outcomes were improvements in quality of well-being, diabetes knowledge, empowerment, and the frequency of self-monitoring of blood glucose. Following the one-year intervention, a significant decline in A1C (-0.6%, P = 0.008)

was observed in the CCM group. The CCM group also reported improvements in high-density lipoprotein cholesterol (HDLc) levels (+5.5 mg/dl, $P < 0.001$), diabetes knowledge test scores (+6.7%, $P = 0.07$), empowerment scores (+0.2, $P = 0.02$), and the proportion of patients who self-monitored blood glucose (+22.2%, $P < 0.001$). Taken together, CCM implementation in the community was effective in improving clinical and behavioral outcomes. Because implementing the full CCM is resource intensive, we sought to determine its cost-effectiveness. Model input parameters were directly obtained from this clinical trial or were drawn from published literature.

Specific Aim 2

Data for Specific Aim 2 were primarily based on a study completed at US Air Force Wilford Hall Medical Center (WHMC) in San Antonio, TX (276). The Diabetes Outreach Clinic (DOC), in which the CCM intervention was applied, opened on January 3rd, 2006 and ended in December 2008 at US Air Force WHMC. At that time, the DOC was operating as a "one-stop-shop" for diabetes patients. The DOC staff consisted of an endocrinologist, nurse practitioner, counselor, ophthalmologist, dietitian, certified diabetes educator, and support staff. All patients were seen for both diabetes treatment as well as their primary care in the DOC.

The population, defined as any individual with an ICD-9 diagnosis of diabetes (250.XX) in the WHMC San Antonio area from January 2005 and December 2008, was included in the analysis. A total of 9,654 people with diabetes (1,171 DOC patients and 8,483 usual care patients) from military database were identified, and their records between January 2005 and December 2008 were obtained, including demographics, clinical data (A1C, systolic/diastolic blood pressure, as well as blood glucose, total cholesterol, HDLc, and low-density lipoprotein cholesterol (LDLc) levels), medical utilization (hospitalizations, primary care visits, and

specialty care visits), and pharmacy records. For DOC patients, we defined the records from one year prior to DOC entry as the pre-DOC data (or baseline), and all records after DOC entry as the post-DOC data (or follow-up); while for UC patients, we defined the records from one year prior to January 2006 (i.e., DOC starting date) as the pre-DOC data (or baseline), and all records after that time as the post-DOC data (or follow-up). Moreover, we only used data when patients were at age 18 years or more by following the Institutional Review Board policy. Hence, a total of 9,405 diabetes patients (97.4% of the original population; 9,405/9,654) were identified to be the final study cohort in this analysis, including 1,171 DOC patients and 8,234 usual care patients.

Effectiveness analysis from the DOC intervention in the military-based setting revealed that the DOC patients reported improvements in A1C (-0.6%, $P < 0.001$), total cholesterol levels (-11.6 mg/dl, $P < 0.001$), and LDLs levels (-6.5 mg/dl, $P < 0.001$). Also, 98% (1,143/1,171) of DOC patients received diabetes self-management education. Using the CCM intervention in a military clinic resulted in significantly improved control for glycemia and dyslipidemia, implying implementation of a team-based comprehensive diabetes clinic is a feasible and effective means for improving clinical outcomes in this population. Since little is known about the cost-effectiveness of implementing the CCM intervention in a military-based setting, we sought to determine the cost-effectiveness of the DOC intervention. Model input parameters were directly obtained from this study or were drawn from published literature.

Specific Aim 3

Data for Specific Aim 3 were primarily based on a pilot clinical trial completed by McTigue et al. (277). McTigue et al. aimed to translate an evidence-based lifestyle program into the clinical

setting by adapting it for delivery via the Internet (i.e., an Online adaptation of the Diabetes Prevention Program lifestyle intervention (ODPP)). They adapted the Diabetes Prevention Program's lifestyle curriculum to an online format, comprising 16 weekly and 8 monthly lessons, and conducted the before-and-after pilot study for evaluating program implementation and feasibility. The program incorporated behavioral tools such as e-mail prompts for online self-monitoring of diet, physical activity, and weight, and automated weekly progress reports. Electronic counseling provided further support. Also, physician referral, automated progress reports, and as-needed communications with lifestyle coaches integrated the intervention with clinical care. Patient with age 18-80 years, a body mass index $\geq$25 kg/m^2, at least one weight-related CVD risk factor, and Internet access were eligible if referring physicians felt the lifestyle goals were safe and medically appropriate. A total of 50 patients from a large academic general internal medicine practice were found eligible and enrolled in this pilot study between November 16, 2006 and February 11, 2007.

They evaluated a one-year pilot program for these 50 patients. Change in body weight (kg) was the primary outcome measure, while change in blood pressure and the frequency of clinically significant weight loss were secondary outcomes. Follow-up measurements were performed every 3 months (±2 weeks), and the final evaluation occurred between 50 and 56 weeks of follow-up. At each follow-up visit, the participants' mean weight was significantly lower than that at baseline. At the end of one year, the mean weight change among participants who completed the measured 12-month weight evaluation (n = 45) was -4.79 kg (95% confidence interval: -7.36 to -2.22); 31% of these participants had at least a 5% weight loss and 18% at least a 7% weight loss. Moreover, systolic blood pressure significantly dropped by 7.33 mmHg (95% confidence interval: -10.75 to -3.92), while diastolic blood pressure changed

minimally (+0.44 mmHg; 95% confidence interval: -2.74 to +2.83). This study demonstrated that an Internet-based lifestyle intervention may overcome significant barriers to preventive counseling and effectively facilitate the incorporation of evidence-based lifestyle interventions into primary care. Since published information is lacking on the economical effectiveness of on Internet-based lifestyle intervention programs, we sought to assess the cost-effectiveness of an Internet-based lifestyle intervention to reduce risk of T2D and CVD in a sample of primarily obese adults in the primary care setting. Model input parameters were directly obtained from this pilot clinical trial or were drawn from published literature.

Parameters of Being Used to Obtain Transition Probabilities, Parameters of Costs, and Parameters of Health Utilities for the Markov Decision Model

The following three tables (Tables 6.1, 6.2, and 6.3) show parameters of estimating transition probabilities, of costs (direct medical and direct non-medical costs), and of health utilities for the Markov decision model. Also, the sources/references for these parameters are listed in tables, including three primarily referred studies (275-277) and other published literature. Application of multiple sources in a modeling-based cost-effectiveness analysis is very common, and the source data that we select and use in our analyses are based on empirical data, pivotal studies, commonly cited references, or published studies at a nationally representative level.

Table 6.1 Parameters used to obtain transition probabilities for the Markov decision model

Parameter	Source (Author, Reference)
Demographic data	Piatt et al. (275); Siminerio et al. (276); McTigue et al. (277); Assumption
Age (years)	
Gender (female/male)	
Race (White/Afro-Caribbean/Asian-Indian)	
Weight (kg)	
Height (cm)	
Body mass index (kg/m^2)	
Duration of diabetes (years)	
Smoking status (non-smoker/ex-smoker/current smoker)	
Clinical data	Piatt et al. (275); Siminerio et al. (276); McTigue et al. (277); Assumption
A1C (%)	
Systolic blood pressure (mmHg)	
Total cholesterol (mg/dl)	
HDLc (mg/dl)	
LDLc (mg/dl)	
Creatinine clearance <100 ml/min (yes/no)	
Atrial fibrillation (yes/no)	
Macroalbuminuria (yes/no)	
Microalbuminuria (yes/no)	
Probability of progression in diabetes complications	
Mortality rates and relative risk of death	Piatt et al. (275); Siminerio et al. (276); McTigue et al. (277); UKPDS risk engine (291-296); Zoungas et al. (297); Arias (283); Lenz et al. (302); Moss et al. (303); Fuller et al. (304); Assumption
Overweight or obesity	
Stable diabetes	
Complicated diabetes	

Abbreviations: A1C, glycated hemoglobin; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; UKPDS, United Kingdom Prospective Diabetes Study.

Table 6.2 Cost parameters for the Markov decision model

Parameter	Source (Author, Reference)
Direct medical costs	
Health care providers for diabetes self-management training sessions, support groups sessions, point-of-service-education sessions, and diabetes education classes and visits	Piatt et al. (275); Siminerio et al. (276); US Bureau of Labor Statistics (285)
Laboratory tests for A1C, lipid panel, and urinalysis	Piatt et al. (275); Siminerio et al. (276); Centers for Medicare & Medicaid Services (284)
Medications for glycemia control, hypertension control, and dyslipidemia control	Piatt et al. (275); Siminerio et al. (276); Red Book 2008 (287); Hoerger et al. (286); Assumption
Physician office visits for primary care and specialty care	Piatt et al. (275); Siminerio et al. (276); Centers for Medicare & Medicaid Services (284)
Internet-based lifestyle intervention (e.g., orientation sessions for participants and staff, coaching services, staff activity/time, and information materials)	McTigue et al. (277); US Bureau of Labor Statistics (285)
Diabetes complications (one-time and annual)	Hoerger et al. (286); Herman et al. (300); Brandle et al. (305)
Death (one-time)	Hoerger et al. (286)
Direct non-medical costs	
Patient time costs for (1) diabetes self-management training sessions, support groups sessions, point-of-service-education sessions, and diabetes education classes and visits; (2) physician office visits for primary care and specialty care; and (3) Internet-based lifestyle intervention (e.g., orientation session, education lessons, and weekly activity review/report)	Piatt et al. (275); Siminerio et al. (276); McTigue et al. (277); US Bureau of Labor Statistics (285); Smith et al. (288)
Patient monetary costs for (1) diabetes self-management training sessions, support groups sessions, point-of-service-education sessions, and diabetes education classes and visits; and (2) physician office visits for primary care and specialty care	Piatt et al. (275); Siminerio et al. (276); US Bureau of Labor Statistics (285); Smith et al. (288)

Abbreviation: A1C, glycated hemoglobin.

Table 6.3 Health utility parameters for the Markov decision model

Parameter	Source (Author, Reference)
No diabetes, overweight or obese	Coffey et al. (289); Herman et al. (300); Zhou et al. (306); Trueman et al. (307)
Diabetes without complications (or stable diabetes)	
Diabetes with microvascular complications	
Diabetes with macrovascular complications	
Diabetes with micro- and macrovascular complications	
Complicated diabetes	
Death	

6.2.3 Model Structure

Specific Aim 1

We developed a Markov decision model (278-280) to estimate the incremental cost-effectiveness of the CCM intervention compared to the PROV intervention and usual care as implemented in Piatt et al.'s clinical trial (275). We used a standard decision analysis software package, TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA), for model construction. The model directly incorporated intervention costs and effectiveness data from Piatt et al.'s clinical trial (275) to estimate life expectancy, quality-adjusted life-expectancy (expressed as quality-adjusted life-years, or QALYs), clinical outcomes (e.g., incidence of diabetes with chronic complications), as well as direct medical and non-medical costs associated with the intervention strategies.

The model is illustrated below in Figure 6.1, which describes the progression of disease through microvascular complications, macrovascular complications, and mortality. We assumed that all patients had uncomplicated diabetes at the start of the model. Over time, diabetes can progress to microvascular complications only (including retinopathy, nephropathy, or neuropathy), macrovascular complications only (including coronary heart disease or stroke), and/or end-stage renal disease (ESRD). We assumed that complications were irreversible and that patients in any health state could die in the next time period.

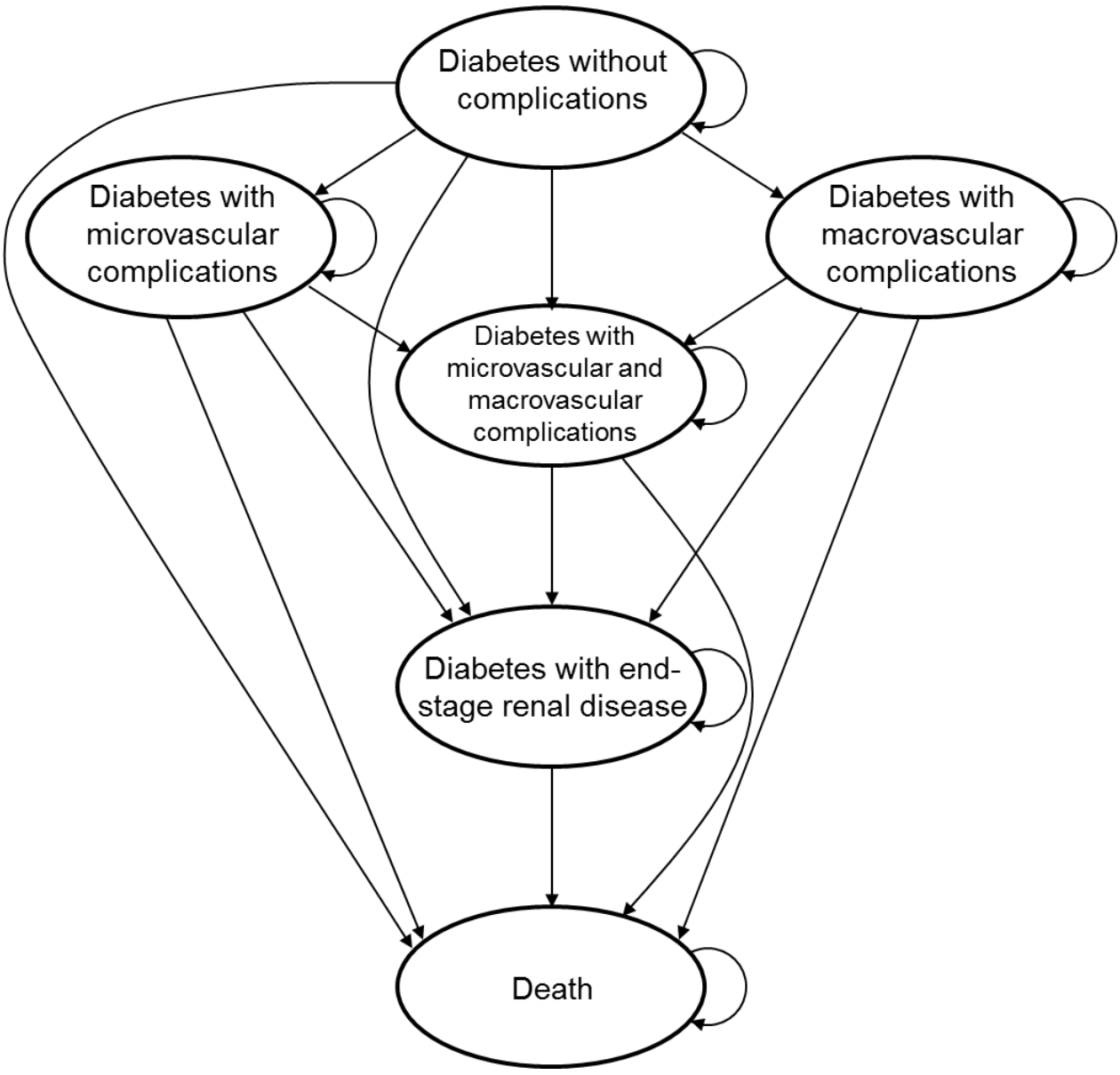

Figure 6.1 Markov-state diagram for the basic model structure for analyzing the cost-effectiveness a Chronic Care Model intervention in an underserved community population

Specific Aim 2

We modified the model for Specific Aim 1 to estimate the incremental cost-effectiveness of the DOC intervention relative to usual care based on results from the study completed at US Air

Force WHMC in San Antonio, TX (276). We used a standard decision analysis software package, TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA), for model construction. The model directly incorporated intervention costs and effectiveness data from the DOC study (276) to estimate life expectancy, quality-adjusted life-expectancy (expressed as quality-adjusted life-years, or QALYs), as well as direct medical and non-medical costs associated with the intervention strategies.

The model is illustrated below in Figure 6.2, which describes the progression of disease through microvascular complications, macrovascular complications, and mortality. We assumed that all patients had uncomplicated diabetes at the start of the model. Over time, diabetes can progress to microvascular complications only (including retinopathy, nephropathy, or neuropathy), macrovascular complications only (including coronary heart disease or stroke), or both. We assumed that complications were irreversible and that patients in any health state could die in the next time period.

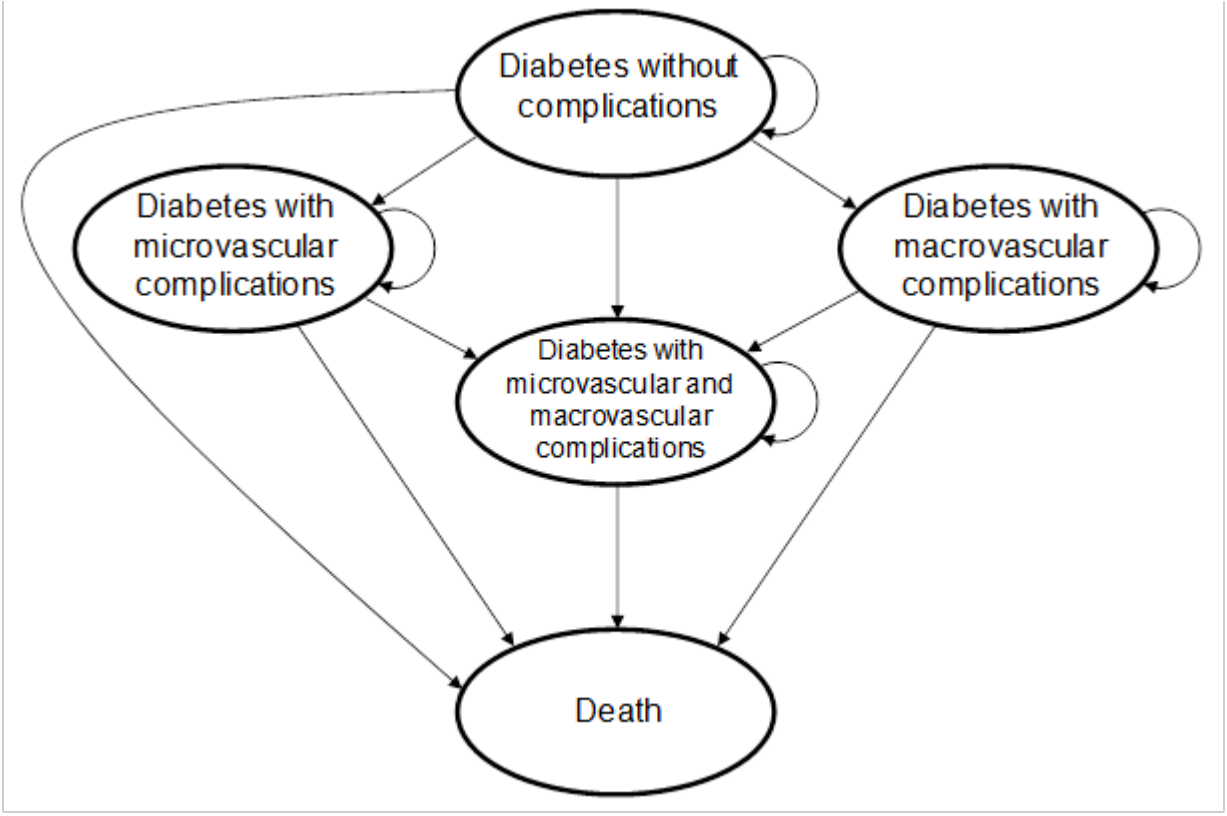

Figure 6.2 Markov-state diagram of the basic model structure for analyzing the cost-effectiveness a Chronic Care Model intervention in a military population

Specific Aim 3

We used TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA) to modify our prior Markov decision model (281) to estimate the incremental cost-effectiveness of an Internet-based lifestyle intervention in the primary care setting as implemented in McTigue et al.'s pilot clinical trial (277). The model directly incorporated intervention costs and effectiveness data from the pilot clinical trial (277) to estimate life expectancy, quality-adjusted life-expectancy (expressed as quality-adjusted life-years, or QALYs), clinical outcomes (e.g., incidence of diabetes without or with chronic complications), as well as direct medical and non-medical costs associated with the intervention strategies.

The model illustrated below in Figure 6.3 is used to evaluate the long-term costs and outcomes associated with weight loss or gain, and describes the progression of disease through stable diabetes (i.e., diabetes without any chronic complications), complicated diabetes (i.e., diabetes with any chronic complications), and mortality. At the start of the base case model, the proportions of subjects in four health states were set to mirror the cohort in the McTigue et al.'s pilot clinical trial. Over time, subject can progress to stable or complicated diabetes. Complications related to diabetes included retinopathy, nephropathy, neuropathy, stroke, or coronary heart disease. We assumed that the transition to complicated diabetes was preceded by a stable diabetes stage in those subjects who developed diabetes, complications were irreversible, and subjects in any health state could die in the next time period. Since diabetes progression was the primary outcome of interest in Specific Aim 3, the major weight-related comorbidities considered in the model were limited to diabetes, making the model conservative.

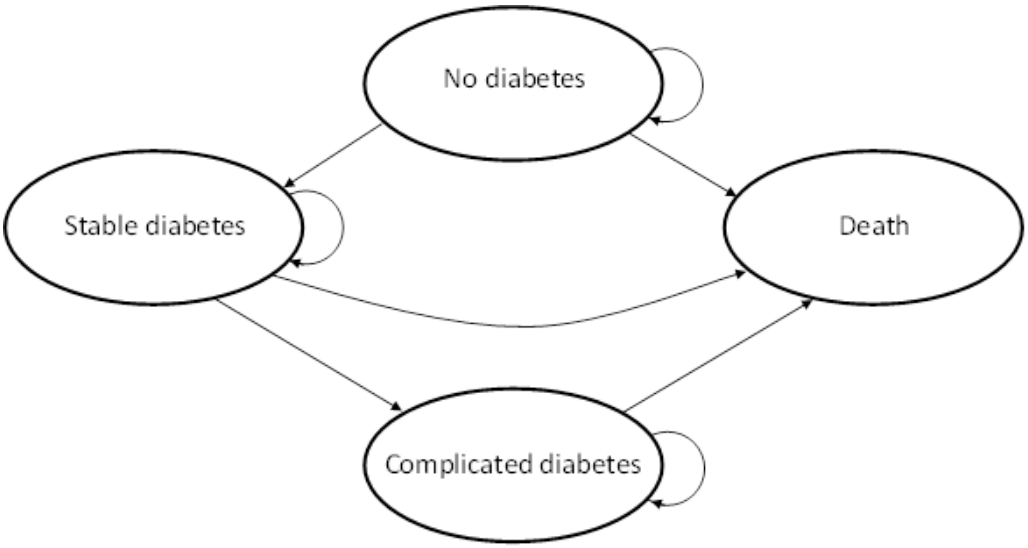

Figure 6.3 Markov-state diagram of the basic model structure for analyzing the cost-effectiveness an Internet-based lifestyle intervention

6.2.4 Study Outcomes

The Table 6.4 below shows three categories of study outcomes which can be estimated from the computational modeling, including cost, effectiveness, and cost-effectiveness analysis outcomes.

Table 6.4 Estimated economic and clinical outcomes in Specific Aims 1, 2, and 3

Category	Outcome variable	Specific aim 1	Specific aim 2	Specific aim 3
Cost outcomes	Direct medical cost	Yes	Yes	Yes
	Direct non-medical cost	Yes	Yes	Yes
Effectiveness outcomes	QALYs	Yes	Yes	Yes
	Stable diabetes (i.e., diabetes without any complications)	-	-	Yes
	Diabetes with micro-, macrovascular complications, either, or both	Yes	Yes	-
	Complicated diabetes (i.e., diabetes with any complications)	Yes	Yes	Yes
CEA outcomes	Cost per QALY gained	Yes	Yes	Yes
	Cost per stable diabetes case averted	-	-	Yes
	Cost per diabetes complication or death averted	Yes	Yes	-
	Cost per complicated diabetes case averted	Yes	Yes	Yes

Abbreviations: QALYs, quality-adjusted life-years; CEA, cost-effectiveness analysis.

6.3 BASE CASE ANALYSIS

Specific Aim 1

We used a base case from a health care system perspective, which examined 68-year-olds with T2D who participated in three intervention strategies (CCM, PROV, or usual care) as implemented in Piatt et al.'s trial (275) at yearly cycles over a 3-year time horizon. We examined a 3-year time horizon in the base case analysis because of uncertainty in long-term strategy effectiveness, and we lengthened the time horizon to 10 years in a sensitivity analysis.

Using baseline and 12-month data from Piatt et al.'s trial (275), we estimated the annual probabilities of intensive treatments and disease progression in the intervention groups. To account for the cluster-design nature of Piatt et al.'s trial (275), we used a multivariable mixed-effects logistic regression model that also adjusted for baseline characteristics with significant clinical differences (A1C and HDLc levels) and those with statistical differences (age at study entry, body mass index, and total cholesterol level) among the three intervention groups. All five covariates were centered at their corresponding mean values. We assumed that the treatment and health benefits associated with the interventions persisted after the study period and thus we applied the same probabilities of either receiving the intensive treatments or moving to another health state (state-transition or disease progression) to subsequent model cycles.

We treated ESRD as a separate health state due to its relative rarity and high cost, estimating the annual probability of developing ESRD using the US Renal Data System Annual Data Report (282) and assuming the same probability for all interventions. Mortality was a rare event in Piatt et al.'s trial (275). We therefore estimated mortality using age-specific US mortality rates (283) and the relative risk of death for people with diabetes (30), and assumed identical mortality for all interventions. For the ESRD state, we estimated mortality using the US Renal Data System Annual Data Report (282), again assuming the same ESRD mortality for all interventions.

Annual direct medical costs related to health care provider consultations, intensive treatments, laboratory tests, physician office visits, diabetic complications, death, and medications were included in the model. We did not include indirect costs, assuming their capture in the assessment of QALYs per the recommendation of the Panel on Cost-Effectiveness in Health and Medicine (258). We used Medicare reimbursement data to estimate laboratory test

costs (A1C, lipid panel, and urinalysis) and physician office visits (284). In addition, we used hourly wage costs for health care providers required by the intervention strategies based on National Occupational Employment and Wage Estimates (285). We identified one-time and annual costs of diabetic complications, as well as one-time costs of death based on data from the models developed by the Centers for Disease Control and Prevention (CDC) and Research Triangle Institute International (286).

We defined intensive treatments as additional prescribed medications for the treatment of three specific conditions in each intervention strategy, including pioglitazone was added for the intensive treatment of glycemia, ramipril was added for the intensive treatment of hypertension, and atorvastatin was added for the intensive treatment of dyslipidemia. Using the average wholesale prices of these drugs (287), we calculated a weighted average cost of each intensified therapy and varied these costs in sensitivity analyses.

In analyses from the societal perspective, we included both direct medical and non-medical costs. Direct non-medical costs included patient time and monetary costs for physician office visits, diabetes self-management training sessions, support groups sessions, and point-of-service-education sessions. Patient time costs for time missed from work or school to receive care and for time donated by others (e.g., for rides or babysitting) to allow care to occur were quantified based on data from Piatt et al.'s trial (275) or published literature (288), then valued based on the average hourly wage of a US nonfarm production worker in 2000 (285) and the average annual numbers of visits/sessions as derived from Piatt et al.'s trial (275). In addition, patient monetary costs including costs of parking or transportation and of babysitting or childcare were quantified based on data from the published literature (288), then valued based on the average annual numbers of visits/sessions as derived from Piatt et al.'s trial (275).

Health utilities are a measure of health-related quality of life, with perfect health = 1 and death = 0. In a cost-effectiveness analysis, this utility weight for each health state is multiplied by time in that state. As an individual's health changes over time, these products are summed to represent the total number of QALYs (258). To estimate health utilities associated with T2D with or without complications in the model, we applied an additive prediction model to estimate health utilities according to demographic, treatment, and complication variables (289). The baseline health utility of 0.689 is the health utility for a nonobese man with T2D who is treated with diet and exercise, and who has no cardiovascular risk factors or microvascular, neuropathic, or cardiovascular complications.

In keeping with the reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine (258), we discounted future costs and benefits by 3% annually. Also, we expressed costs in 2000 US dollars using the US Consumer Price Index (290), converting all monetary costs to the US dollar rate for the year 2000.

Specific Aim 2

We used a base case from a health care system perspective, which examined 50-year-olds with T2D who participated in two intervention strategies (DOC or usual care) as implemented in the DOC study (276) at yearly cycles over a 20-year time horizon.

We aimed to evaluate the incremental cost-effectiveness over next 20 years following the intervention period, assuming that treatments continued for the duration. We applied the United Kingdom Prospective Diabetes Study (UKPDS) risk engine/equations to predict long-term (over next 20 years) probabilities of developing micro- (291-293) and macrovascular (294-296; http://www.dtu.ox.ac.uk/riskengine/) diabetes complications based on post-intervention

demographic and clinical data in those diabetes patients who were alive and without any diabetes complications at the study end. Each post-intervention clinical data was adjusted for imbalanced baseline characteristics as appropriate using regression analyses. To be conservative, the effect of the intervention strategies on disease progression was assumed to be identical on patients who already had diabetes complications. Annual transition probabilities of death and of disease progression related to diabetes were predicted using the UKPDS risk equations and/or derived from the ***A***ction in ***D***iabetes and ***V***ascular Disease: Preter***A***x and Diamicro***N*** Modified Release ***C***ontrolled ***E***valuation (ADVANCE) trial (297) and other published literature.

Annual direct medical costs related to health care providers, laboratory tests, physician office visits, diabetes complications, death, and medications were included in the model. We did not include indirect costs, assuming their capture in the assessment of QALYs per the recommendation of the Panel on Cost-Effectiveness in Health and Medicine (258). We used Medicare reimbursement data to estimate laboratory test costs (A1C, lipid panel, and urinalysis) and physician office visits (284). We used hourly wage costs for health care providers required by the intervention strategies based on National Occupational Employment and Wage Estimates (285). We identified one-time and annual costs of diabetes complications, one-time costs of death, as well as medication costs for diabetes, hypertension, and cholesterol control using data from the models developed by the Centers for Disease Control and Prevention and Research Triangle Institute International (286).

In analyses from the societal perspective, we included both direct medical and non-medical costs. Direct non-medical costs included patient time and monetary costs for physician office visits, and diabetes education classes/visits. Patient time costs for time missed from work or school to receive care and for time donated by others (e.g., for rides or babysitting) to allow

care to occur were quantified based on data from the DOC study (276) or published literature (288), then valued based on the average hourly wage of a US nonfarm production worker (285) and the average annual numbers of visits and classes as derived from the DOC study (276). In addition, patient monetary costs including costs of parking or transportation and of babysitting or childcare were estimated from the published literature (288), then valued based on the average annual numbers of visits and classes as derived from the DOC study (276).

Health utilities are a measure of health-related quality of life, with perfect health = 1 and death = 0. In a cost-effectiveness analysis, this utility weight for each health state is multiplied by time in that state. As an individual's health changes over time, these products are summed to represent the total number of QALYs (258). To estimate health utilities associated with T2D with or without complications in the model, we applied an additive prediction model to estimate health utilities according to demographic, treatment, and complication variables (289). The baseline health utility of 0.689 is the health utility for a nonobese man with T2D who is treated with diet and exercise, and who has no cardiovascular risk factors or microvascular, neuropathic, or cardiovascular complications.

In keeping with the reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine (258), we discounted future costs and benefits by 3% annually. Also, we expressed costs in 2010 US dollars using the US Consumer Price Index (290), converting all monetary costs to the US dollar rate for the year 2010.

Specific Aim 3

We used a base case from a health care system perspective, which examined the cohort of 53-year-old adults who participated in the ODPP pilot study (277) at yearly intervals for 10 years.

We aimed to evaluate the incremental cost-effectiveness over next 10 years following the intervention period. In the model, usual care was the absence of the online-based lifestyle intervention. The intervention effectiveness of the ODPP on weight change was obtained from the ODPP pilot study (277), while the weight change status through usual care was derived from the same primary care population for the ODPP pilot study - based on patients who were referred for an in-person DPP-based lifestyle intervention, but did not enroll (298). In the model, the incidence of diabetes as a function of baseline body mass index (BMI) and the odds ratios for diabetes risk as a function of weight change were derived from the published reports of studying a nationally representative sample of US adults (113,299). These odds ratios for diabetes risk were adjusted for age, baseline BMI, sex, race, education, systolic blood pressure, skinfold ratio and reported change in physical activity (299).

Other clinical outcomes related to stable diabetes and complicated diabetes for both the Internet-based lifestyle intervention and usual care were derived from the DPP study (300), the UKPDS (295), and the Framingham Heart Study (301). Mortality rates were based on age- and gender-specific US mortality (which accounts for baseline mortality) (283) and the relative risks for overweight/obesity (302), stable diabetes (303), and complicated diabetes (304). To be conservative, the ODPP and usual care were assumed to have identical effects on the progression of disease in patients who already had stable diabetes, thus implying that the model only examined differences between strategies in delaying or preventing the development of stable diabetes.

Costs related to stable diabetes and complicated diabetes were derived from published literature (300,305), while costs of the Internet-based lifestyle intervention (e.g., orientation sessions for participants and staff, coaching services, staff activity/time, and information

materials) and direct non-medical costs (e.g., costs of participant time for participating in the ODPP) were obtained from the ODPP pilot study (277). To account for changes in life expectancy and quality of life for diabetes-related health states, we used QALYs, which adjust for quality based on a utility weight or preference, for the health state ranging from 0 (death, least preferred) to 1 (perfect health, most preferred). Health utility scores associated with diabetes were derived from published literature, adjusted for demographic, treatment, and disease state variables (289,300,306,307).

In keeping with the reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine (258), we discounted future costs and benefits by 3% annually. Also, we expressed costs in 2010 US dollars using the US Consumer Price Index (290), converting all monetary costs to the US dollar rate for the year 2010.

6.4 SENSITIVITY ANALYSES

Many new intervention strategies or programs are more costly but also more effective. In such cases, the new interventions may be considered cost-effective if the cost-effectiveness ratio is below some ceiling or threshold value such that the decision makers deem the added expense worth the added benefits. However, different decision makers may value benefits differently. Hence, extensive sensitivity analyses will be conducted to assess variations on the assumptions of the base case model (308).

First, we conducted one-way sensitivity analyses for model parameters to assess the effect of varying individual parameter estimates within clinically plausible ranges, identifying

those parameters whose variation changed the base case incremental cost-effectiveness ratio (ICER) by 20% or greater.

Second, we performed several scenario analyses (one-way or two-way) to examine the effect of varying original assumptions made for the base case model on the base case ICER. For example, (1) for Specific Aims 1, 2, and 3, we calculated the ICER of cost per QALY gained from societal perspective, and (2) for Specific Aim 2, we tested the original assumption that all DOC and usual care patients had uncomplicated diabetes at the start of the model by changing initial proportions of patients in five heath states (i.e., no complications, microvascular complications only, macrovascular complications only, both micro- and macrovascular complications, or death) at the start of the model to mirror the DOC cohort, and then to calculate the ICER of cost per QALY gained from societal perspective.

Third, uncertainty around the ICER of cost per QALY gained will be assessed through the use of probabilistic sensitivity analysis. We performed a probabilistic sensitivity analysis from a health care system or societal perspective, where model parameters were simultaneously varied over distributions (309). Distributions for parameters were chosen based on the level of certainty and the characteristics of the parameter range, e.g. beta distribution was assigned for probabilities; uniform, triangular, or log normal distributions were assigned for costs; and normal or uniform distributions were chosen for utilities. A value from each parameter's probability distribution was randomly selected during each of 10,000 Monte Carlo iterations, and then these values were used to compute strategy cost-effectiveness for each iteration. We used the cost-effectiveness acceptability curve (310) to summarize probabilistic sensitivity analysis results, showing the likelihood that a given strategy would be favored for a given willingness-to-pay threshold (311). A willingness-to-pay (or acceptability) threshold is the maximum amount that

society is willing to pay for an incremental gain in health (311). Although there is no absolute threshold, it is argued (312,313) that this threshold should not be static and a plausible range of society's willingness-to-pay threshold for incremental cost-effectiveness of modern health care may be between $100,000 and $300,000 per QALY gained.

7.0 MANUSCRIPT 1: COST-EFFECTIVENESS OF IMPLEMENTING THE CHRONIC CARE MODEL FOR DIABETES CARE IN THE COMMUNITY

Shihchen Kuo, RPh, MSCP[1]
Kenneth J. Smith, MD, MS[2]
Janice C. Zgibor, RPh, PhD[1]
Gretchen A. Piatt, CHES, MPH, PhD[3]
Mark S. Roberts, MD, MPP[4]
Cindy L. Bryce, PhD[4]

[1]Department of Epidemiology
University of Pittsburgh, Pittsburgh, PA

[2]Section of Decision Sciences and Clinical Systems Modeling
University of Pittsburgh, Pittsburgh, PA

[3]Department of Medical Education
University of Michigan, Ann Arbor, MI

[4]Department of Health Policy and Management
University of Pittsburgh, Pittsburgh, PA

7.1 ABSTRACT

Context: Applying the comprehensive six-element chronic care model (CCM) for diabetes care can improve patient and system outcomes, but its relative cost-effectiveness is not known.

Objective: To estimate the incremental cost-effectiveness of implementing the CCM relative to a provider continuing medical education intervention (PROV) and to usual care (UC).

Design, Setting, and Patients: A Markov decision model estimated the cost-effectiveness of type 2 diabetes management strategies in a CCM randomized controlled trial. Intervention costs and outcomes, and disease progression data were directly obtained from the clinical trial. Other costs, mortality rates, and utilities were drawn from published literature.

Interventions: CCM, PROV, and UC intervention strategies as implemented in the CCM randomized controlled trial.

Main Outcome Measures: Cumulative incidence of diabetes with either microvascular or macrovascular complications, direct medical and direct nonmedical costs (in 2000 US dollars), quality-adjusted life-years (QALYs), cost per QALY gained, and cost per diabetes complication averted.

Results: Compared to the PROV and UC strategies over a 3-year period, the CCM strategy reduced the incidence of diabetes with either microvascular or macrovascular complications by an absolute 41.3 and 3.9 percentage points, respectively. From a health care system perspective, the costs over 3 years for the CCM strategy compared to the UC strategy were $70,317 per QALY gained and $29,573 per diabetes complication averted; the CCM strategy dominated the PROV strategy in both analyses. Over 10 years, the costs per QALY gained from a health care

system and a societal perspective for the CCM strategy compared to the UC strategy were $42,179 and $113,280 respectively.

Conclusions: The application of the full chronic care model for diabetes care in underserved communities is a sound and cost-saving investment compared to the provider continuing medical education intervention, and is economically reasonable relative to usual care.

7.2 INTRODUCTION

Diabetes is an increasingly and costly prevalent cause of morbidity and mortality, resulting in major clinical and public health problems in the United States (1-7). Quality diabetes care is essential to prevent acute complications and to reduce the risk of long-term complications (8). Although highly effective therapies and evidence-based treatment guidelines are available (8,9), diabetes care and outcomes often fall short of recommended standards (10-14).

The Chronic Care Model (CCM) (15), a multifaceted framework for enhancing health care delivery, is used in many health care settings to guide systematic improvement for chronic illness care, including diabetes (16-18). The premise of the CCM is that quality care can be enhanced by six elements: self-management support, delivery system design, community resources, organizational support, decision support, and clinical information systems, enhancing patient-provider interactions and improve outcomes (19-27). Previous studies demonstrate the effectiveness of CCM-based diabetes interventions (16-19,22-26,28-37).

An integral component of effectively implementing the CCM is the practice of patient-centered, team-based care. Although the team interventions improve diabetes outcomes (25,38), little is known about the cost-effectiveness of this approach. In this analysis we estimate the costs, clinical outcomes, and cost-effectiveness of implementing the CCM based on the results of a randomized controlled trial (RCT) (25).

7.3 METHODS

Piatt et al conducted the first multifaceted, cluster-design RCT to determine the effectiveness of implementing the comprehensive CCM in a community-based setting. This trial took place in an underserved urban community of Pittsburgh, PA, between 1999 and 2003, and included a 1-year follow-up (25). Participating patients had a confirmed diagnosis of diabetes, based on ICD-9 codes, problem lists, laboratory results, or diabetes medication use. Eleven primary care practices and their patients were randomly assigned to one of three study groups: a Chronic Care Model intervention (CCM), a provider continuing medical education intervention (PROV), or usual care (UC). The CCM group (3 practices; 30 patients) involved implementation and provision of all six CCM elements. PROV (3 practices; 38 patients) consisted of providers attending one continuing medical education session, an in-person review of chart audit results by a certified diabetes educator, and the availability of a certified diabetes educator for consultation. Providers in the UC group (5 practices; 51 patients) were mailed their practices' chart audit results. Baseline patient characteristics are presented in Table 7.1.

The primary outcomes of the RCT included reductions in glycated hemoglobin (A1C), blood pressure levels, and non-high-density lipoprotein cholesterol (non-HDLc) levels. Secondary outcomes were improvements in quality of well-being, diabetes knowledge, empowerment, and the frequency of self-monitoring of blood glucose. Following the 1-year intervention, a significant decline in A1C (-0.6%) and in non-HDLc levels, and an increase in the proportion of patients who self-monitor blood glucose were observed in the CCM group. The CCM also reported improvements in HDLc levels (+5.5 mg/dL), diabetes knowledge test scores (+6.7%), and empowerment scores (+0.2). Taken together, CCM implementation in the

community was effective in improving clinical and behavioral outcomes. Because the full CCM is resource intensive, we sought to determine its cost-effectiveness.

The Markov Decision Model Framework

Model Structure

We developed a Markov decision model (39-41) to estimate the incremental cost-effectiveness of the CCM compared to PROV and UC in the RCT (25). We used a standard decision analysis software package, TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA). The model directly incorporated intervention costs and effectiveness data as well as event probabilities from the RCT to estimate life expectancy, quality-adjusted life-expectancy (QALE) (expressed as quality-adjusted life-years, or QALYs), clinical outcomes (diabetes with chronic complications), and direct medical and nonmedical costs associated with the intervention strategies. In our initial base-case analysis, we examined 68-year-olds (the average age of the RCT patients) with type 2 diabetes who participated in three intervention strategies and evaluated clinical outcomes over a 3-year period. We examined a 3-year time horizon in the base-case analysis because of uncertainty in long-term strategy effectiveness, and we lengthened the time horizon to 10 years in a sensitivity analysis.

The model is illustrated in Figure 7.1, which describes the progression of disease through microvascular complications, macrovascular complications, and mortality. We assumed that all patients had uncomplicated diabetes at the start of the model. Over time, diabetes can progress to microvascular complications (including retinopathy, nephropathy, or neuropathy), macrovascular complications (including coronary heart disease, neurological disease, or peripheral vascular

disease), and/or end-stage renal disease (ESRD). We assumed that complications were irreversible and that patients in any health state could die in the next time period.

The base-case values, ranges, and probability distributions of all parameters are summarized in Tables 7.2-7.4. Using baseline and 12-month RCT data, we estimated the annual probabilities of intensive treatments and disease progression in the intervention groups (Table 7.2). To account for the cluster-design nature of the RCT, we used a multivariable mixed-effects logistic regression model that also adjusted for baseline characteristics with significant clinical differences (A1C and HDLc levels) and those with statistical differences (age at study entry, body mass index, and total cholesterol level) among the three intervention groups (Table 7.1). All five covariates were centered at their corresponding mean values. We assumed that the treatment and health benefits associated with the interventions persisted after the study period (42) and thus we applied the same probabilities of either receiving the intensive treatments or moving to another health state (state-transition or disease progression) to subsequent model cycles.

We treated ESRD as a separate health state due to its relative rarity and high cost, estimating the annual probability of developing ESRD using the US Renal Data System Annual Data Report (43) and assuming the same probability for all interventions. Mortality was a rare event in the RCT. We therefore estimated mortality using age-specific US mortality rates (44) and the relative risk of death for people with diabetes (45), and assumed identical mortality for all interventions. For the ESRD state, we estimated mortality using the US Renal Data System Annual Data Report (43), again assuming the same ESRD mortality for all interventions.

Annual direct medical costs related to health care provider consultation, intensive treatments, laboratory tests, physician office visits, diabetic complications, and death were

included in the model (Table 7.3). We did not include indirect costs, assuming their capture in the assessment of QALYs per the recommendation of the Panel on Cost-Effectiveness in Health and Medicine (46). We used Medicare reimbursement data to estimate laboratory test costs (A1C, lipid panel, and urinalysis) and physician office visits (47). In addition, we used hourly wage costs for health care providers required by the CCM (i.e., registered nurses and medical assistants) based on National Occupational Employment and Wage Estimates (48).

For each intervention strategy, we defined intensive treatments as additional prescribed medications in the treatment of specific conditions: pioglitazone was added for the intensive treatment of glycemia, ramipril was added for the intensive treatment of hypertension, and atorvastatin was added of the intensive treatment for dyslipidemia (Table 7.3). Using 2008 average wholesale prices of these drugs (49), we calculated a weighted average cost of intensified therapy and varied these costs in sensitivity analyses. In addition, we identified one-time and annual costs of diabetic complications and ESRD based on data from models developed by the CDC and Research Triangle Institute International (50).

In analyses from the societal perspective, we included both direct medical and nonmedical costs. Direct nonmedical costs included patient time and monetary costs for physician office visits, diabetes self-management training sessions, support groups sessions, and point-of-service-education sessions (Table 7.3). Patient time costs for time missed from work or school to receive care and for time donated by others (e.g., for rides or babysitting) to allow care to occur were quantified based on data from the RCT or published literature (51), then valued based on the average hourly wage of a US nonfarm production worker in 2000 (48) and the average annual numbers of visits/sessions as derived from the RCT. We expressed costs in 2000

US dollars using the US Consumer Price Index (52), converting all monetary costs to the US dollar rate for the year 2000.

Health utilities are a measure of health-related quality of life, with perfect health=1 and death=0. In a cost-effectiveness analysis, this utility weight for each health state is multiplied by time in that state. As an individual's health changes over time, these products are summed to represent the total number of quality-adjusted life-years (QALYs) (46). To estimate health utilities associated with type 2 diabetes with or without complications, we applied an additive prediction model to estimate health utilities according to demographic, treatment, and complication variables (53). The baseline health utility of 0.689 is the health utility for a nonobese man with type 2 diabetes who is treated with diet and exercise and who has no cardiovascular risk factors or microvascular, neuropathic, or cardiovascular complications. Table 7.4 shows the health utilities used in the model.

Sensitivity Analyses

We first conducted one-way sensitivity analyses for model parameters (Tables 7.2-7.4) to assess the effect of varying parameter estimates within clinically plausible ranges, identifying those parameters whose variation caused the incremental cost-effectiveness ratio (ICER) to become greater than $100,000 per QALY gained. We also examined the effect of lengthening the model time horizon, changing to a societal perspective, and hypothesizing lower mortality in CCM patients. In addition, we examined the cost-effectiveness of assuming identical microvascular or macrovascular complication rates among intervention strategies, given few RCT subjects and the possibility of spurious observed differences between interventions.

We performed a probabilistic sensitivity analysis, where model parameters were simultaneously varied over distributions (54). Distributions for parameters were chosen based on the level of certainty and the characteristics of the parameter range: beta or triangular distributions were assigned for probabilities; log normal, triangular, or uniform distributions were assigned for costs; and normal or uniform distributions were chosen for utilities. A value from each parameter's probability distribution was randomly selected during each of 10,000 Monte Carlo iterations, and then these values were used to compute strategy cost-effectiveness for each iteration. We used the cost-effectiveness acceptability curve (55) to summarize probabilistic sensitivity analysis results, showing the likelihood that a given strategy would be favored for a given willingness-to-pay threshold (56). A willingness-to-pay (or acceptability) threshold is the maximum amount that society is willing to pay for an incremental gain in health (56). Although there is no absolute threshold, Braithwaite and colleagues (57) argue that a plausible range of society's willingness-to-pay for incremental cost-effectiveness of modern health care may be $100,000 per QALY or more.

7.4 RESULTS

Base-Case Analysis

Table 7.5 summarizes clinical outcome and cost-effectiveness analysis results. Generally, clinical outcomes were most favorable for the CCM strategy, intermediate for the UC strategy, and worst for the PROV strategy. Compared to PROV, the CCM increased QALE by 0.0793 QALYs and reduced the cumulative incidence of diabetes with microvascular complications by an absolute 36.4 percentage points, diabetes with macrovascular complications by an absolute

19.8 percentage points, and diabetes with either microvascular or macrovascular complications by an absolute 41.3 percentage points (results do not sum due to portions of the cohort having both microvascular and macrovascular complications). Compared to UC, the CCM increased QALE by 0.0162 QALYs and reduced the cumulative incidence of diabetes with either microvascular or macrovascular complications by an absolute 3.9 percentage points.

Over a 3-year time horizon of the model, the UC cost least ($10,795), while PROV cost most ($12,427). The PROV produced the lowest QALE (1.7294 QALYs), while CCM produced the greatest (1.8087 QALYs). Compared to UC, the CCM cost $1,140 more over 3 years and produced a gain of 0.0162 QALYs, resulting in an ICER of $70,317 per QALY gained. Compared to UC, the PROV cost an additional $1,633 but produced 0.0631 fewer QALYs, and thus was dominated (more expensive and less effective) by UC. Finally, compared to PROV, the CCM cost $493 less but produced a gain of 0.0793 QALYs, and was thus cost-saving relative to PROV.

For microvascular complications alone, the CCM cost $2,714 per microvascular complication averted compared to UC, and was cheaper and more effective than PROV. For macrovascular complications alone, UC was more effective and less costly than the other strategies. When considering either microvascular or macrovascular complications, the CCM again dominated PROV and cost slightly less than $30,000 per complication averted compared to UC.

Sensitivity Analyses

We performed one-way sensitivity analyses to assess the effect of individual variation of parameter values on model results. Parameter values were varied as shown in Tables 7.2-7.4.

Sensitive parameters were identified, whose variation resulted in an ICER higher than $100,000/QALY, with threshold values (i.e., values for those parameters where results were >$100,000/QALY) listed in Table 7.6. Cost parameters had relatively greater differences between the base-case value and threshold values. Results were sensitive to more subtle variation of diabetes complication utilities and to strategy-specific probabilities of complication onset and treatment intensification.

Over a 10-year time horizon, the CCM compared to UC cost $42,179 per QALY gained from a health care system perspective and $113,280 per QALY gained from a societal perspective (Table 7.5, bottom) under the base-case assumption of no mortality difference between intervention strategies. If we hypothesized an 1% per year absolute mortality reduction with the CCM over 10 years, the CCM cost $14,164 per QALY gained from a health care system perspective and $32,028 per QALY gained from a societal perspective (data not shown). Finally, given the possibility of little or no complication rate differences between intervention strategies in the small RCT, we examined the cost-effectiveness of intervention strategies if no differences in either micro- or macrovascular complications existed between intervention strategies. In this analysis, the CCM cost $61,288 per QALY gained when identical microvascular complication rates among strategies were assumed and $256,481 per QALY gained when identical macrovascular complication rates (data not shown), suggesting that much of the CCM's effect was due to modification of macrovascular complication rates.

When parameter values were simultaneously varied over their corresponding probability distributions in the probabilistic sensitivity analysis, the PROV was unlikely to be favored over CCM or UC (Figure 7.2). Using a willingness-to-pay threshold of $50,000/QALY, the CCM was

favored in 45% of model iterations (compared to 50% for UC and 5% for PROV); with a $100,000/QALY threshold, the CCM was favored in 51%.

7.5 DISCUSSION

Health care organizations seeking to reform their practices in accord with the CCM must expend considerable resources. Although available evidence suggests that such a transformation can lead to improved patient care and outcomes, the impact on health care costs and revenues remains uncertain and probably varies by condition (17). Furthermore, health care providers and payers have become increasingly interested in understanding how to improve care and how to pay for it; hence, cost-effectiveness analysis from a health care system perspective is particularly compelling. To our knowledge, our study is the first to determine the cost-effectiveness of implementing the full CCM for diabetes care based on data from a community-based RCT. From the perspective of a health care system over 3 years, the CCM cost about $70,500/QALY compared to UC. Both CCM and UC were cost-saving relative to the PROV (the traditional approach to health care improvements). Over 10 years, the CCM was further more cost-effective from the health care system perspective, costing about $42,200/QALY compared to UC.

Knowledge about quality improvement via the CCM for diabetes care is still nascent; few studies available in the literature document its consequences and cost-effectiveness (34,58-64). Some evidence suggests that improved glycemic control reduces total health care costs for people with diabetes and higher A1C levels (58,59), and that intensive blood pressure control for people with diabetes and hypertension is a cost-saving intervention (50,65). In addition, Gilmer et al. confirm that interventions focusing on clinical meetings to discuss patient care problems

and registries for diabetes care are associated with lower future costs (60), and those involving disease management programs, clinical management, and self-management training for diabetes management are considered to be cost-effective (61).

One of the most thorough CCM cost-effectiveness studies was recently published by Huang et al, comparing the costs of implementing the CCM to the benefits of improved health outcomes in people with diabetes in US federally qualified community health centers (63). They found that reduced risk of blindness, ESRD, and coronary artery disease cost $33,386/QALY. Compared to that study, our estimate of the CCM's cost-effectiveness over 10 years from the societal perspective, $113,280/QALY, is higher. This discrepancy is likely due to a number of differences between models: our patient cohort was older (68 vs. 54), less racially diverse, and transitioned through a model where a variety of assumptions were made to bias against the CCM (see below). Despite this, both studies found that community-based efforts to implement the CCM were economically reasonable, although our 10-year societal perspective results touch on the border of generally accepted willingness-to-pay thresholds for modern health care today (57). Furthermore, our work includes data from a RCT rather than pre-and-post comparisons, evaluates cost-effectiveness for implementing all six CCM elements for diabetes care, and compares a CCM-based intervention to other plausible strategies.

Pay-for-performance contracts in diabetes care, where physician reimbursement is tied to diabetes treatment guideline adherence, are increasingly being viewed as a viable and desirable option by Medicare and private insurers (66). National efforts encourage and will eventually mandate adherence to quality of care standards for certain types of reimbursement. Undoubtedly, quantifying the cost of implementing quality improvement efforts is important for staffing and patient access plans. Our analyses provide the first comprehensive attempt to

quantify the cost and effectiveness of full CCM implementation in a community setting. Using common metrics, economic evaluations can estimate the relative value of various interventions. Rather than depending on long-term, expensive trials, this information can often be supplied via a computational modeling approach, which provides a feasible and reasonable means to evaluate the cost-effectiveness of interventions for type 2 diabetes that produce benefits years or even decades after the interventions begin. These evaluation results will provide information for health care policy makers as they decide whether to adopt the interventions.

Like all modeling efforts (67), the computational model developed here has several limitations. First, subjects in the RCT were representative of the population with diabetes in an underserved urban community, and thus extrapolation to other populations or health care settings requires caution. Second, we restricted our long-term predictions about costs, quality of life, and clinical outcomes to 3 and 10 years since we employed the empirically observed data on complications directly from the RCT with 12-month follow-up data. Indeed, to have longer length of simulated follow-up and more robust predicted rates of complications, we would consider using one of the publicly available epidemiological models of diabetes complications which would allow accounting for improvements in intermediate risk factors attributable to the CCM. Third, because of this short-term follow-up period, mortality was rare in the RCT. For this reason, we conservatively assumed identical mortality for all three intervention strategies, perhaps biasing the model against the CCM since evidence suggests reduced mortality with the CCM (17,68,69). Similarly, applying the same incidence of ESRD to all three intervention strategies biases our model against the CCM, which has the potential to reduce lifetime incidence of ESRD (17,63). In a sensitivity analysis, assuming identical macrovascular complication incidence rates among intervention strategies significantly worsened the CCM's cost-

effectiveness, again possibly biasing against the CCM given its evidence of improved outcomes. Fourth, due to lack of utility data, we applied the same literature-based utility weights to all three intervention strategies. Again, this is a conservative response that may underestimate the CCM's potential to improve quality of life (36,37,70).

The provision of usual care, as anticipated, costs less than facilitating more comprehensive approaches, such as provider continuing medical education or a comprehensive six-element CCM intervention. More surprising, however, the conventional approach used most widely for improving health care – provider continuing medical education – incurred greater costs than the CCM but yielded fewer benefits in terms of QALYs. Unfortunately, for a variety of reasons, quality improvement efforts have been directed to improving provider knowledge. Evidence demonstrates that improvements in patient knowledge do not necessarily translate into effective patient behavior change (71,72), and, apparently, this lesson may also apply to health care providers. Recently, a systematic review and meta-analysis report also provided evidence that compared with usual care, the quality improvement strategies solely targeting health care providers (e.g., clinician education, clinician reminders, or audit and feedback) did not seem to be beneficial for reduction in intermediate outcomes for diabetes control (i.e., A1C, LDL cholesterol, or systolic and diastolic blood pressure) (73). Indeed, our findings raise questions about these traditional quality improvement efforts for diabetes management and reaffirm the need for health systems to explore innovative new approaches beyond provider education.

Status quo is not an option; reforms at the delivery system level are imperative to address significant lapses in quality of care as well as the high and rapidly increasing cost of care (74,75). A recent systematic review provides evidence that CCM is effective in improving the health of people who have diabetes and receive care in the US primary care settings (76).

American Diabetes Association (ADA) suggests that collaborative, multidisciplinary teams are best suited to provide such care for people with chronic conditions such as diabetes and to facilitate patients' performance of appropriate self-management (77). Specifically, ADA recommends that diabetes care should be aligned with components of the CCM to ensure productive interactions between a prepared proactive practice team and an informed activated patient (77). Furthermore, one of the most important tools to slow the growth of health care expenditures is providing reliable information regarding the cost-effectiveness of alternative interventions. Such information, especially when combined with appropriate incentives and improved access to supporting technology and nonphysician personnel, can slow the growth of health care spending (78). Although further work is needed in examining the costs associated with these types of multifaceted interventions, this report adds supporting evidence that not only is the CCM effective in improving practice and patient outcomes, it is also an economically reasonable approach to diabetes care.

7.6 LITERATURE CITED

1. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. http://www.cdc.gov/diabetes/pubs/factsheet07.htm; Accessed May 16, 2009.
2. Centers for Disease Control and Prevention. State-specific incidence of diabetes among adults-participating states, 1995-1997 and 2005-2007. MMWR. 2008;57(43):1169-1173.
3. Engelgau MM, Geiss LS, Saaddine JB, et al. The evolving diabetes burden in the United States. Ann Intern Med. 2004;140(11):945-950.
4. Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. Diabetes Care. 2006;29(9):2114-2116.
5. Hogan P, Dall T, Nikolov P; American Diabetes Association. Economic costs of diabetes in the US in 2002. Diabetes Care. 2003;26(3):917-932.
6. Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994-2007. Arch Intern Med. 2008;168(19):2088-2094.
7. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. Diabetes Care. 2008;31(3):596-615.
8. American Diabetes Association. Standards of medical care in diabetes-2009. Diabetes Care. 2009;32(suppl 1):S13-S61.
9. Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2

diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32(1):193-203.

10. Zgibor JC, Rao H, Wesche-Thobaben J, Gallagher N, McWilliams J, Korytkowski MT. Improving the quality of diabetes care in primary care practice. J Healthc Qual. 2004;26(4):14-21.

11. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA. 2004;291(3):335-342.

12. Grant RW, Buse JB, Meigs JB; University HealthSystem Consortium (UHC) Diabetes Benchmarking Project Team. Quality of diabetes care in U.S. academic medical centers: low rates of medical regimen change. Diabetes Care. 2005;28(2):337-342.

13. McFarlane SI, Jacober SJ, Winer N, et al. Control of cardiovascular risk factors in participants with diabetes and hypertension at urban academic medical centers. Diabetes Care. 2002;25(4):718-723.

14. Kemp TM, Barr EL, Zimmet PZ, et al. Glucose, lipid, and blood pressure control in Australian adults with type 2 diabetes: the 1999-2000 AusDiab. Diabetes Care. 2005;28(6):1490-1492.

15. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? Eff Clin Pract. 1998;1(1):2-4.

16. Si D, Bailie R, Weeramanthri T. Effectiveness of chronic care model-oriented interventions to improve quality of diabetes care: a systematic review. Prim Health Care Res Dev. 2008;9(1):25-40.

17. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the chronic care model in the new millennium. Health Aff (Millwood). 2009;28(1):75-85.

18. Warm EJ. Diabetes and the chronic care model: a review. Curr Diabetes Rev. 2007;3(4):219-225.

19. Wagner EH, Grothaus LC, Sandhu N, et al. Chronic care clinics for diabetes in primary care: a system-wide randomized trial. Diabetes Care. 2001;24(4):695-700.

20. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288(14):1775-1779.

21. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. JAMA. 2002;288(15):1909-1914.

22. Siminerio L, Zgibor J, Solano FX. Implementing the chronic care model for improvements in diabetes practice and outcomes in primary care: the University of Pittsburgh Medical Center experience. Clin Diabetes. 2004;22(2):54-58.

23. Siminerio LM, Piatt G, Zgibor JC. Implementing the chronic care model for improvements in diabetes care and education in a rural primary care practice. Diabetes Educ. 2005;31(2):225-234.

24. Siminerio LM, Piatt GA, Emerson S, et al. Deploying the chronic care model to implement and sustain diabetes self-management training programs. Diabetes Educ. 2006;32(2):253-260.

25. Piatt GA, Orchard TJ, Emerson S, et al. Translating the chronic care model into the community: results from a randomized controlled trial of a multifaceted diabetes care intervention. Diabetes Care. 2006;29(4):811-817.

26. Piatt GA, Zgibor JC. Novel approaches to diabetes care: a population perspective. Curr Opin Endocrinol Diabetes Obes. 2007;14(2):158-165.

27. Siminerio LM, Drab SR, Gabbay RA, et al. Diabetes educators: implementing the chronic care model. AADE Position Statement. Diabetes Educ. 2008;34(3):451-456.

28. Chin MH, Cook S, Drum ML, et al; Midwest cluster health disparities collaborative. Improving diabetes care in midwest community health centers with the health disparities collaborative. Diabetes Care. 2004;27(1):2-8.

29. Landon BE, Hicks LS, O'Malley AJ, et al. Improving the management of chronic disease at community health centers. N Engl J Med. 2007;356(9):921-934.

30. Chin MH, Drum ML, Guillen M, et al. Improving and sustaining diabetes care in community health centers with the health disparities collaboratives. Med Care. 2007;45(12):1135-1143.

31. Battersby MW. Health reform through coordinated care: SA HealthPlus. BMJ. 2005;330(7492):662-665.

32. Olivarius NF, Beck-Nielsen H, Andreasen AH, Hørder M, Pedersen PA. Randomised controlled trial of structured personal care of type 2 diabetes mellitus. BMJ. 2001;323(7319):970-975.

33. Hiss RG, Armbruster BA, Gillard ML, McClure LA. Nurse care manager collaboration with community-based physicians providing diabetes care: a randomized controlled trial. Diabetes Educ. 2007;33(3):493-502.

34. Smith SA, Shah ND, Bryant SC, et al; Evidens Research Group. Chronic care model and shared care in diabetes: randomized trial of an electronic decision support system. Mayo Clin Proc. 2008;83(7):747-757.

35. Peterson KA, Radosevich DM, O'Connor PJ, et al. Improving Diabetes Care in Practice: findings from the TRANSLATE trial. Diabetes Care. 2008;31(12):2238-2243.

36. Hung DY, Glasgow RE, Dickinson LM, et al. The chronic care model and relationships to patient health status and health-related quality of life. Am J Prev Med. 2008;35(suppl 5):S398-S406.

37. Schillinger D, Handley M, Wang F, Hammer H. Effects of self-management support on structure, process, and outcomes among vulnerable patients with diabetes: a three-arm practical clinical trial. Diabetes Care. 2009;32(4):559-566.

38. Shojania KG, Ranji SR, McDonald KM, et al. Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. JAMA. 2006;296(4):427-440.

39. Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5-Working with Markov processes. Med Decis Making. 1997;17(2):152-159.

40. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17(5):479-500.

41. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993;13(4):322-338.

42. Piatt GA. Implementing the chronic care model to improve diabetes care in the community: Translating theory to practice [dissertation]. Pittsburgh, PA: University of Pittsburgh; 2006.

43. United States Renal Data System. Annual Data Report Atlas of End-Stage Renal Disease in the United States, 2008. Minneapolis, MN: USRDS Coordinating Center. http://www.usrds.org/; Accessed May 16, 2009.

44. Arias E. United States life tables, 2004. National Vital Statistics Reports; vol 59, no 9. Hyattsville, MD: National Center for Health Statistics; 2007.

45. Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC. Mortality trends in men and women with diabetes, 1971 to 2000. Ann Intern Med. 2007;147(3):149-155.

46. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-Effectiveness in Health and Medicine. New York: Oxford Univ Pr; 1996.

47. Medicare Fee-for-Service Payment. Baltimore, MD: Centers for Medicare & Medicaid Services; 2009. http://www.cms.hhs.gov/home/medicare.asp; Accessed May 16, 2009.

48. US Bureau of Labor Statistics; 2009. http://www.bls.gov/data/; Accessed May 16, 2009.

49. Thomson Healthcare. Red Book 2008 (Red Book Drug Topics). Montvale, NJ: Thomson Healthcare; 2008.

50. CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA. 2002;287(19):2542-2551.

51. Smith KJ, Cook RL, Ness RB. Cost comparisons between home- and clinic-based testing for sexually transmitted diseases in high-risk young women. Infect Dis Obstet Gynecol. 2007;2007:62467.

52. US Consumer Price Index. NE Washington, DC: US Bureau of Labor Statistics; 2009. http://www.bls.gov/data/; Accessed May 16, 2009.

53. Coffey JT, Brandle M, Zhou H, et al. Valuing health-related quality of life in diabetes. Diabetes Care. 2002;25(12):2238-2243.

54. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making. 1985;5(2):157-177.

55. Löthgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Econ. 2000;9(7):623-630.

56. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making. 1998;18(suppl 2):S68-S80.

57. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care. 2008;46(4):349-356.

58. Wagner EH, Sandhu N, Newton KM, McCulloch DK, Ramsey SD, Grothaus LC. Effect of improved glycemic control on health care costs and utilization. JAMA. 2001;285(2):182-189.

59. Goetzel RZ, Ozminkowski RJ, Villagra VG, Duffy J. Return on investment in disease management: a review. Health Care Financ Rev. 2005;26(4):1-19.

60. Gilmer TP, O'Connor PJ, Rush WA, et al. Impact of office systems and improvement strategies on costs of care for adults with diabetes. Diabetes Care. 2006;29(6):1242-1248.

61. Gilmer T, O'Connor PJ. Cost effectiveness of diabetes mellitus management programs: a health plan perspective. Dis Manage Health Outcomes. 2003;11(7):439-453.

62. Huang ES, Brown SE, Zhang JX, et al. The cost consequences of improving diabetes care: the community health center experience. Jt Comm J Qual Patient Saf. 2008;34(3):138-146.

63. Huang ES, Zhang Q, Brown SE, Drum ML, Meltzer DO, Chin MH. The cost-effectiveness of improving diabetes care in U.S. federally qualified community health centers. Health Serv Res. 2007;42(6 Pt 1):2174-2193; discussion 2294-2323.

64. Gilmer TP, Roze S, Valentine WJ, et al. Cost-effectiveness of diabetes case management for low-income populations. Health Serv Res. 2007;42(5):1943-1959.

65. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):720-726.

66. Leichter SB. Pay-for-performance contracts in diabetes care. Clin Diabetes. 2006;24(2):56-59.

67. Herman WH. Diabetes modeling. Diabetes Care. 2003;26(11):3182-3183.

68. Vargas RB, Mangione CM, Asch S, et al. Can a chronic care model collaborative reduce heart disease risk in patients with diabetes? J Gen Intern Med. 2007;22(2):215-222.

69. Parchman ML, Zeber JE, Romero RR, Pugh JA. Risk of coronary artery disease in type 2 diabetes and the delivery of care consistent with the chronic care model in primary care settings: a STARNet study. Med Care. 2007;45(12):1129-1134.

70. Coleman K, Mattke S, Perrault PJ, Wagner EH. Untangling practice redesign from disease management: how do we best care for the chronically ill? Annu Rev Public Health. 2009;30:385-408.

71. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. Diabetes Care. 2001;24(3):561-587.

72. Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. Diabetes Care. 2002;25(7):1159-1171.

73. Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. Lancet. 2012;379(9833):2252-2261.

74. Rittenhouse DR, Shortell SM. The patient-centered medical home: will it stand the test of health reform? JAMA. 2009;301(19):2038-2040.

75. Oldham J. Achieving large system change in health care. JAMA. 2009;301(9):965-966.

76. Stellefson M, Dipnarine K, Stopka C. The Chronic Care Model and diabetes management in US primary care settings: a systematic review. Prev Chronic Dis. 2013;10:120180. DOI: http://dx.doi.org/10.5888/pcd10.120180

77. American Diabetes Association. Standards of medical care in diabetes-2013. Diabetes Care. 2013;36(Suppl 1):S11-S66.

78. Fuchs VR. Reforming US health care: key considerations for the new administration. JAMA. 2009;301(9):963-964.

7.7 TABLES AND TABLE LEGENDS

Table 7.1 Baseline sociodemographic, clinical, and lifestyle behaviors characteristics of participants by three intervention strategies in the chronic care model randomized controlled trial

Characteristics	CCM (n=30)	PROV (n=38)	UC (n=51)	*P* Value[a]
Demographic characteristics				
Mean age (SD), years	69.7 (10.7)	64.4 (8.9)	68.6 (8.6)	.04
Mean age at diabetes diagnosis (SD), years	60.0 (12.4)	53.1 (12.4)	55.8 (12.6)	.34
Mean duration of diabetes (SD), years	10.3 (8.4)	11.5 (9.0)	13.1 (10.9)	.70
Gender, n (%)				.58
Male	15 (50.0)	15 (39.5)	30 (58.8)	
Female	15 (50.0)	23 (60.5)	21 (41.2)	
Race, n (%)				.54
Non-white	4 (13.3)	1 (2.6)	5 (9.8)	
White	26 (86.7)	37 (97.4)	46 (90.2)	
Mean weight (SD), kg	83.6 (15.3)	91.9 (17.9)	88.3 (17.1)	.45
Mean height (SD), cm	167.3 (10.0)	167.7 (9.9)	171.0 (10.0)	.61
Mean BMI (SD), kg/m^2	29.9 (5.4)	32.7 (5.8)	30.1 (4.4)	.04
Current insulin use, n (%)				.45
Yes	8 (26.7)	16 (42.1)	13 (25.5)	
No	22 (73.3)	22 (57.9)	38 (74.5)	
Education, n (%)				.80
<High school education	15 (50.0)	22 (57.9)	31 (60.8)	
≥High school education	15 (50.0)	16 (42.1)	20 (39.2)	
Income, n (%)				>.95
<$20,000/year	12 (40.0)	19 (50.0)	20 (39.2)	
≥$20,000/year	15 (50.0)	17 (44.7)	25 (49.0)	
Missing	3 (10.0)	2 (5.3)	6 (11.8)	
Clinical characteristics				
Mean A1C (SD), %	7.7 (1.5)	7.5 (1.6)	6.9 (1.3)	.39
Mean systolic blood pressure (SD), mmHg	143.1 (21.0)	142.7 (18.0)	147.5 (28.4)	.87
Mean diastolic blood pressure (SD), mmHg	73.1 (7.7)	78.7 (11.5)	75.8 (9.5)	.30
Mean total cholesterol level (SD), mg/dL	195.7 (49.0)	214.2 (48.0)	192.5 (31.0)	.05
Mean HDLc level (SD), mg/dL	39.3 (10.2)	48.4 (13.4)	43.7 (10.1)	.39
Mean non-HDLc level (SD), mg/dL	156.4 (50.7)	165.8 (50.1)	148.8 (31.3)	.55
Mean LDLc level (SD), mg/dL	103.7 (32.2)	115.9 (44.8)	104.9 (27.6)	.32
Mean triglyceride level (SD), mg/dL	259.7 (189.2)	270.8 (180.2)	239.1 (143.7)	.61
Microalbuminuria , n (%)				
<30 µg/dL	20 (66.7)	27 (71.1)	38 (74.5)	.80
≥30 µg/dL	9 (30.0)	10 (26.3)	12 (23.5)	
Missing	1 (3.3)	1 (2.6)	1 (2.0)	
Lifestyle behaviors				
Currently smoke, n (%)				.92
Yes	2 (6.7)	4 (10.5)	4 (7.8)	
No	27 (90.0)	34 (89.5)	46 (90.2)	
Missing	1 (3.3)	0 (0.0)	1 (2.0)	
Self-monitor blood glucose, n (%)				.79
Yes	24 (80.0)	31 (81.6)	42 (82.4)	
No	6 (20.0)	7 (18.4)	9 (17.6)	
Physician office visits in the past 1 year, n (%)				.88
<2 visits	1 (3.3)	2 (5.3)	3 (5.9)	
≥2 visits	29 (96.7)	36 (94.7)	47 (92.2)	
Missing	0 (0.0)	0 (0.0)	1 (2.0)	

Abbreviations: CCM, chronic care model; PROV, provider continuing medical education; UC, usual care; BMI, body mass index; A1C, glycated hemoglobin; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

[a]The comparisons of all baseline characteristics among three study groups were conducted using the univariate mixed-effects linear regression or mixed-effects logistic regression model that incorporated correlation due to the clustering of patients within practices; however, the random clustering effect was taken out of the models if the clustering variance component was close or equal to zero.

Table 7.2 Probabilities of intensive treatments and disease progression, and the risk of death for the Markov decision model

Parameter	Value		Reference or source
	Base-case analysis	Probabilistic sensitivity analysis distribution	
Probabilities of intensive treatments			
Probability of intensive treatments for glycemia, %			CCM data
CCM	33.64	Beta (5.09 to 73.71)	
PROV	42.96	Beta (12.60 to 76.75)	
UC	40.00	Beta (14.36 to 69.23)	
Probability of intensive treatments for hypertension, %			CCM data
CCM	30.00	Beta (14.68 to 47.66)	
PROV	26.32	Beta (13.65 to 41.49)	
UC	27.45	Beta (16.03 to 40.28)	
Probability of intensive treatments for dyslipidemia, %			CCM data
CCM	5.62	Beta (0.011 to 26.10)	
PROV	2.70	Beta (0.016 to 11.53)	
UC	4.06	Beta (0.121 to 13.66)	
Probabilities of disease progression			
Yearly probability of disease progression in diabetes patients without Any complications, %			CCM data
Remain in the status without any complications			
CCM	80.00	Beta (37.95 to 99.61)	
PROV	42.86	Beta (18.62 to 69.39)	
UC	77.78	Beta (45.13 to 97.43)	
Develop microvascular complications			
CCM	0.00	Triangular (0.00 to 4.00)	
PROV	14.29	Beta (1.40 to 35.07)	
UC	11.11	Beta (0.27 to 21.93)	
Develop macrovascular complications			
CCM	20.00	Triangular (16.00 to 20.00)	
PROV	38.10	Beta (14.54 to 55.03)	
UC	0.00	Triangular (0.00 to 4.44)	
Yearly probability of disease progression in diabetes patients with microvascular complications, %			CCM data
Develop macrovascular complications			
CCM	50.00	Beta (20.50 to 79.63)	
PROV	0.00	Triangular (0.00 to 20.00)	
UC	0.00	Triangular (0.00 to 20.00)	
Yearly probability of disease progression in diabetes patients with macrovascular complications, %			CCM data
Develop microvascular complications			
CCM	14.29	Beta (0.33 to 47.55)	
PROV	0.00	Triangular (0.00 to 20.00)	
UC	50.00	Beta (24.48 to 75.87)	
Yearly probability of developing ESRD in diabetes patients, %	0.4114	Beta (0.3990 to 0.4237)	2008 USRDS Annual Data Report [43]
Risk of death			
Rate ratio of death in people with diabetes compared to those without diabetes	2.31	Not varied	Gregg et al., [45]
Yearly probability of death in diabetes patients with ESRD, %	25.61	Beta (24.76 to 26.47)	2008 USRDS Annual Data Report [43]

Abbreviations: CCM, chronic care model; PROV, provider continuing medical education; UC, usual care; ESRD, end-stage renal disease; USRDS, United States Renal Data System.

Table 7.3 Parameters of costs for the Markov decision model

Parameter	Value		Reference or source
	Base-case analysis	Probabilistic sensitivity analysis distribution	
Direct medical costs			
Added annual health care provider costs per patient for the CCM strategy			
Registered nurse/certified diabetes educator costs, US$	687	Uniform (563 to 819)	CCM data; US Bureau of Labor Statistics [48]
Medical assistant costs, US$	238	Uniform (198 to 279)	
Annual costs of drugs for the intensive treatments, laboratory tests, and physician office visits per patient			
Added costs of drugs for the intensive treatments, US$			2008 Red Book [49]
For glycemia	1,985	Uniform (993 to 2,978)	
For hypertension	681	Uniform (341 to 1,022)	
For dyslipidemia	1,099	Uniform (550 to 1,649)	
Laboratory test costs, US$			CCM data; CMS [47]
During the first year			
CCM	64	Uniform (32 to 96)	
PROV	62	Uniform (31 to 93)	
UC	59	Uniform (30 to 89)	
After the first year			
CCM	56	Uniform (28 to 84)	
PROV	61	Uniform (31 to 92)	
UC	55	Uniform (28 to 83)	
Physician office visit costs, US$			CCM data; CMS [47]
CCM	713	Uniform (561 to 865)	
PROV	389	Uniform (306 to 472)	
UC	629	Uniform (495 to 763)	
One-time and annual costs of complications per patient			
One-time costs, US$			Hoerger et al. [50]
No complications	0	Not varied	
Microvascular complications	1,710	Triangular (263 to 3,158)	
Macrovascular complications	2,932	Log normal (0 to 23,189)	
Microvascular and macrovascular complications	4,642	Log normal (263 to 26,347)	
Annual costs, US$			Hoerger et al. [50]
No complications	0	Not varied	
Microvascular complications	2,280	Triangular (1,140 to 3,420)	
Macrovascular complications	1,199	Log normal (0 to 8,153)	
Microvascular and macrovascular complications	3,479	Log normal (1,140 to 11,573)	
ESRD	77,772	Triangular (38,886 to 116,658)	
One-time costs of death per patient			
Age=65-74 years, US$	11,337	Not varied	Hoerger et al. [50]
Age=75-84 years, US$	10,080	Not varied	
Direct nonmedical costs			
Annual time costs per patient			
Costs for physician office visits, US$			CCM data; US Bureau of Labor Statistics [48]; Smith et al. [51]
CCM	666	Not varied	
PROV	364	Not varied	
UC	588	Not varied	
Costs for DSMT sessions for the CCM strategy, US$	263	Not varied	
Costs for support groups sessions for the CCM strategy, US$	168	Not varied	
Costs for POSE sessions for the CCM strategy, US$	70	Not varied	
Annual monetary costs per patient			
Costs for physician office visits, US$			CCM data; US Bureau of Labor Statistics [48]; Smith et al. [51]
CCM	36	Not varied	
PROV	20	Not varied	
UC	32	Not varied	
Costs for DSMT sessions for the CCM strategy, US$	14	Not varied	
Costs for support groups sessions for the CCM strategy, US$	12	Not varied	
Costs for POSE sessions for the CCM strategy, US$	8	Not varied	

Abbreviations: CCM, chronic care model; PROV, provider continuing medical education; UC, usual care; ESRD, end-stage renal disease; CMS, Centers for Medicare and Medicaid Services; DSMT, diabetes self-management training; POSE, point-of-service-education.

Table 7.4 Parameters of health utilities and discount rates for the Markov decision model

Parameter	Value		Reference or source
	Base-case analysis	Probabilistic sensitivity analysis distribution	
Health utilities			
Diabetes without complications	0.689	Normal (0.662 to 0.716)	Coffey et al. [53]
Diabetes with microvascular complications	0.599	Uniform (0.519 to 0.678)	
Diabetes with macrovascular complications	0.615	Uniform (0.584 to 0.645)	
Diabetes with microvascular and macrovascular complications	0.599	Uniform (0.519 to 0.678)	
Diabetes with end-stage renal disease	0.611	Normal (0.560 to 0.662)	
Discount rates			
Discount rate applied to costs, %	3.00	(2.00 to 5.00)[a]	Assumed
Discount rate applied to quality-adjusted life-expectancy, %	3.00	(2.00 to 5.00)[a]	Assumed

[a](a to b)=(minimum to maximum). This parameter was not varied in the probabilistic sensitivity analysis.

Table 7.5 Incremental cost-effectiveness by interventions from base-case analysis and sensitivity analyses: Simulated economic and clinical outcomes in the chronic care model randomized controlled trial cohort

Cost-effectiveness analysis	Study group	Cost (US$)	Effectiveness	ICER
3 years, health care system perspective				
Cost vs. Quality-adjusted life-expectancy	UC	$10,795	1.7925 QALY	-
	CCM	$11,935	1.8087 QALY	70,317
	PROV	$12,427	1.7294 QALY	Dominated
Cost vs. Cumulative incidence of diabetes with microvascular complications	UC	$10,795	48.7%	-
	CCM	$11,935	6.72%	2,714
	PROV	$12,427	43.1%	Dominated
Cost vs. Cumulative incidence of diabetes with macrovascular complications	UC	$10,795	24.4%	-
	CCM	$11,935	44.9%	Dominated
	PROV	$12,427	64.7%	Dominated
Cost vs. diabetes with either microvascular or macrovascular complications	UC	$10,795	48.7%	-
	CCM	$11,935	44.9%	29,573
	PROV	$12,427	86.2%	Dominated
10 years, health care system perspective				
Cost vs. Quality-adjusted life-expectancy	PROV	$34,808	4.2498 QALY	-
	UC	$35,295	4.3645 QALY	4,247
	CCM	$37,800	4.4239 QALY	42,179
10 years, societal perspective				
Cost vs. Quality-adjusted life-expectancy	PROV	$37,437	4.2498 QALY	-
	UC	$39,539	4.3645 QALY	18,334
	CCM	$46,267	4.4239 QALY	113,280

Abbreviations: ICER, incremental cost-effectiveness ratio; CCM, chronic care model; PROV, provider continuing medical education; UC, usual care; QALY, quality-adjusted life-year.

Table 7.6 One-way sensitivity analyses of the chronic care model strategy compared to the usual care strategy for incremental cost-effectiveness thresholds >$100,000 per quality-adjusted life-year gained

Parameter	Base-case value	Threshold value
Probabilities, %		
Probability of intensive treatments for glycemia in CCM	33.64	>42.61
Probability of intensive treatments for glycemia in UC	40.00	<31.03
Probability of intensive treatments for dyslipidemia in CCM	5.62	>21.82
Yearly probability of CCM patients with macrovascular complications developing microvascular complications	14.29	>37.99
Yearly probability of CCM patients without complications developing macrovascular complications	20.00	<16.90
Yearly probability of UC patients without complications developing macrovascular complications	0.00	>8.15
Yearly probability of CCM patients without complications developing microvascular complications	0.00	>5.42
Yearly probability of UC patients without complications developing microvascular complications	11.11	>15.75
Costs, US$		
Annual costs of micro- and macrovascular complications	3,479	<1,993
One-time costs of micro- and macrovascular complications	4,642	<2,620
Annual costs of macrovascular complications	1,199	>1,956
One-time costs of macrovascular complications	2,932	>4,030
Utilities		
Utility for diabetes with micro- and macrovascular complications	0.599	>0.613
Utility for diabetes with macrovascular complications	0.615	<0.608
Utility for diabetes with microvascular complications	0.599	>0.611

Abbreviations: CCM, chronic care model; UC, usual care.

7.8 FIGURES

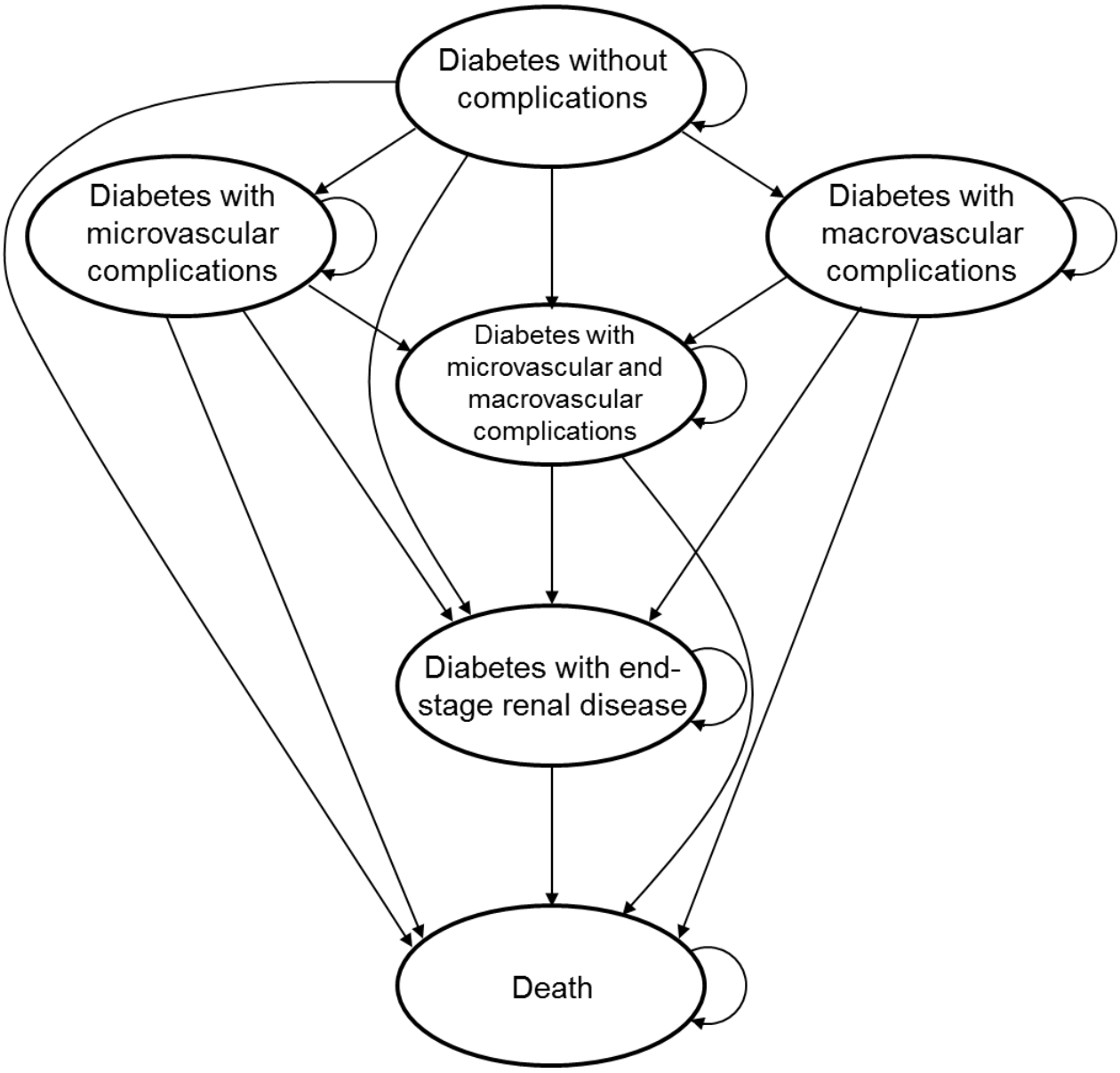

Figure 7.1 Markov-state diagram for the basic model structure

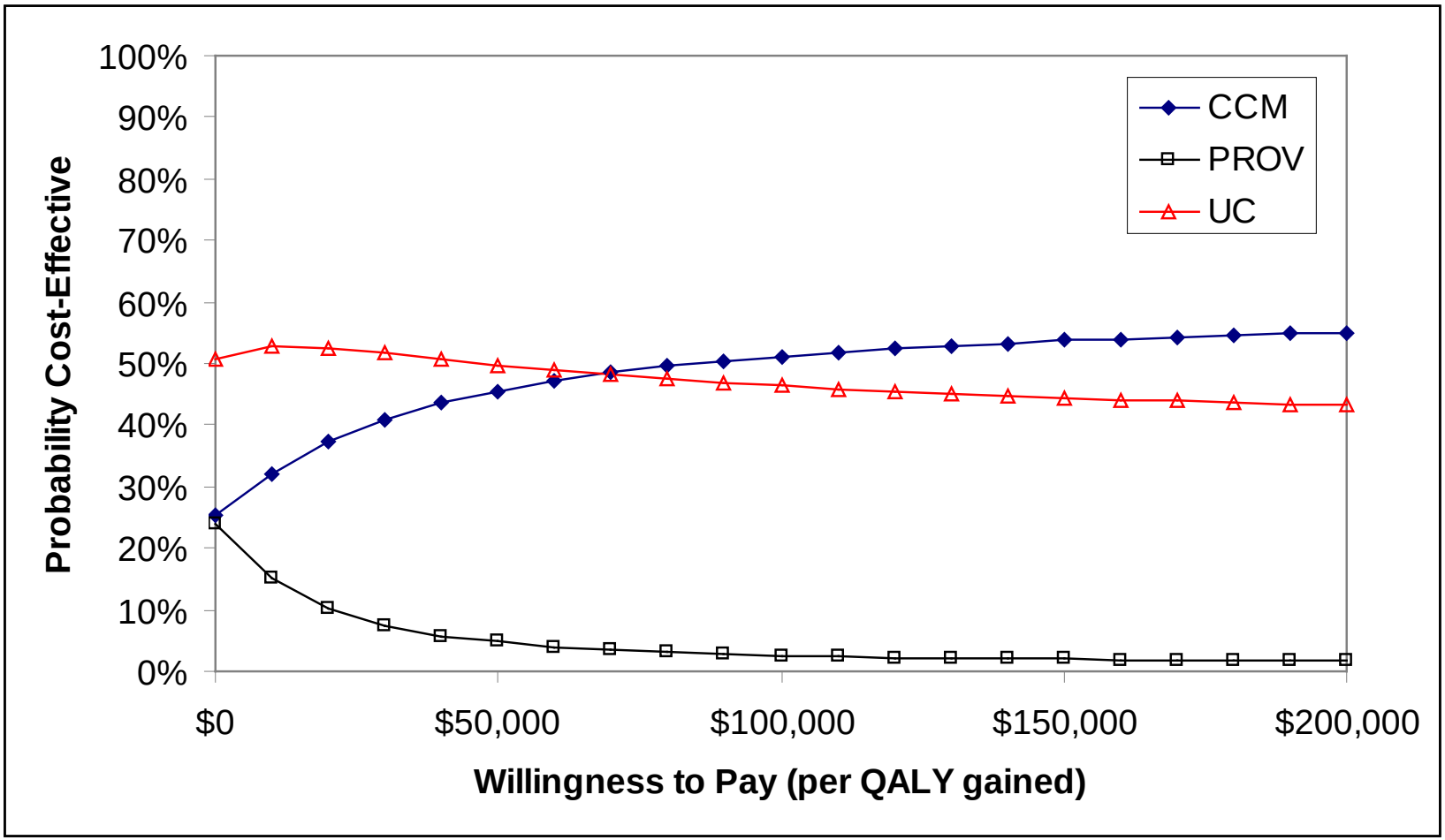

Figure 7.2 Probabilistic (second-order Monte Carlo) sensitivity analysis among all three intervention strategies

7.9 FIGURE LEGENDS

Figure 7.1 Markov-state diagram for the basic model structure

Ovals indicate health states. Subjects may remain within a health state (short curved arrow) or may move to a different health state (straight arrow or long curved arrow).

Figure 7.2 Probabilistic (second-order Monte Carlo) sensitivity analysis among all three intervention strategies

The acceptability curve depicts the likelihood of an intervention strategy being favored for a given cost-effective threshold (willingness-to-pay). CCM, PROV, and UC indicate chronic care model, provider continuing medical education, and usual care respectively. QALY indicates quality-adjusted life-year.

8.0 MANUSCRIPT 2: COST-EFFECTIVENESS OF IMPLEMENTING THE CHRONIC CARE MODEL FOR DIABETES CARE IN A MILITARY POPULATION

Shihchen Kuo, RPh, MSCP[1]
Cindy L. Bryce, PhD[2]
Janice C. Zgibor, RPh, PhD[1]
Donna L. Wolf, PhD[3]
Mark S. Roberts, MD, MPP[2]
Kenneth J. Smith, MD, MS[4]

[1]Department of Epidemiology
University of Pittsburgh, Pittsburgh, PA

[2]Department of Health Policy and Management
University of Pittsburgh, Pittsburgh, PA

[3]Department of Exercise and Rehabilitative Sciences
Slippery Rock University, Slippery Rock, PA

[4]Section of Decision Sciences and Clinical Systems Modeling
University of Pittsburgh, Pittsburgh, PA

This manuscript has been published in *Journal of Diabetes Science and Technology*:
Kuo S, Bryce CL, Zgibor JC, Wolf DL, Roberts MS, Smith KJ. Cost-effectiveness of implementing the chronic care model for diabetes care in a military population.
J Diabetes Sci Technol 2011;5:501-513.

8.1 ABSTRACT

Background: Applying the Chronic Care Model (CCM) for diabetes management helps improve health outcomes and patient care. The CCM was implemented at US Air Force Wilford Hall Medical Center through the Diabetes Outreach Clinic (DOC) in 2006, but its cost-effectiveness in this setting is unknown.

Methods: We constructed a Markov decision model to estimate DOC cost-effectiveness compared to usual care (UC) over a 20-year period. Based on empirical, post-intervention demographic and clinical data, we applied UKPDS risk equations to predict long-term probabilities of developing micro- or macrovascular complications. Health care system and societal perspectives were considered, discounting costs and benefits at 3% annually. Intervention costs and outcomes were obtained from military data, while other costs, disease progression data, and utilities were drawn from published literature.

Results: From a health care system perspective, the DOC cost $45,495 per quality-adjusted life-year (QALY) compared to UC; from a societal perspective, the DOC compared to UC cost $42,051/QALY (when the model started with the uncomplicated diabetes cohort), $61,243/QALY (when starting with the DOC cohort), or $61,813/QALY (when starting with the UC cohort). In one-way sensitivity analyses, results were most sensitive to yearly costs for specialty care visits. In probabilistic sensitivity analysis, the DOC was favored in 51% of model iterations using an acceptability threshold of $50,000/QALY and in 72% at a threshold of $100,000/QALY.

Conclusions: The DOC strategy for diabetes care, performed with the CCM methodology in a military population, appears to be economically reasonable compared to UC.

8.2 INTRODUCTION

Diabetes is a major cause of morbidity and mortality in the US, resulting in substantial human and economic costs (1-3). Diabetes management is complicated, requiring continuous patient involvement and the assistance of a team of health care professionals (4,5). Despite the availability of effective medications and evidence-based practice recommendations (5,6), most diabetic patients do not achieve therapeutic goals, and significant opportunities remain to improve diabetes management (7-9). Moreover, broad variations persist in the quality of diabetes care across both health care providers and practice settings (5).

The Chronic Care Model (CCM) (10), a multifaceted framework to redesign daily medical practices and enhance health care delivery, is used in many health care settings to guide systematic and individual improvements in chronic illness management, including diabetes (4,11-14). The premise of the CCM is that quality care is not delivered in isolation but that each of the CCM elements works in tandem (15). Six key elements are identified by the CCM, including four interdependent elements at the practice level (self-management support, decision support, delivery system design, and clinical information systems); a higher-level element (organizations of health care) at the health systems, which plays an overarching role in guiding practice-level development; and a broader-level element (linkages of resources and policies) at the community, which provides necessary resources and establishes policies linked to chronic illness care (12,15-18). Previous studies show that CCM-based diabetes interventions improve patient outcomes, including better processes of care (e.g., diabetic foot examinations and glycated hemoglobin [A1C] checks) and intermediate outcomes (e.g., A1C, blood pressure, and lipids), reduced risk for cardiovascular events, and higher health status and health-related quality

of life (4,11-16,19-35). However, little is known about the cost-effectiveness of implementing the CCM for diabetes care.

Through its TRICARE program, the US Department of Defense Military Health System (MHS) is one of the largest providers of health care in the US, providing care to approximately 9.5 million beneficiaries at an annual cost of $48.5 billion (FY 2010) (36). Diabetes is a critical issue for the MHS, with a prevalence of 5% among MHS enrollees and even greater prevalence rates in overweight (8-11%) and obese (16-37%) retirees and their dependents (37-42). The total annual cost of TRICARE beneficiaries aged 20-65 years with diagnosed diabetes was approximately $300 million in 2006; the average additional medical cost per beneficiary diagnosed with diabetes was $2,150 annually (43,44).

In an effort to improve outcomes and reduce the costs associated with diabetes, the US Air Force Wilford Hall Medical Center (WHMC) implemented the CCM in 2006 through the Diabetes Outreach Clinic (DOC), which restructured health care for diabetic beneficiaries by delivering services through a single, centralized location. Our analysis aimed to estimate the costs, clinical outcomes, and cost-effectiveness of implementing the CCM for diabetes care in this military setting.

8.3 METHODS

The Diabetes Outreach Clinic at Wilford Hall Medical Center

The DOC operated during the calendar years 2006-2008 at WHMC. It was operating as a "one-stop-shop" for diabetic patients, which allowed patients to obtain comprehensive care with

one visit. The DOC staff consisted of an endocrinologist, nurse practitioner, counselor, ophthalmologist, dietitian, certified diabetes educator, and support staff. Diabetic patients were seen for both diabetes-related treatments and routine primary care in DOC.

The population for these analyses included individuals with an ICD-9-CM diagnosis of diabetes (250.xx) receiving care in the WHMC San Antonio area between January 2005 and December 2008. A total of 9,654 diabetic patients, including 1,171 DOC patients and 8,483 usual care (UC) patients, from the military Population Health database were identified. Administrative data included demographics, clinical data (e.g., A1C, blood pressure, and lipids), medical utilization (e.g., primary and specialty care visits), and pharmacy records. For DOC patients, we defined the records from one year prior to DOC entry as pre-DOC data (or baseline), and all records after DOC entry as post-DOC data (or follow-up); for UC patients, we defined the records from one year prior to January 2006 (i.e., DOC starting date) as baseline data, and all records after that time as follow-up data. A total of 249 patients less than 18 years of age were excluded, and thus the study cohort in this analysis comprised 9,405 diabetic patients (or 97.4% of the original population), including 1,171 DOC and 8,234 UC patients (**Table 8.5**).

The Framework of a Markov Decision Model

Using TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA), we modified a prior Markov decision model (45) to estimate the incremental cost-effectiveness of DOC compared to UC. The model directly incorporated intervention costs and effectiveness from military data to estimate life expectancy, quality-adjusted life-expectancy (expressed as quality-adjusted life-years, or QALYs), clinical outcomes, as well as direct medical and nonmedical

costs associated with DOC and UC. Our base case model examined 50-year-olds with type 2 diabetes who participated in DOC or UC in yearly cycles over a 20-year time horizon from the health care system perspective. Future costs and benefits were discounted at 3% annually (46), and the US Consumer Price Index (47) was used to convert all monetary costs to 2010 US dollars.

Basic Model Structure

The model is illustrated in **Figure 8.1**, which describes the progression of disease through microvascular complications, macrovascular complications, and mortality. In this model, all patients were assumed to have uncomplicated diabetes at the start of the model. Over time, diabetes could progress to microvascular complications (including retinopathy, nephropathy, or neuropathy), macrovascular complications (including coronary heart disease or stroke), or both. Complications were assumed to be irreversible. To be conservative, DOC and UC were assumed to have identical effects on the progression of disease in patients who already had diabetes complications, thus implying that the model only examined differences between strategies in delaying or preventing the development of complications.

In the model, cost-effectiveness was estimated over a 20-year period following the intervention period, assuming that treatments continued for the duration. The United Kingdom Prospective Diabetes Study (UKPDS) risk equations were applied to predict treatment effects, i.e. long-term probabilities of developing microvascular (48-50) and macrovascular (51-53) complications, using empirical, post-intervention demographic and clinical data in those diabetic patients who were alive and without diabetes complications at study end. Among 9,405 diabetic

patients, 1,417 diabetic patients who fulfilled these criteria were identified (196 DOC and 1,221 UC patients; **Table 8.6**). **Table 8.1** summarizes the parameters applied in the UKPDS risk equations and the Markov decision model.

Model input parameters are shown in **Tables 8.2-8.3** and **Tables 8.7-8.11**. Probabilities of death and of micro- or macrovascular complications were predicted using the UKPDS risk equations and/or derived from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation study (54) (**Tables 8.7-8.10**).

Annual direct medical costs related to health care providers, laboratory tests, physician office visits, diabetes complications, death, and medications were included in the model (**Table 8.2** and **Table 8.11**). Indirect costs were not included, assuming their capture in the assessment of QALYs, per the recommendation of the Panel on Cost-Effectiveness in Health and Medicine (46). Medicare reimbursement data were used to estimate costs of laboratory tests (A1C and lipid panel) and physician office visits (55). Hourly wage costs for health care providers in both DOC and UC were based on National Occupational Employment and Wage Estimates (56). One-time and annual costs of diabetes complications, one-time costs of death, as well as medication costs for diabetes, hypertension, and cholesterol control were based on data from the models developed by the Centers for Disease Control and Prevention and Research Triangle Institute International (57).

In analyses from the societal perspective, both direct medical and nonmedical costs were included. Direct nonmedical costs included patient time and monetary costs for physician office visits, and diabetes education classes/visits (**Table 8.2**). Patient time costs for time missed from work or school to receive care and for time donated by others (e.g., for rides or babysitting) to allow care to occur were quantified based on DOC data or published literature (58) and then

valued according to the average hourly wage of a US nonfarm production worker (56) and the average annual frequency of visits and classes as measured in DOC data. In addition, monetary costs to the patient for expenses such as transportation, parking, and babysitting or childcare were estimated from published literature (58), and then valued based on the average annual frequency of visits and classes as derived from DOC data.

Health utilities are a measure of health-related quality of life, with perfect health=1 and death=0. In a cost-effectiveness analysis, this utility weight for each health state is multiplied by time in that state. As an individual's health changes over time, these products are summed to represent the total number of QALYs (46). To estimate health utilities associated with type 2 diabetes with or without complications, an additive prediction model was applied to estimate health utilities according to demographic, treatment, and complication variables (59). The baseline health utility of 0.689 depicts a nonobese man with type 2 diabetes, who is treated with diet and exercise and has no cardiovascular risk factors, nor any microvascular, neuropathic, or cardiovascular complications (**Table 8.3**).

Sensitivity Analyses

One-way sensitivity analyses were conducted for model parameters (**Table 8.9** and **Tables 8.2-8.3**) to assess the effect of varying parameter estimates within clinically plausible ranges and identify parameters whose variation changed the base case incremental cost-effectiveness ratio (ICER) >20%. Next, the ICER was recalculated using the societal perspective instead of the health care system perspective. Finally, the original assumption that all DOC and UC patients had uncomplicated diabetes at the start of the model was tested by changing initial

proportions of patients in health states to mirror the DOC cohort and then the UC cohort, recalculating cost-effectiveness for each starting cohort from the societal perspective.

A probabilistic sensitivity analysis was performed from the health care system perspective, where model parameters were simultaneously varied over distributions (60). Distributions for parameters were chosen to reflect the level of certainty and the characteristics of the parameter range: beta distribution was assigned for probabilities; uniform, triangular, or log normal distributions for costs; and normal or uniform distributions for utilities. A value from each parameter's probability distribution was randomly selected during each of 10,000 Monte Carlo iterations, and then these values were used to compute the cost-effectiveness among strategies of being studied for each iteration. The cost-effectiveness acceptability curve (61) was used to summarize results, showing the likelihood that a given strategy would be favored for a given acceptability threshold, which is defined as the maximum amount that society is willing to pay for an incremental gain in health (62).

8.4 RESULTS

Over the study period, DOC patients had better glycemic control (from 7.8% to 7.2% vs. from 6.8% to 7.0%) and dyslipidemic control (total cholesterol: 173 mg/dL vs. 184 mg/dL; low-density lipoprotein cholesterol: 93 mg/dL vs. 102 mg/dL), fewer annual primary care visits (2.0 vs. 3.0), and more annual A1C (2.2 vs. 1.7) and lipids (1.7 vs. 1.4) checks compared to UC patients. **Tables 8.5 and 8.6** summarize the observed demographic, clinical, and medical utilization characteristics at baseline and follow-up.

Base Case Analysis

Table 8.4 summarizes the cost-effectiveness results. DOC cost $5,311 more than UC and produced 0.117 more QALYs, resulting in an ICER of $45,495 per QALY over 20 years from the health care system perspective.

Sensitivity Analyses

Figure 8.2 shows the results of one-way sensitivity analyses, where six parameters whose variations changed the base case ICER >20% were identified. Of these, only the yearly cost for specialty care visits in the DOC patients could drive the ICER >$100,000/QALY. Variation of parameters not shown in **Figure 8.2** did not increase the ICER above $50,000/QALY. Analysis from the societal perspective showed that DOC cost $4,909 more than UC and gained 0.117 QALYs, resulting in an ICER of $42,051/QALY over 20 years (**Table 8.4**). Changing the initial proportion of cohorts in the five health states at the start of model to mirror the complication rates of DOC patients and then again of UC patients resulted in ICERs of $61,243/QALY and $61,813/QALY respectively from the societal perspective (**Table 8.4**).

When parameters were simultaneously varied over the distributions in the probabilistic sensitivity analysis, DOC was more likely to be favored with an acceptability threshold >$48,000/QALY (**Figure 8.3**). In addition, at a threshold of $50,000/QALY, DOC was favored in 51% of model iterations; at $100,000/QALY, DOC was favored in 72%.

8.5 DISCUSSION

The CCM is a multifaceted intervention intended to provide effective and comprehensive care for diabetes and other chronic conditions. Although transformation of health care organizations using the CCM must expend considerable resources, in theory their expenditures will be offset downstream with the delay or elimination of diabetes-related complications. In this regard, cost-effectiveness analysis from a health care system perspective may be particularly compelling. Our study showed that, from a health care system perspective over 20 years, the CCM strategy performed through DOC in a military-based setting was quite cost-effective, costing about $45,500/QALY. From a societal perspective, it was even more favorable, with an ICER less than $42,100/QALY.

Diabetes care involves complex interactions among patients, physicians, health care system, and society as a whole, with barriers occurring at every level (11). A major contributor to suboptimal diabetes care is a delivery system that too often is fragmented, lacks clinical information capabilities, duplicates services, and is poorly designed for the delivery of chronic care (5). The American Diabetes Association suggests that the CCM may be well suited to the management of diabetes because it addresses these complex issues, redefines the role of providers, and promotes patient self-management (5,14).

Knowledge on CCM cost-effectiveness in diabetes care is nascent (14); more research is needed to understand the costs and benefits to practices, payers, and patients. We found only one full economic evaluation (63) published by Huang et al (64), comparing CCM implementation costs to the benefits of improved health outcomes in diabetic patients in US federally qualified community health centers. In that study, CCM reduced lifetime risks of

blindness, end-stage renal disease, and coronary artery disease, resulting in an increase in benefits at a cost of $33,386/QALY. Compared to that study, our estimate of CCM cost-effectiveness over 20 years from the societal perspective, $42,051/QALY, is higher. This discrepancy is likely due to a number of differences in models; for instance, our patient cohort was a military population, younger (50 vs. 55 years), less racially diverse, and transitioned through a model where some assumptions were made to bias against the CCM effect (see below). Furthermore, we used costs in 2010 US$ rather than 2004 US$, and included data from a two-group effectiveness study rather than pre-and-post comparisons. Despite these differences, both studies found that implementation of the CCM was economically reasonable and consistent with accepted societal cost-effectiveness thresholds (65).

Cost-saving medical interventions are rare. Most new diabetes treatment strategies are more effective but also more costly, requiring incremental resources per QALY gained (66). There is no absolute cost-effectiveness threshold, and the long-cited benchmark from the literature of $50,000/QALY is unsupported (65,67). A recent analysis (67) argues that a more plausible threshold of society's willingness to pay for modern health care ranges between $100,000 and $300,000 per QALY, which is substantially higher than the traditional threshold.

Health care costs in the US are increasing unsustainably, and efforts to control expenditures should focus on the value of health care interventions, reflecting health benefits that justify their costs (68). High-cost interventions may provide good value when they are highly beneficial. The ICER estimates the additional cost required to obtain additional health benefits and provides a key measure of the value of a health care intervention (68). Based on our analysis, the CCM strategy through DOC in a military-based setting appears to be a good-value care for diabetes, but unfortunately further data on DOC do not exist since it was closed in 2009

due to considerations on military priorities. We recognize that the cost-effectiveness of an intervention should not solely determine its application; at the same time, however, cost-effectiveness should be one of several factors when considering the delivery of high-value, cost-conscious health care (68). Furthermore, the goal of policy should be to preserve the delivery of interventions that do have good value (69).

Like all modeling efforts (70), the computational model developed here has several limitations. First, interpretations of study results are contingent on data quality and model assumptions. Second, subjects in this analysis were representative of the diabetes population in a military community, although they may not be fully generalizable to other populations or health care settings. Third, our effectiveness data were not from a randomized controlled trial, resulting in differences in baseline characteristics, but our analyses adjusted for significant differences in demographics and clinical characteristics at baseline. Fourth, assuming an identical risk of disease progression for DOC and UC patients with diabetes complications was a conservative strategy that potentially biases the model against the CCM effect. Fifth, because there is no empirical utility data, we applied the same literature-based utility weights to both strategies, which again may underestimate the CCM's potential to improve quality of life (13,34,35). Lastly, our base case analysis was assumed to model the cost-effectiveness over a 20-year time frame; however, the base case ICERs over shorter time horizons, e.g. at five years ($189,138/QALY) and ten years ($87,092/QALY), are still below the currently suggested cost-effectiveness thresholds for modern health care (67).

Status quo is not an option; reforms at the delivery system level are imperative to address significant lapses in quality of care as well as the high and rapidly increasing cost of care (71,72). One potentially important tool for slowing the growth of health care expenditures is

reliable information regarding the cost-effectiveness of alternative interventions. Information on the cost-effectiveness of implementing the CCM strategy for diabetes care is just beginning to emerge, and our study adds evidence to document that, compared to UC, the CCM strategy provides greater health benefits at an attractive cost. From the perspective of a health care system or society, the CCM strategy provides good value. When the CCM strategy is used for diabetes care in the military-based setting, not only is it effective in improving patient outcomes, but it is also an economically reasonable, promising investment.

8.6 LITERATURE CITED

1. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
2. Zhang P, Zhang X, Brown J, Vistisen D, Sicree R, Shaw J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87:293-301.
3. Dall TM, Zhang Y, Chen YJ, Quick WW, Yang WG, Fogli J. The economic burden of diabetes. Health Aff (Millwood). 2010;29:297-303.
4. Dancer S, Courtney M. Improving diabetes patient outcomes: framing research into the chronic care model. J Am Acad Nurse Pract. 2010;22:580-5.
5. American Diabetes Association. Standards of medical care in diabetes-2011. Diabetes Care. 2011;34 Suppl 1:S11-61.
6. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193-203.
7. Davidson MB. The effectiveness of nurse- and pharmacist-directed care in diabetes disease management: a narrative review. Curr Diabetes Rev. 2007;3:280-6.

8. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999-2002: the National Health and Nutrition Examination Survey. Diabetes Care. 2006;29:531-7.

9. Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. Am J Med. 2009;122:443-53.

10. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? Eff Clin Pract. 1998;1:2-4.

11. Warm EJ. Diabetes and the chronic care model: a review. Curr Diabetes Rev. 2007;3:219-25.

12. Si D, Bailie R, Weeramanthri T. Effectiveness of chronic care model-oriented interventions to improve quality of diabetes care: a systematic review. Prim Health Care Res Dev. 2008;9:25-40.

13. Coleman K, Mattke S, Perrault PJ, Wagner EH. Untangling practice redesign from disease management: how do we best care for the chronically ill? Annu Rev Public Health. 2009;30:385-408.

14. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the chronic care model in the new millennium. Health Aff (Millwood). 2009;28:75-85.

15. Siminerio LM. The role of technology and the chronic care model. J Diabetes Sci Technol. 2010;4:470-5.

16. Wagner EH, Grothaus LC, Sandhu N, Galvin MS, McGregor M, Artz K, et al. Chronic care clinics for diabetes in primary care: a system-wide randomized trial. Diabetes Care. 2001;24:695-700.

17. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288:1775-9.

18. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. JAMA. 2002;288:1909-14.

19. Siminerio L, Zgibor J, Solano FX. Implementing the chronic care model for improvements in diabetes practice and outcomes in primary care: the University of Pittsburgh Medical Center experience. Clin Diabetes. 2004;22:54-8.

20. Siminerio LM, Piatt G, Zgibor JC. Implementing the chronic care model for improvements in diabetes care and education in a rural primary care practice. Diabetes Educ. 2005;31:225-34.

21. Siminerio LM, Piatt GA, Emerson S, Ruppert K, Saul M, Solano F, et al. Deploying the chronic care model to implement and sustain diabetes self-management training programs. Diabetes Educ. 2006;32:253-60.

22. AADE; Siminerio LM, Drab SR, Gabbay RA, Gold K, McLaughlin S, Piatt GA, et al. Diabetes educators: implementing the chronic care model. Diabetes Educ. 2008;34:451-6.

23. Piatt GA, Orchard TJ, Emerson S, Simmons D, Songer TJ, Brooks MM, et al. Translating the chronic care model into the community: results from a randomized controlled trial of a multifaceted diabetes care intervention. Diabetes Care. 2006;29:811-7.

24. Piatt GA, Zgibor JC. Novel approaches to diabetes care: a population perspective. Curr Opin Endocrinol Diabetes Obes. 2007;14:158-65.

25. Piatt GA, Anderson RM, Brooks MM, Songer T, Siminerio LM, Korytkowski MM, et al. 3-year follow-up of clinical and behavioral improvements following a multifaceted diabetes care intervention: results of a randomized controlled trial. Diabetes Educ. 2010;36:301-9.

26. Chin MH, Cook S, Drum ML, Jin L, Guillen M, Humikowski CA, et al; Midwest cluster health disparities collaborative. Improving diabetes care in midwest community health centers with the health disparities collaborative. Diabetes Care. 2004;27:2-8.

27. Landon BE, Hicks LS, O'Malley AJ, Lieu TA, Keegan T, McNeil BJ, et al. Improving the management of chronic disease at community health centers. N Engl J Med. 2007;356:921-34.

28. Chin MH, Drum ML, Guillen M, Rimington A, Levie JR, Kirchhoff AC, et al. Improving and sustaining diabetes care in community health centers with the health disparities collaboratives. Med Care. 2007;45:1135-43.

29. Battersby MW. Health reform through coordinated care: SA HealthPlus. BMJ. 2005;330:662-5.

30. Olivarius NF, Beck-Nielsen H, Andreasen AH, Hørder M, Pedersen PA. Randomised controlled trial of structured personal care of type 2 diabetes mellitus. BMJ. 2001;323:970-5.

31. Hiss RG, Armbruster BA, Gillard ML, McClure LA. Nurse care manager collaboration with community-based physicians providing diabetes care: a randomized controlled trial. Diabetes Educ. 2007;33:493-502.

32. Smith SA, Shah ND, Bryant SC, Christianson TJ, Bjornsen SS, Giesler PD, et al; Evidens Research Group. Chronic care model and shared care in diabetes: randomized trial of an electronic decision support system. Mayo Clin Proc. 2008;83:747-57.

33. Peterson KA, Radosevich DM, O'Connor PJ, Nyman JA, Prineas RJ, Smith SA, et al. Improving Diabetes Care in Practice: findings from the TRANSLATE trial. Diabetes Care. 2008;31:2238-43.

34. Hung DY, Glasgow RE, Dickinson LM, Froshaug DB, Fernald DH, Balasubramanian BA, et al. The chronic care model and relationships to patient health status and health-related quality of life. Am J Prev Med. 2008;35 Suppl 5:S398-406.

35. Schillinger D, Handley M, Wang F, Hammer H. Effects of self-management support on structure, process, and outcomes among vulnerable patients with diabetes: a three-arm practical clinical trial. Diabetes Care. 2009;32:559-66.

36. TRICARE Management Activity, Health Program Analysis and Evaluation Directorate, in the Office of the Assistant Secretary of Defense (Health Affairs). Evaluation of the TRICARE program: fiscal year 2010 report to Congress [Internet]. Available from: http://www.tricare.mil/tma/downloads/TRICARE201002_28_10v7.pdf. Accessed January 31, 2011.

37. Kress AM, Hartzel MC, Peterson MR. Burden of disease associated with overweight and obesity among U.S. military retirees and their dependents, aged 38-64, 2003. Prev Med. 2005;41:63-9.

38. Gibson TB, Lee TA, Vogeli CS, Hidalgo J, Carls GS, Sredl K, et al. A four-system comparison of patients with chronic illness: the Military Health System, Veterans Health Administration, Medicaid, and commercial plans. Mil Med. 2009;174:936-43.

39. Boyko EJ, Jacobson IG, Smith B, Ryan MA, Hooper TI, Amoroso PJ, et al.; Millennium Cohort Study Team. Risk of diabetes in U.S. military service members in relation to combat deployment and mental health. Diabetes Care. 2010;33:1771-7.

40. Gorham ED, Barrett-Connor E, Highfill-McRoy RM, Mohr SB, Garland CF, Garland FC, et al. Incidence of insulin-requiring diabetes in the US military. Diabetologia. 2009;52:2087-91.

41. Armed Forces Health Surveillance Center. Diabetes mellitus, active component, U.S. Armed Forces, 1997-2007. Medical Surveillance Monthly Report. 2009;16:7-9.

42. Army Medical Surveillance Activity. Incidence of diabetes mellitus among active duty servicemembers, U.S. Armed Forces, 1998. Medical Surveillance Monthly Report. 1999;5:7-9.

43. Navy and Marine Corps Public Health Center, 2009 Research to Practice Fourth Quarter Newsletter. Type 2 diabetes in the military [Internet]. Available from: http://www-nehc.med.navy.mil/downloads/healthyliv/PreventCompLifeManagement/fy09-4qtr_diabetes-military.pdf. Accessed January 31, 2011.

44. Dall TM, Zhang Y, Chen YJ, Wagner RC, Hogan PF, Fagan NK, et al. Cost associated with being overweight and with obesity, high alcohol consumption, and tobacco use within the military health system's TRICARE prime-enrolled population. Am J Health Promot. 2007;22:120-39.

45. Kuo S, Smith KJ, Zgibor JC, Piatt GA, Roberts MS, Bryce CL. Cost-effectiveness of implementing the chronic care model for diabetes care in the community [abstract]. Med Decis Making. 2010;30:NP78.

46. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

47. US Consumer Price Index [Internet]. NE Washington, DC: US Bureau of Labor Statistics; 2011. Available from: http://www.bls.gov/data/. Accessed January 31, 2011.

48. Coleman RL, Stevens RJ, Aldington SJ, Holman RR. Estimating risk of clinically evident retinopathy in type 2 diabetes [abstract]. Diabetes. 2006;55 Suppl 1:A53.

49. Coleman RL, Stevens RJ, Holman RR. Estimating risk of clinically evident neuropathy in type 2 diabetes: a UKPDS risk equation [abstract]. Diabet Med. 2006;23 Suppl 2:51.

50. Coleman RL, Stevens RJ, Holman RR. Incident nephropathy in type 2 diabetes: a UKPDS risk equation [abstract]. Diabetologia. 2005;48 Suppl 1:A32.

51. Stevens RJ, Kothari V, Adler AI, Stratten IM, Holman RR. UKPDS 56: The UKPDS Risk Engine: a model for the risk of coronary heart disease in type 2 diabetes. Clin Sci. 2001;101:671-9.

52. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke. 2002;33:1776-81.

53. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. UKPDS 66: Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes. Diabetes Care. 2004;27:201-7.

54. Zoungas S, de Galan BE, Ninomiya T, Grobbee D, Hamet P, Heller S, et al; ADVANCE Collaborative Group, Cass A, Glasziou P, Harrap S, Lisheng L, Mancia G, Pillai A, et al. Combined effects of routine blood pressure lowering and intensive glucose control on

macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. Diabetes Care. 2009;32:2068-74.

55. Medicare Fee-for-Service Payment [Internet]. Baltimore, MD: Centers for Medicare & Medicaid Services; 2011. Available from: http://www.cms.hhs.gov/home/medicare.asp. Accessed January 31, 2011.

56. US Bureau of Labor Statistics; 2011 [Internet]. Available from: http://www.bls.gov/data/. Accessed January 31, 2011.

57. CDC Diabetes Cost-Effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA. 2002;287:2542-51.

58. Smith KJ, Cook RL, Ness RB. Cost comparisons between home- and clinic-based testing for sexually transmitted diseases in high-risk young women. Infect Dis Obstet Gynecol. 2007;2007:62467.

59. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, et al. Valuing health-related quality of life in diabetes. Diabetes Care. 2002;25:2238-43.

60. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. Med Decis Making. 1985;5:157-77.

61. Löthgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Econ. 2000;9:623-30.

62. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making. 1998;18 Suppl 2:S68-80.

63. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. New York: Oxford University Press; 2005.

64. Huang ES, Zhang Q, Brown SE, Drum ML, Meltzer DO, Chin MH. The cost-effectiveness of improving diabetes care in U.S. federally qualified community health centers. Health Serv Res. 2007;42:2174-93; discussion 2294-323.

65. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med. 2003;163:1637-41.

66. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al; Diabetes Prevention Program Research Group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005;142:323-32.

67. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care. 2008;46:349-56.

68. Owens DK, Qaseem A, Chou R, Shekelle P; for the Clinical Guidelines Committee of the American College of Physicians. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. Ann Intern Med. 2011;154:174-80.

69. Gusmano MK, Callahan D. "Value for money": use with care. Ann Intern Med. 2011;154:207-8.

70. Herman WH. Diabetes modeling. Diabetes Care. 2003;26:3182-3.

71. Rittenhouse DR, Shortell SM. The patient-centered medical home: will it stand the test of health reform? JAMA. 2009;301:2038-40.

72. Oldham J. Achieving large system change in health care. JAMA. 2009;301:965-6.

8.7 TABLES AND TABLE LEGENDS

Table 8.1 Parameters used in UKPDS risk equations and the Markov decision model

Parameter used in UKPDS risk equations (based on 1,417 diabetic patients surviving without diabetes complications at study end)	**DOC (n=196)**	**UC (n=1,221)**
Adjusted mean A1C (%)[a]	6.8	7.1
Adjusted mean SBP (mmHg)[a]	128.4	130.2
Adjusted mean total cholesterol (mg/dL)[a]	173.7	185.0
Adjusted mean HDLc (mg/dL)[a]	49.6	48.2
Adjusted mean LDLc (mg/dL)[a]	94.7	104.0
Gender	M: 100 (51.0%); F: 96 (49.0%)	M: 506 (41.4%); F: 715 (58.6%)
Age at study end (years)[b]	50	50
Race (White/Afro-Caribbean/Asian-Indian)[c]	Assumption	Assumption
Weight (kg)[d]	88.8	88.8
Height (cm)[d]	167.9	167.9
BMI (kg/m^2)[d]	31.4	31.4
Smoking status (Nonsmoker/Ex-smoker/Current Smoker)[e]	Assumption	Assumption
Creatinine clearance <100 ml/min (Yes/No)[f]	Assumption	Assumption
Atrial fibrillation (Yes/No)[g]	Assumption	Assumption
Macroalbuminuria (Yes/No)[h]	No	No
Microalbuminuria (Yes/No)[i]	No	No
Duration of diabetes[j]	Assumption	Assumption
Parameter used in the Markov decision model (based on all 9,405 diabetic patients)	**DOC (n=1,171)**	**UC (n=8,234)**
Diabetes complications at study end, n (%)		
No complications	196 (16.93)	1,221 (15.11)
Microvascular complications only	678 (58.55)	3,165 (39.18)
Macrovascular complications only	27 (2.33)	302 (3.74)
Micro- and macrovascular complications	257 (22.19)	3,391 (41.97)
Adjusted mean yearly number of primary care visits per patient (SE; 95% CI; median)[k]	2.7 (0.2; 2.3-3.1; 2.0)	3.9 (0.1; 3.7-4.1; 3.0)
Adjusted mean yearly number of specialty care visits per patient (SE; 95% CI; median)[k]	15.3 (0.4; 14.4-16.1; 9.0)	16.1 (0.3; 15.6-16.7; 10.3)
Adjusted mean yearly number of A1C tests per patient (SE; 95% CI)	2.6 (0.04; 2.58-2.72)	2.1 (0.02; 2.07-2.17)
Adjusted mean yearly number of lipid panel tests per patient (SE; 95% CI)	2.1 (0.03; 2.03-2.15)	1.6 (0.02; 1.55-1.63)

Abbreviations: UKPDS, United Kingdom Prospective Diabetes Study; DOC, Diabetes Outreach Clinic; UC, usual care; A1C, glycated hemoglobin; SBP, systolic blood pressure; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; M, male; F, female; BMI, body mass index.
[a]The mean value of each clinical data was adjusted for age at study entry, A1C at baseline, and gender.

[b]The mean age at study end from 1,417 patients was used in the model.
[c]White population was assumed for the base case analysis.
[d]The most current post-study data (mean weight, height, and BMI) from 1,417 patients were used in the model.
[e]Patients were assumed to be non-smokers (since less than 10% of our population was the current smoker) for the base case analysis.
[f]Patients were assumed to have creatinine clearance <100 ml/min for the base case analysis.
[g]Patients were assumed to have no atrial fibrillation (since no DOC patients had atrial fibrillation and only 15 (1.2%) UC patients had atrial fibrillation) for the base case analysis.
[h]Patients had no macroalbuminuria for the base case analysis.
[i]Patients had no microalbuminuria for the base case analysis.
[j]The mean duration of diabetes for patients was assumed to be 5 years.
[k]The mean numbers were used for the base case analysis.

Table 8.2 Cost parameters for the Markov decision model

Parameter	Value		Reference
	Base case analysis	Probabilistic sensitivity analysis distribution[a]	
Direct medical costs			
Annual health care provider costs per patient for diabetes education class and visit			DOC data; US Bureau of Labor Statistics [56]
Costs for GDC for the DOC and UC strategies, US$			
Endocrinologist	23	Uniform (11 to 34)	
Registered nurse/Certified diabetes educator	20	Uniform (16 to 24)	
Exercise physiologist	8	Uniform (4 to 11)	
Costs for DIGMA visit for the DOC strategy, US$			
Endocrinologist/Nurse practitioner	32	Uniform (16 to 48)	
Rotated staff	16	Uniform (14 to 20)	
Medical assistant	8	Uniform (6 to 9)	
Annual costs of laboratory tests and physician office visits per patient			DOC data; CMS [55]
Costs for laboratory tests, US$			
Glycated hemoglobin			
DOC	47	Uniform (24 to 71)	
UC	38	Uniform (19 to 57)	
Lipid panel			
DOC	53	Uniform (27 to 80)	
UC	41	Uniform (20 to 61)	
Costs for physician office visits, US$			
Primary care			
DOC	205	Triangular (118 to 371)	
UC	301	Triangular (170 to 536)	
Specialty care			
DOC	1,035	Triangular (666 to 2,101)	
UC	1,149	Triangular (700 to 2,211)	
One-time and annual costs of complications per patient			CDC Diabetes Cost-Effectiveness Group [57]
One-time costs, US$			
No complications	0	Not varied	
Microvascular complications	2,165	Triangular (333 to 3,999)	
Macrovascular complications	3,713	Log normal (0 to 37,924)	

Table 8.2 (Continued)

Microvascular and macrovascular complications	5,878	Log normal (333 to 41,923)	
Annual costs, US$			
No complications	0	Not varied	
Microvascular complications	6,264	Triangular (3,133 to 9,397)	
Macrovascular complications	1,518	Log normal (0 to 12,914)	
Microvascular and macrovascular complications	7,783	Log normal (3,133 to 22,311)	
One-time costs of death per patient			CDC Diabetes Cost-Effectiveness Group [57]
Age<65 years, US$	14,199	Not varied	
Age=65-74 years, US$	14,356	Not varied	
Direct nonmedical costs			
Annual time costs per patient			DOC data; US Bureau of Labor Statistics [56]; Smith et al. [58]
Costs for physician office visits, US$			
Primary care			
DOC	191	Not varied	
UC	276	Not varied	
Specialty care			
DOC	1,085	Not varied	
UC	1,142	Not varied	
Costs for GDC for the DOC and UC strategies, US$	71	Not varied	
Costs for DIGMA visit for the DOC strategy, US$	89	Not varied	
Annual monetary costs per patient			DOC data; US Bureau of Labor Statistics [56]; Smith et al. [58]
Costs for physician office visits, US$			
Primary care			
DOC	10	Not varied	
UC	15	Not varied	
Specialty care			
DOC	58	Not varied	
UC	61	Not varied	
Costs for GDC for the DOC and UC strategies, US$	15	Not varied	
Costs for DIGMA visit for the DOC strategy, US$	11	Not varied	

Abbreviations: DOC, Diabetes Outreach Clinic; GDC, Group Diabetes Class; DIGMA, Drop-In Group Medical Appointments; UC, usual care; CMS, Centers for Medicare and Medicaid Services.

[a]Uniform (a to b)=uniform distribution (minimum to maximum); Triangular (a to b)=triangular distribution (minimum to maximum); Log normal (a to b)=log normal distribution (95% CI).

Table 8.3 Parameters of health utilities and discount rates for the Markov decision model

Parameter	Value		Reference
	Base case analysis	Probabilistic sensitivity analysis distribution[a]	
Health utilities			Coffey et al. [59]
Diabetes without complications	0.689	Normal (0.662 to 0.716)	
Diabetes with microvascular complications	0.599	Uniform (0.519 to 0.678)	
Diabetes with macrovascular complications	0.631	Uniform (0.617 to 0.645)	
Diabetes with microvascular and macrovascular complications	0.599	Uniform (0.519 to 0.678)	
Discount rates			
Discount rate applied to costs, %	3.00	(2.00 to 5.00)[b]	Assumption
Discount rate applied to quality-adjusted life-expectancy, %	3.00	(2.00 to 5.00)[b]	Assumption

[a]Normal (a to b)=normal distribution (95% CI); Uniform (a to b)=uniform distribution (minimum to maximum).
[b](a to b)=(minimum to maximum). This parameter was not varied in the probabilistic sensitivity analysis.

Table 8.4 Incremental cost-effectiveness of cost per quality-adjusted life-year by strategies from the base case analysis and three one-way sensitivity analyses over a 20-year time horizon of model

Scenario	Strategy	Cost (US$)	Incremental cost (US$)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (Cost per QALY)
Base case analysis	UC	$116,242	-	8.351	-	-
	DOC	$121,553	$5,311	8.467	0.117	$45,495
Societal perspective[a]	UC	$137,084	-	8.351	-	-
	DOC	$141,993	$4,909	8.467	0.117	$42,051
Mirror the DOC cohort[b]	UC	$152,647	-	7.236	-	-
	DOC	$157,859	$5,212	7.321	0.085	$61,243
Mirror the UC cohort[c]	UC	$153,333	-	7.214	-	-
	DOC	$158,552	$5,219	7.299	0.084	$61,813

Abbreviations: DOC, Diabetes Outreach Clinic; UC, usual care; QALYs, quality-adjusted life-years; ICER, incremental cost-effectiveness ratio.
[a]The ICER of cost per QALY was calculated from the societal perspective.
[b]Initial proportions of patients in five heath states at the start of the model were changed to mirror the DOC cohort, and then the ICER of cost per QALY was calculated from the societal perspective.
[c]Initial proportions of patients in five heath states at the start of the model were changed to mirror the UC cohort, and then the ICER of cost per QALY was calculated from the societal perspective.

8.8 FIGURES

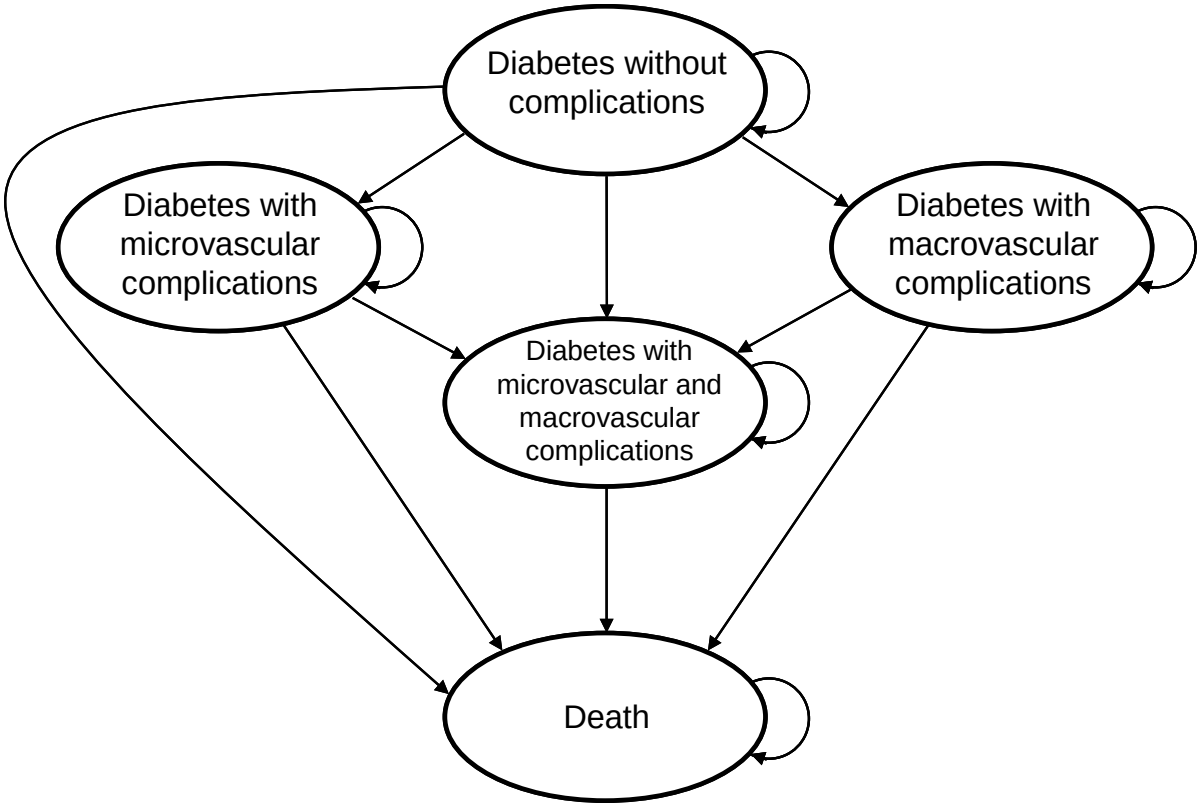

Figure 8.1 Markov-state diagram for the basic model structure

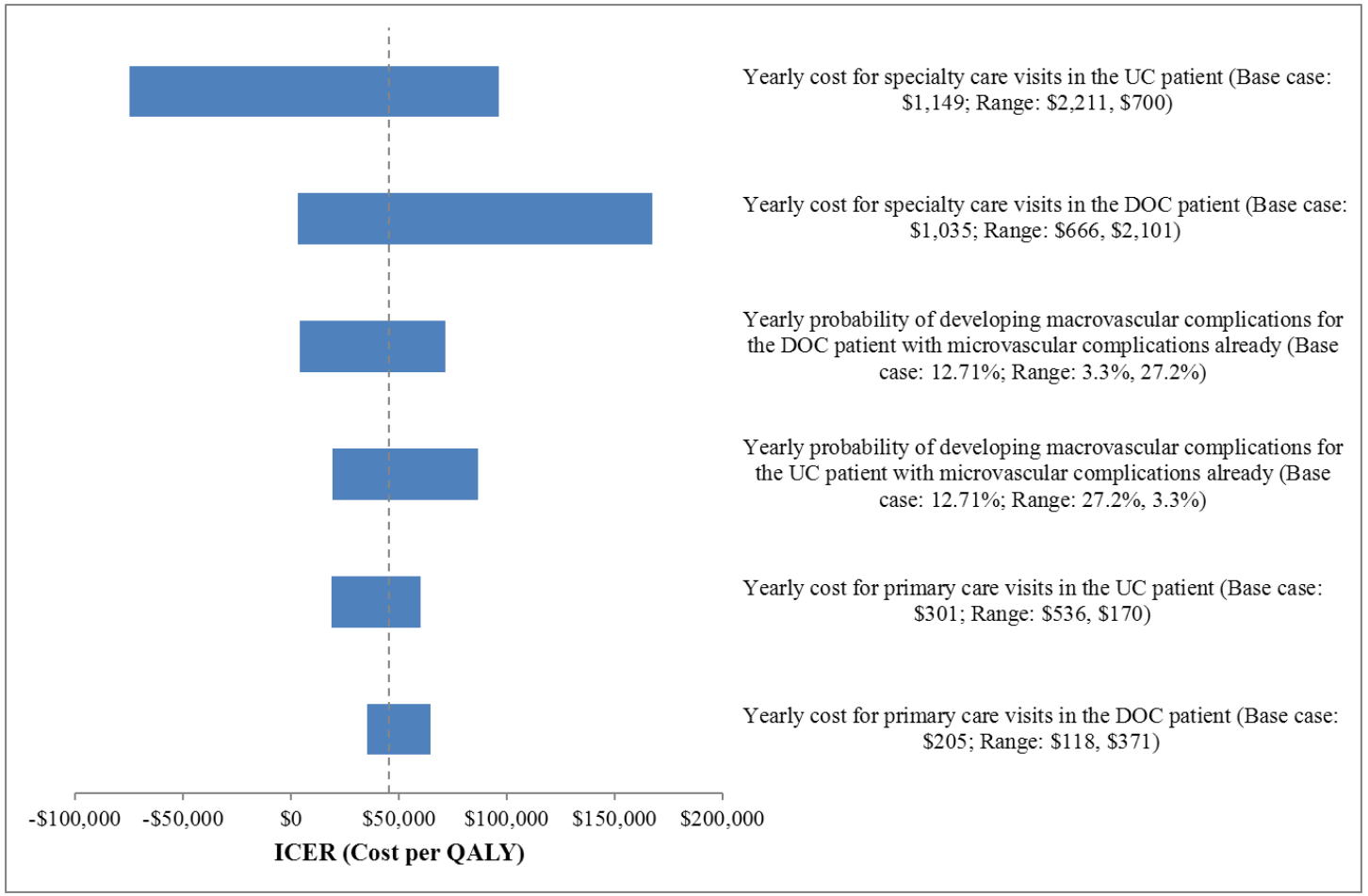

Figure 8.2 One-way sensitivity analyses for the Diabetes Outreach Clinic (DOC) and usual care (UC) strategy

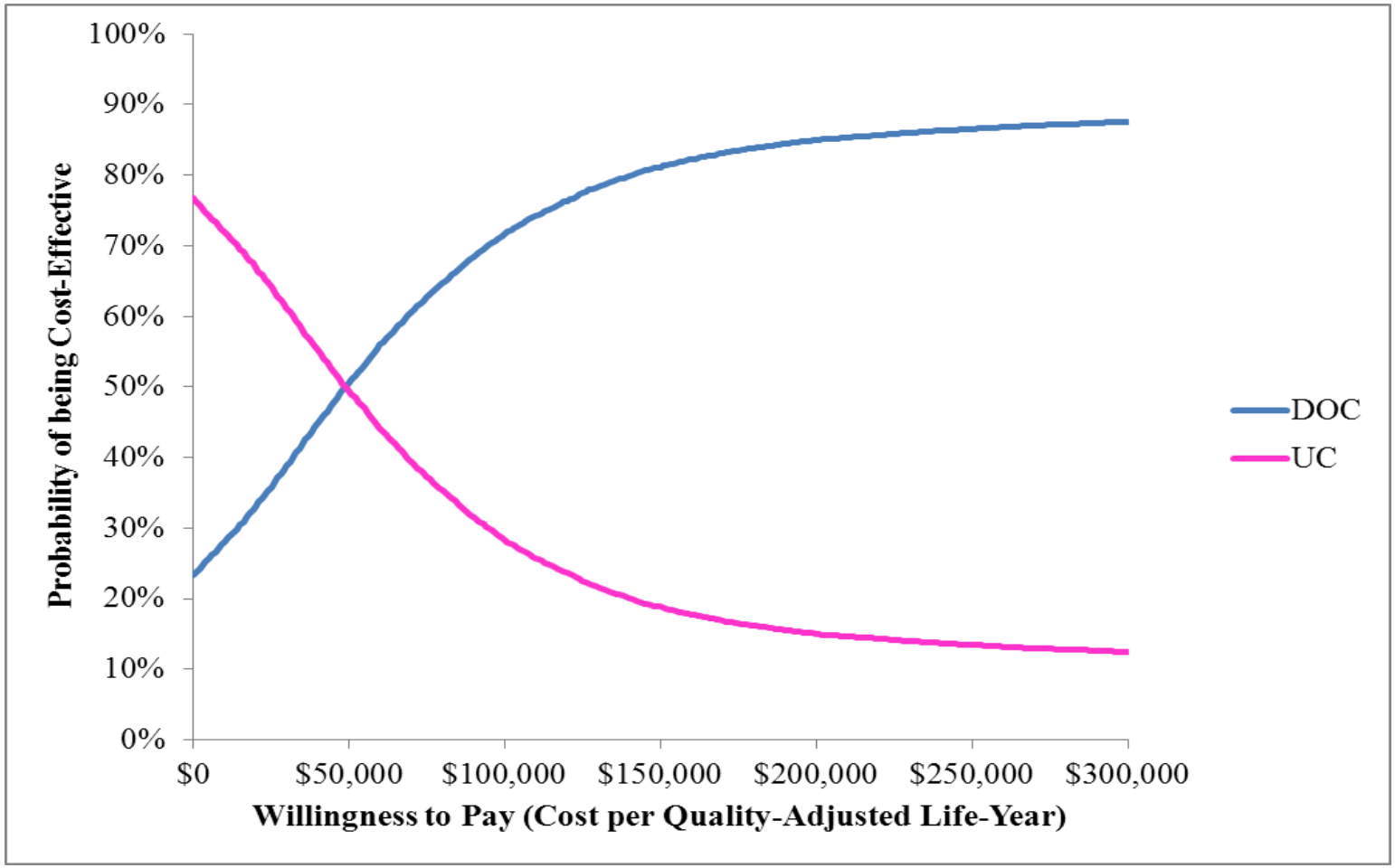

Figure 8.3 Probabilistic (second-order Monte Carlo) sensitivity analysis for the Diabetes Outreach Clinic (DOC) and usual care (UC) strategy

8.9 FIGURE LEGENDS

Figure 8.1 Markov-state diagram for the basic model structure

Ovals indicate health states. Subjects may remain within a health state (short curved arrow) or may move to a different health state (straight arrow or long curved arrow).

Figure 8.2 One-way sensitivity analyses for the Diabetes Outreach Clinic (DOC) and usual care (UC) strategy

One-way sensitivity analyses of parameters whose variations changed the base case incremental cost-effectiveness ratio (ICER; x-axis) by more than 20%. Horizontal bars depicted the range of incremental cost-effectiveness ratios corresponding to the values shown in each parameter. The vertical dotted line depicted the base case ICER. Variation of all other parameters not shown in the figure did not increase the ICER above $50,000 per quality-adjusted life-year (QALY).

Figure 8.3 Probabilistic (second-order Monte Carlo) sensitivity analysis for the Diabetes Outreach Clinic (DOC) and usual care (UC) strategy

The acceptability curve depicted the likelihood of the DOC or UC strategy being favored for a given cost-effectiveness acceptability threshold (willingness to pay).

8.10 SUPPLEMENTAL TABLES

Table 8.5 Changes in demographic, clinical, and medical utilization characteristics by two intervention strategies in all 9,405 diabetic patients

Characteristic	**DOC (n=1,171)**		**UC (n=8,234)**		**P value for baseline comparison[b]**	**Adjusted P value for follow-up comparison[c]**
	Baseline	**Follow-up**	**Baseline**	**Follow-up**		
Demographic characteristics						
Mean age at study entry (SD), years	55.5 (9.2)	---	62.3 (14.3)	---	**<.001**	---
Gender, n (%)					.07	---
Female	516 (44.1)	---	3,864 (46.9)	---		
Male	655 (55.9)	---	4,370 (53.1)	---		
Race, n (%)					.50	---
White	370 (31.6)	---	1,399 (17.0)	---		
Non-White	193 (16.5)	---	780 (9.5)	---		
Missing	608 (51.9)	---	6,055 (73.5)	---		
Mean weight (SD), kg	---	94.5 (21.8)	---	88.4 (21.5)	---	---
Mean height (SD), cm	---	169.9 (10.9)	---	169.1 (10.7)	---	---
Mean BMI (SD), kg/m^2	---	32.6 (6.3)	---	30.9 (6.7)	---	---
Insulin usage, n (%)					**.001**	.07
Yes	293 (25.0)	394 (33.6)	1,625 (19.7)	2,324 (28.2)		
No	874 (74.6)	774 (66.1)	6,124 (74.4)	5,667 (68.8)		
Missing	4 (0.3)	3 (0.3)	485 (5.9)	243 (3.0)		
Clinical characteristics						
Mean A1C (SD), %	7.8 (1.6)	7.2 (1.2)	7.0 (1.4)	7.0 (1.3)	**<.001**	**<.001**
Mean SBP (SD), mmHg	129.8 (18.5)	131.4 (14.9)	126.6 (12.8)	132.7 (15.3)	.18	**<.001**
Mean DBP (SD), mmHg	79.4 (10.1)	77.4 (8.9)	78.4 (9.1)	75.2 (8.4)	.42	.41
Mean total cholesterol (SD), mg/dL	176.0 (33.8)	164.4 (31.4)	170.1 (35.4)	165.7 (33.1)	**<.001**	**<.001**
Mean HDLc (SD), mg/dL	48.9 (12.7)	47.9 (12.0)	49.7 (12.7)	49.5 (12.2)	.08	**.02**
Mean LDLc (SD), mg/dL	94.1 (27.8)	87.6 (24.9)	89.0 (27.8)	86.4 (26.4)	**<.001**	**<.001**
Diabetes complications, n (%)					**<.001**	**<.001**
No complications	522 (44.6)	196 (16.7)	3,007 (36.5)	1,221 (14.8)		
Microvascular complications only[a]	477 (40.7)	678 (57.9)	2,656 (32.3)	3,165 (38.4)		
Macrovascular complications only[a]	46 (3.9)	27 (2.3)	656 (8.0)	302 (3.7)		
Micro- and macrovascular complications[a]	115 (9.8)	257 (21.9)	1,605 (19.5)	3,391 (41.2)		
Missing	11 (0.9)	13 (1.1)	310 (3.8)	155 (1.9)		
Medical utilization characteristics						
Mean yearly number of hospitalizations per patient (SD)	1.6 (1.2)	1.5 (1.0)	1.9 (1.7)	2.0 (1.6)	**<.001**	.12
Mean yearly number of primary care visits per patient (SD)	3.7 (2.9)	2.6 (2.5)	4.2 (3.9)	3.9 (4.2)	**<.001**	**<.001**
Mean yearly number of specialty care visits per patient (SD)	10.5 (11.8)	11.9 (9.9)	14.2 (15.0)	15.0 (14.9)	**<.001**	.06
Mean yearly number of dispensed medications per prescription per patient (SD)	2.8 (1.2)	2.6 (1.1)	2.3 (1.0)	2.3 (0.9)	**<.001**	.09
Mean yearly number of dispensed medications per patient (SD)	16.7 (8.5)	16.0 (7.2)	16.0 (9.1)	16.9 (8.5)	**.006**	**<.001**
Mean yearly number of A1C tests per patient (SD)	2.4 (1.3)	2.6 (1.0)	2.1 (1.2)	1.9 (0.9)	**<.001**	**<.001**
Mean yearly number of lipid panel tests per patient (SD)	2.0 (1.1)	2.1 (1.0)	1.7 (1.0)	1.5 (0.7)	**<.001**	**<.001**

Abbreviations: WHMC, Wilford Hall Medical Center; DOC, Diabetes Outreach Clinic; UC, usual care; SD, standard deviation; BMI, body mass index; A1C, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.
[a]Microvascular complications included retinopathy, neuropathy, or nephropathy, while macrovascular complications included coronary heart disease (fatal or non-fatal myocardial infarction, sudden death, angina, ischemic heart disease, heart failure) or stroke (fatal or non-fatal stroke).
[b]P value was derived from two-sample t test or chi-square test for comparing non-missing data in 2 study groups.
[c]P value was derived from multiple linear or logistic regression analysis for comparing non-missing data in 2 study groups. Significant baseline demographic and clinical characteristics were adjusted in all analyses, while significant baseline medical utilization characteristics were only adjusted when analyzing each follow-up medical utilization characteristic.

Table 8.6 Changes in demographic, clinical, and medical utilization characteristics by two intervention strategies in the 1,417 diabetic patients surviving without diabetes complications at study end

Characteristic	DOC (n=196)		UC (n=1,221)		P value for baseline comparison[a]	Adjusted P value for follow-up comparison[b]
	Baseline	Follow-up	Baseline	Follow-up		
Demographic characteristics						
Mean age at study entry (SD), years	51.1 (10.1)	---	47.3 (14.2)	---	**<.001**	---
Gender, n (%)					**.01**	---
Female	96 (49.0)	---	715 (58.6)	---		
Male	100 (51.0)	---	506 (41.4)	---		
Race, n (%)					.06	---
White	70 (35.7)	---	322 (26.4)	---		
Non-White	24 (12.2)	---	178 (14.6)	---		
Missing	102 (52.0)	---	721 (59.0)	---		
Mean weight (SD), kg	---	90.0 (19.6)	---	88.6 (21.8)	---	---
Mean height (SD), cm	---	169.1 (10.3)	---	167.7 (10.6)	---	---
Mean BMI (SD), kg/m^2	---	31.4 (5.6)	---	31.4 (7.0)	---	---
Insulin usage, n (%)					.21	**.02**
Yes	28 (14.3)	37 (18.9)	113 (9.3)	220 (18.0)		
No	167 (85.2)	158 (80.6)	898 (73.6)	967 (79.2)		
Missing	1 (0.5)	1 (0.5)	210 (17.2)	34 (2.8)		
Clinical characteristics						
Mean A1C (SD), %	7.8 (1.8)	7.2 (1.5)	6.8 (1.5)	7.0 (1.5)	**<.001**	**.004**
Mean SBP (SD), mmHg	121.8 (14.2)	130.3 (15.3)	126.1 (12.8)	129.2 (13.4)	.11	.29
Mean DBP (SD), mmHg	76.0 (9.5)	79.4 (9.5)	77.5 (8.7)	78.5 (7.7)	.42	.58
Mean total cholesterol (SD), mg/dL	183.9 (32.2)	172.8 (30.6)	183.5 (34.3)	184.3 (33.2)	.92	**.002**
Mean HDLc (SD), mg/dL	49.6 (13.3)	49.4 (12.6)	49.7 (11.6)	49.4 (11.6)	.94	.27
Mean LDLc (SD), mg/dL	100.7 (28.3)	93.2 (25.8)	102.1 (27.6)	102.3 (27.7)	.61	**.002**
Medical utilization characteristics						
Mean yearly number of hospitalizations per patient (SD)	1.5 (1.2)	1.3 (0.6)	1.5 (1.1)	1.3 (0.7)	.99	.95
Mean yearly number of primary care visits per patient (SD)	3.1 (2.0)	2.0 (1.4)	3.5 (2.8)	3.0 (2.1)	**.04**	**.004**
Mean yearly number of specialty care visits per patient (SD)	7.1 (9.1)	7.2 (4.8)	8.7 (11.1)	8.1 (9.0)	**.04**	.51
Mean yearly number of dispensed medications per prescription per patient (SD)	2.6 (1.1)	2.6 (1.3)	2.1 (0.9)	2.2 (0.9)	**<.001**	.38
Mean yearly number of dispensed medications per patient (SD)	13.6 (6.3)	12.1 (5.1)	10.5 (7.2)	11.1 (6.2)	**<.001**	.46
Mean yearly number of A1C tests per patient (SD)	2.0 (1.1)	2.2 (0.9)	1.8 (1.1)	1.7 (0.8)	**.03**	**<.001**
Mean yearly number of lipid panel tests per patient (SD)	1.9 (1.0)	1.7 (0.8)	1.7 (0.9)	1.4 (0.6)	**.04**	**<.001**

Abbreviations: WHMC, Wilford Hall Medical Center; DOC, Diabetes Outreach Clinic; UC, usual care; SD, standard deviation; BMI, body mass index; A1C, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

[a]P value was derived from the two-sample t test or chi-square test for comparing non-missing data in 2 study groups.

[b]P value was derived from multiple linear or logistic regression analysis for comparing non-missing data in 2 study groups. Significant baseline demographic and clinical characteristics were adjusted in all analyses, while significant baseline medical utilization characteristics were only adjusted when analyzing each follow-up medical utilization characteristic.

Table 8.7 Annual transition probability of developing CHD, stroke, nephropathy, neuropathy, and retinopathy in diabetic patients without any complications

Year	Fatal CHD		Nonfatal CHD		Fatal stroke		Nonfatal stroke		Nephropathy		Neuropathy		Retinopathy	
	DOC	UC	DOC	UC	DOC	UC	DOC	UC	DOC	UC	DOC	UC	DOC	UC
1	0.0013	0.0017	0.0029	0.0034	0.0001	0.0001	0.0009	0.0009	0.0135	0.0142	0.0350	0.0348	0.0555	0.0603
2	0.0015	0.0019	0.0030	0.0036	0.0001	0.0001	0.0010	0.0010	0.0152	0.0160	0.0515	0.0512	0.0624	0.0678
3	0.0017	0.0022	0.0031	0.0037	0.0001	0.0002	0.0011	0.0012	0.0163	0.0171	0.0601	0.0598	0.0668	0.0725
4	0.0020	0.0025	0.0032	0.0038	0.0002	0.0002	0.0013	0.0013	0.0171	0.0179	0.0665	0.0661	0.0701	0.0761
5	0.0023	0.0029	0.0033	0.0039	0.0002	0.0002	0.0015	0.0015	0.0177	0.0186	0.0715	0.0711	0.0727	0.0790
6	0.0026	0.0033	0.0034	0.0040	0.0002	0.0002	0.0017	0.0018	0.0183	0.0192	0.0757	0.0752	0.0750	0.0814
7	0.0029	0.0037	0.0035	0.0041	0.0002	0.0003	0.0019	0.0020	0.0188	0.0197	0.0793	0.0788	0.0769	0.0836
8	0.0033	0.0042	0.0036	0.0042	0.0003	0.0003	0.0022	0.0023	0.0192	0.0202	0.0824	0.0819	0.0787	0.0854
9	0.0038	0.0047	0.0037	0.0042	0.0003	0.0003	0.0025	0.0026	0.0196	0.0206	0.0852	0.0847	0.0802	0.0871
10	0.0042	0.0053	0.0037	0.0043	0.0004	0.0004	0.0029	0.0030	0.0199	0.0210	0.0877	0.0871	0.0817	0.0887
11	0.0048	0.0059	0.0038	0.0043	0.0004	0.0004	0.0033	0.0035	0.0203	0.0213	0.0899	0.0894	0.0830	0.0901
12	0.0053	0.0066	0.0038	0.0044	0.0005	0.0005	0.0038	0.0040	0.0206	0.0216	0.0920	0.0914	0.0842	0.0914
13	0.0060	0.0074	0.0038	0.0044	0.0005	0.0006	0.0043	0.0045	0.0208	0.0219	0.0938	0.0932	0.0853	0.0926
14	0.0066	0.0082	0.0038	0.0044	0.0006	0.0007	0.0049	0.0052	0.0211	0.0222	0.0955	0.0949	0.0864	0.0938
15	0.0074	0.0091	0.0038	0.0043	0.0007	0.0008	0.0056	0.0059	0.0214	0.0224	0.0970	0.0965	0.0874	0.0948
16	0.0082	0.0101	0.0038	0.0043	0.0008	0.0009	0.0065	0.0068	0.0216	0.0227	0.0984	0.0979	0.0883	0.0959
17	0.0090	0.0111	0.0038	0.0042	0.0009	0.0010	0.0074	0.0078	0.0218	0.0229	0.0998	0.0993	0.0892	0.0968
18	0.0100	0.0122	0.0037	0.0042	0.0010	0.0011	0.0084	0.0089	0.0220	0.0231	0.1010	0.1005	0.0900	0.0977
19	0.0110	0.0134	0.0037	0.0041	0.0011	0.0013	0.0096	0.0101	0.0222	0.0234	0.1021	0.1017	0.0909	0.0986
20	0.0120	0.0146	0.0036	0.0040	0.0013	0.0014	0.0110	0.0116	0.0224	0.0236	0.1031	0.1028	0.0916	0.0994

Abbreviations: CHD, coronary heart disease; DOC, Diabetes Outreach Clinic; UC, usual care.

Table 8.8 Annual transition probability of death and of developing macro- or microvascular complications in diabetic patients without any complications

Year	Death from any cause[a,b]		Development of macrovascular complications in patients staying live[a]		Development of microvascular complications with or without macrovascular complications[a]	
	DOC	UC	DOC	UC	DOC	UC
1	0.0022	0.0028	0.0038	0.0043	0.1010	0.1061
2	0.0025	0.0032	0.0040	0.0046	0.1244	0.1300
3	0.0029	0.0036	0.0042	0.0049	0.1375	0.1434
4	0.0033	0.0042	0.0045	0.0052	0.1472	0.1533
5	0.0038	0.0047	0.0048	0.0055	0.1549	0.1611
6	0.0043	0.0054	0.0051	0.0058	0.1613	0.1678
7	0.0049	0.0061	0.0055	0.0062	0.1669	0.1735
8	0.0055	0.0069	0.0058	0.0065	0.1718	0.1785
9	0.0063	0.0078	0.0062	0.0069	0.1762	0.1830
10	0.0071	0.0088	0.0066	0.0074	0.1802	0.1871
11	0.0079	0.0098	0.0071	0.0079	0.1838	0.1909
12	0.0089	0.0110	0.0076	0.0084	0.1872	0.1944
13	0.0100	0.0123	0.0082	0.0090	0.1903	0.1977
14	0.0111	0.0137	0.0088	0.0097	0.1932	0.2007
15	0.0124	0.0152	0.0096	0.0104	0.1959	0.2036
16	0.0138	0.0168	0.0104	0.0112	0.1985	0.2064
17	0.0152	0.0185	0.0113	0.0122	0.2010	0.2090
18	0.0169	0.0204	0.0123	0.0133	0.2034	0.2115
19	0.0186	0.0225	0.0135	0.0145	0.2056	0.2140
20	0.0205	0.0247	0.0149	0.0159	0.2078	0.2164

Abbreviations: DOC, Diabetes Outreach Clinic; UC, usual care.

[a]Microvascular complications included retinopathy, neuropathy, or nephropathy, while macrovascular complications included coronary heart disease or stroke. We assumed that (1) retinopathy, neuropathy, and nephropathy are independent but not mutually exclusive events, (2) coronary heart disease and stroke are independent but not mutually exclusive events, and (3) micro- and macrovascular complications are independent but not mutually exclusive events.

[b]We assumed that deaths from coronary heart disease or stroke account for 65% of all deaths in diabetes patients.

Table 8.9 Annual transition probability of disease progression in diabetic patients with microvascular complications only and those with macrovascular complications only

Parameter	Value		Reference
	Base case analysis	Probabilistic sensitivity analysis distribution[a]	
Annual probability of disease progression in DOC and UC patients with microvascular complications only			Zoungas et al. [54]
Development of macrovascular complications	0.1271	Beta (0.0330 to 0.2720)	
Annual probability of disease progression in DOC and UC patients with macrovascular complications only			Zoungas et al. [54]
Development of microvascular complications	0.0649	Beta (0.0182 to 0.1389)	

Abbreviations: DOC, Diabetes Outreach Clinic; UC, usual care.
[a]Beta (a to b)=beta distribution (95% CI).

Table 8.10 Annual death probability in diabetic patients with microvascular complications only, those with macrovascular complications only, and those with both complications

Year	Death from any cause in diabetes patients with microvascular complications only, those with macrovascular complications only, and those with both complications[a]	
	DOC	**UC**
1	0.0202	0.0208
2	0.0206	0.0212
3	0.0209	0.0217
4	0.0213	0.0222
5	0.0218	0.0228
6	0.0223	0.0234
7	0.0229	0.0241
8	0.0235	0.0249
9	0.0242	0.0258
10	0.0250	0.0267
11	0.0259	0.0278
12	0.0268	0.0289
13	0.0279	0.0301
14	0.0290	0.0315
15	0.0303	0.0330
16	0.0316	0.0346
17	0.0331	0.0363
18	0.0347	0.0382
19	0.0364	0.0402
20	0.0382	0.0423

Abbreviations: DOC, Diabetes Outreach Clinic; UC, usual care.

[a]The death probability for diabetes patients with complications was an additive probability by adding the constant risk of death to the age- and strategy-specific risk of death for diabetes patients without complications. The constant risk of death was based on medical literature (Zoungas et al. [54]), while the age- and strategy-specific risk of death for diabetes patients without complications was calculated using the United Kingdom Prospective Diabetes Study risk equations [51-53; http://www.dtu.ox.ac.uk/riskengine/].

Table 8.11 Medication costs of diabetes control, hypertension control, and cholesterol control for the Markov decision model

Medication cost	Diabetes control		Hypertension control		Cholesterol control		Reference
	DOC	UC	DOC	UC	DOC	UC	
Year 1	188.01	43.88	693.08	207.20	1602.24	1602.24	CDC Diabetes Cost-Effectiveness Group [57]
Year 2	226.41	78.36	734.94	255.72	1602.24	1602.24	
Year 3	260.21	126.21	770.70	269.23	1602.24	1602.24	
Year 4	304.72	178.98	780.95	275.46	1602.24	1602.24	
Year 5	352.12	243.40	785.76	288.32	1602.24	1602.24	
Year 6	398.10	298.25	796.34	291.57	1602.24	1602.24	
Year 7	421.18	341.62	815.28	353.06	1602.24	1602.24	
Year 8	462.17	387.32	810.50	353.06	1602.24	1602.24	
Year 9	486.83	415.46	833.91	428.45	1602.24	1602.24	
Year 10	509.89	452.13	833.91	428.45	1602.24	1602.24	
Year 11	533.44	538.77	833.91	428.45	1602.24	1602.24	
Year 12	556.84	564.80	833.91	428.45	1602.24	1602.24	
Year 13	558.78	577.45	833.91	428.45	1602.24	1602.24	
Year 14	560.72	577.45	833.91	428.45	1602.24	1602.24	
Year 15 and up	564.58	577.45	833.91	428.45	1602.24	1602.24	

Abbreviations: DOC, Diabetes Outreach Clinic; UC, usual care.

9.0 MANUSCRIPT 3: COST-EFFECTIVENESS OF AN INTERNET-DELIVERED LIFESTYLE INTERVENTION IN PRIMARY CARE PATIENTS WITH HIGH CARDIOVASCULAR RISK

Shihchen Kuo, RPh, MSCP[1]
Janice C. Zgibor, RPh, PhD[1]
Kenneth J. Smith, MD, MS[2]
Kathleen M. McTigue, MD, MS, MPH[3]
Rachel Hess, MD, MS[3]
Tina Bhargava, DrPH[4]
Cindy L. Bryce, PhD[5]

[1]Department of Epidemiology
University of Pittsburgh, Pittsburgh, PA

[2]Section of Decision Sciences and Clinical Systems Modeling
University of Pittsburgh, Pittsburgh, PA

[3]Department of Medicine
University of Pittsburgh, Pittsburgh, PA

[4]College of Public Health
Kent State University, Kent, Ohio

[5]Department of Health Policy and Management
University of Pittsburgh, Pittsburgh, PA

9.1 ABSTRACT

Background: While Internet-delivered lifestyle interventions are effective for weight control, there is limited research on their cost-effectiveness for diabetes prevention and risk reduction in primary care settings.

Methods: A Markov state-transition model was developed to estimate the cost-effectiveness of using an Online adaptation of the Diabetes Prevention Program lifestyle intervention (ODPP) compared to usual care to reduce metabolic risk in an overweight/obese cohort (mean age 53) over a 10-year time horizon. Intervention costs and weight change outcomes were obtained from a prospective ODPP pilot study; other costs, disease progression data, and utilities were drawn from published reports. In the model, diabetes risk was a function of weight change with/without the program.

Results: Compared to usual care, the base case incremental cost-effectiveness ratio (ICER) of the ODPP in our pilot study cohort (30% with diabetes) was $14,351 and $29,331 per quality-adjusted life-year (QALY) gained from a health care system or societal perspective, respectively. In a hypothetical cohort without diabetes, the ICER was $7,777 and $18,263 per QALY gained, respectively. Results were robust in sensitivity analyses, but enrolling cohorts with lower annual risk of developing diabetes (≤1.8%), enrolling fewer participants (≤15), or increasing the hourly cost (≥$91.2) or the annual per-participant time required (≥1.45 hours) for ODPP technical support could increase the ODPP to cost >$20,000 per QALY gained. In probabilistic sensitivity analyses, the ODPP was cost-effective in 20-58% of model iterations using an acceptability threshold of $20,000, 73-92% at $50,000, and 95-99% at $100,000 per QALY gained.

Conclusions: The ODPP delivered in primary care settings for weight management appears to be an economically reasonable intervention.

9.2 INTRODUCTION

Overweight and obesity are common, serious, and costly. These conditions are complicated, multifactorial diseases that develop from the interaction between genotype and the environment (1), and rank prominently among current major public health problems. Recent data from the Centers of Disease Control and Prevention show that approximately 69% of US adults aged 20 years and older were overweight or obese in 2009-2010, and 36% (over 78 million) were obese (2,3). Overweight and obesity are the major risk factors for morbidity from a wide range of medical conditions (e.g., type 2 diabetes, cardiovascular diseases, and certain types of cancer), social conditions (e.g., discrimination in employment and education settings), psychological conditions (e.g., depression), and impaired quality of life (1,4-9). Higher body weights are also associated with an increase in mortality from all causes (1). A collaborative analysis of data from almost 900,000 adults in 57 prospective studies estimated that optimal survival is achieved at a body mass index (BMI) of 22.5-25 kg/m^2 with reduction in life expectancy by about 2-4 and 8-10 years for individuals who would become obese (30-35 kg/m^2) and would become morbidly obese (40-50 kg/m^2), respectively (10).

Overweight and obesity are also costly. It is estimated that medical costs associated with adult obesity in the US range from $147 billion to nearly $210 billion per year (11,12). People who are classified as obese spend $1,429 (42 percent) more on health care costs compared to those of normal-weight. The additional costs attributable to obesity are almost entirely a result of costs generated from treating the diseases that obesity promotes (11,13).

Development of effective weight loss programs that are widely accessible is a health care priority given that overweight and obesity are common. Further, without intervention,

people that are already obese will steadily gain more weight over time. Also, weight loss is recommended to reduce the health and economic impact of obesity (13-15). Randomized controlled trials (RCTs) demonstrate that evidence-based lifestyle interventions leading to dietary and physical activity change can produce significant weight loss, reduce the incident type 2 diabetes, and improve cardiovascular disease risk factors (16,17). Existing translational studies show that these RCT-based intensive lifestyle interventions can be translated to weight loss programs that can be effectively delivered in primary care and community-based settings, resulting in a greater weight loss in intervention subjects than in control subjects (18-20). Although the individual or group behavioral-based face-to-face programs involving clinic visits are the most effective treatment approach available for obesity, they are expensive and often inaccessible (21). Also, most adults would prefer to lose weight without having to participate in a structure face-to-face treatment program (22). To accommodate the needs of these individuals and to make the weight control treatment more accessible, an Internet-delivered intervention allows individuals with barriers including geography, access to transportation, or time constraints to participate in these lifestyle interventions.

Several reviews indicate that the Internet-based lifestyle intervention may be effective in facilitating weight control among overweight or obese individuals. Although the evidence for effectiveness is modest due to mixed results, heterogeneity of designs, and limited generalizability of findings (23-29), a meta-analysis published by the Cochrane Collaboration indicated that online weight loss programs work almost as well as face-to-face interventions (30,31). Moreover, the American Heart Association Scientific Statement suggests that the Internet is a vehicle through which lifestyle interventions can be delivered and could be a promising tool to promote weight loss (29).

One approach to successfully systematic implementation of Internet-based lifestyle weight loss programs into an existing health care system is to ensure that they are integrated with care delivery, cost-effective, and broadly supported (32,33). Moreover, policy makers are increasingly asking not only whether an obesity intervention works, but also whether it offers value given costs (34). Although current literature demonstrates that most lifestyle interventions delivered through a variety of approaches in different settings are among the intervention options usually regarded as cost-effective, evidence on the cost-effectiveness of an Internet-based lifestyle weight management intervention in coordination with primary care delivery is increasing but still relatively limited (17,34-38).

The parent study (39) used for the current analysis hypothesized that an Online adaptation of the Diabetes Prevention Program (DPP) lifestyle intervention (ODPP) could facilitate the translation of an evidence-based lifestyle approach into ongoing clinical care in primary care practice. In this analysis, the cost-effectiveness of the ODPP compared with usual care was assessed.

9.3 METHODS

Online Adaptation of the Diabetes Prevention Program Lifestyle Intervention (ODPP) at University of Pittsburgh Medical Center

The implementation methods and pilot results of the ODPP have been previously described (39). Briefly, the faculty at University of Pittsburgh and University of Pittsburgh Medical Center developed the ODPP by translating the DPP's lifestyle curriculum (40,41) into

an online delivery format, which was integrated into primary clinical care. As people with diabetes can also benefit from such a lifestyle curriculum with relatively low-fat, low-calorie diet and moderate physical activity recommendations, the curriculum was further adapted to be appropriate for this group, incorporating diabetes-related concerns such as the need for careful foot care when initiating physical activity and the possibility that weight loss may alter needs for antihyperglycemic agents.

The ODPP comprised 16 weekly and 8 monthly lessons, incorporating behavioral tools such as e-mail prompts for online self-monitoring of diet, physical activity, and weight; automated weekly progress reports; and links to community resources. Participants received regular, brief, individualized counseling via electronic messaging as the further support. Referring physicians were notified of their patients' progress and were contacted by the health coaches whenever health-relevant issues arose.

At 12 months of follow-up, on average, 50 patients who were enrolled in the ODPP pilot study lost 4.94 kg (95% CI: 2.48 to 7.39), had reduced systolic blood pressure by 6.56 mmHg (95% CI: 3.39 to 9.73), and had minimally changed diastolic blood pressure (+0.28 mm Hg; 95% CI: -2.25 to +2.81) (39). Outcomes of weight change in the pilot study provided the foundation for this cost-effectiveness analysis to compare the ODPP with usual care (without ODPP).

The Framework of a Markov Decision Model

Using TreeAge Pro Suite 2009 (TreeAge Software, Williamstown, MA) decision analysis software, a Markov decision model (42) was modified to estimate the incremental cost-effectiveness of the ODPP. The model directly incorporated intervention costs and effectiveness

from ODPP pilot study (39) to estimate life expectancy, quality-adjusted life-expectancy (expressed as quality-adjusted life-years, or QALYs), clinical outcomes, as well as direct medical and nonmedical costs associated with the ODPP. Our base case model examined the cohort of 53-year-old adults who participated in the ODPP pilot study at yearly intervals for 10 years from a health care system perspective. The incremental cost-effectiveness ratio (ICER) was defined as the additional cost of applying the ODPP compared with usual care, divided by the additional clinical effectiveness of applying the ODPP compared with usual care. In the light of the reference case recommendations of the Panel on Cost-Effectiveness in Health and Medicine (43), future costs and benefits were discounted at 3% annually. The US Consumer Price Index (44) was used to convert all monetary costs to 2010 US dollars.

Basic Model Structure

A four-state Markov decision model was used to analyze the cost-effectiveness of the ODPP (Figure 9.1). The target population included ODPP pilot study participants with a body mass index $\geq$25 kg/m^2 and history of at least one weight-related cardiovascular risk factor (e.g., hypertension, dyslipidemia, diabetes, or impaired fasting glucose). At the start of the base case model, the proportions of subjects in four health states were set to mirror the cohort in the ODPP pilot study. Over time, subjects could progress to have diabetes without complications (stable diabetes), diabetes with complications (complicated diabetes), or die. In subjects who developed diabetes, the transition to complicated diabetes was preceded by a stable diabetes stage. Complications from diabetes included retinopathy, nephropathy, neuropathy, coronary heart disease, or stroke, and they were assumed to be irreversible. To be conservative, the ODPP and

usual care were assumed to have identical effects on the progression of disease in patients who already had stable diabetes, thus implying that the model only examined differences between strategies in delaying or preventing the development of stable diabetes. In the model, subjects in all health states can die; rates of death are based on age- and sex-specific US mortality (which accounts for baseline mortality) and the relative risks of death for overweight/obesity, stable diabetes, and complicated diabetes (45-48).

Clinical outcomes and progress related to stable and complicated diabetes for both the ODPP and usual care were derived from published literature (Table 9.1). The intervention effectiveness of the ODPP on weight change was obtained from the ODPP pilot study (39). The weight change status through usual care was derived from the WiLLoW (Weight Loss through Living Well) study (49). Comparable with the ODPP pilot study, the WiLLoW study was conducted by the same research team at the same medical practice setting within the overlapped time period, using similar inclusion and exclusion criteria to examine weight change in the referral primary care patients who were or were not enrolled to the WiLLoW program. The WiLLoW program was an in-person, group-based version of DPP-based lifestyle curriculum which is the same intervention used in the ODPP. Hence, the non-enrolled group in the WiLLoW study could be considered as a usual care group of primary care patients who were from the main general internal practice represented in the ODPP pilot study and were referred for the DPP-based lifestyle management.

In the model, the incidence of diabetes as a function of baseline BMI and the odds ratios for diabetes risk as a function of weight change were derived from the published reports of studying a nationally representative sample of US adults (50,51). These odds ratios for diabetes risk were adjusted for age, baseline BMI, sex, race, education, systolic blood pressure, skinfold

ratio and reported change in physical activity (50). These outcomes and effectiveness data are shown in Table 9.1.

According to patient demographic characteristics, cardiovascular risk factors and macrovascular complications, the annual direct medical costs related to stable and complicated diabetes were estimated using published data (42,52). Indirect costs were not included, assuming their capture in the assessment of QALYs, per the recommendation of the Panel on Cost-Effectiveness in Health and Medicine (43). Patient demographics and ODPP-related intervention costs were derived from the ODPP pilot study (39), being shown in Tables 9.1-9.3.

To account for changes in life expectancy and quality of life for diabetes-related health states, we used QALYs which adjust for quality based on a utility weight (or preference) for the health state, ranging from 0 (death) to 1 (perfect health). This utility weight for each health state is multiplied by time in that state. As an individual's health changes over time, these products are summed to represent the total number of QALYs (43).

Sensitivity Analyses

Many new intervention strategies or programs are more costly but also more effective. In such cases, the new strategies may be considered cost-effective if the ICER is below some threshold value such that the decision makers deem the added expense is worth the added benefits. However, different decision makers may value benefits differently. Hence, extensive sensitivity analyses were conducted to assess the effect of varying original assumptions made for the base case model on the ICERs.

First, the base case ICER was estimated using three other clinical effectiveness measurements, including incidence of stable diabetes, complicated diabetes, and deaths due to stable or complicated diabetes. Second, the cost-utility was assessed from a societal perspective by including the direct nonmedical costs of the ODPP intervention (i.e., costs of participant time to partake in the ODPP). Third, the original assumption that the study cohort was set to mirror the ODPP pilot study cohort at the start of the model was tested by starting the model with a hypothetical cohort without diabetes and then recalculating the ICER. Fourth, one-way sensitivity analyses were performed for model input parameters (Tables 9.1-9.3) to assess the effect of varying parameter estimates within clinically plausible ranges and identify parameters whose variation changed the base case ICER ≥20%. Fifth, the effect of lower and higher overall Website-related costs of the ODPP on cost-effectiveness was evaluated. Sixth, the effect of variation in the number of participants enrolled in the ODPP was assessed. Seventh, a two-way sensitivity analysis was performed to evaluate the effect of variation in both overall Website-related costs of the ODPP and the number of participants enrolled in the ODPP.

Probabilistic sensitivity analyses were performed from a health care system and a societal perspective, where model parameters were simultaneously varied over distributions (Tables 9.1-9.3). Distributions for parameters were chosen to reflect the level of certainty and the characteristics of the parameter range: Prevalence, incidence, and probability parameters were varied over beta distributions; odds ratios and relative risks were varied over normal or log-normal distributions; utility and cost data were varied over uniform or triangular distributions; and cost multipliers were varied over normal distributions. A value from each parameter's probability distribution was randomly selected during each of 10,000 Monte Carlo iterations, and then these values were used to compute the cost-effectiveness among strategies of being studied

for each iteration. The cost-effectiveness acceptability curve (59) was used to summarize results, showing the likelihood that a given strategy would be favored for a given acceptability threshold, which is defined as the maximum amount that society is willing to pay for an incremental gain in health (60).

9.4 RESULTS

Base Case Analysis

The simulated incremental cost-effectiveness analysis results under base case assumptions are summarized in Table 9.4. Over 10 years, the ODPP cost $591 more than usual care and produced 0.0412 more QALYs, resulting in an ICER of $14,351 per QALY gained from the health care system perspective. When using the incidence of stable diabetes, complicated diabetes, and deaths due to stable or complicated diabetes as the effectiveness measurement, the ODPP cost $13,977, $47,889, and $177,109 per case or death averted, respectively.

Sensitivity Analyses

When a societal perspective was adopted and the direct nonmedical cost was included, the cost of the ODPP increased by $617 and the ICER increased to $29,331 per QALY gained. If starting the model with a hypothetical cohort without diabetes, the ODPP cost $7,777 and

$18,263 per QALY gained from a health care system and a societal perspective, respectively (Table 9.4).

Table 9.5 and Figure 9.2 show the results of one-way sensitivity analyses, where nine parameters whose variations changed the base case ICER ≥20% were identified. Results were robust in one-way sensitivity analyses, but enrolling the cohort with lower annual risk of developing diabetes (≤1.8%), enrolling fewer participants (≤15), or increasing the hourly cost (≥$91.2) or the annual per-participant time required (≥1.45 hours) for ODPP technical support could increase the ODPP to cost >$20,000 per QALY gained. Variation of all other model parameters did not increase the ODPP to cost $20,000 or more per QALY gained.

Two components (i.e., hourly cost billed for providing and participant time for requiring technical support of the ODPP) of the Website-related costs for the ODPP and the number of participants enrolled in the ODPP were amongst the most influential variables in the base case analysis and were the parameters that we could modify (Table 9.5 and Figure 9.2). Therefore, two separate one-way sensitivity analyses and a two-way sensitivity analysis were performed to examine the effect of their variations on the base case ICER. If the overall Website-related costs for the ODPP were set at low-range estimates, the ODPP relative to usual care could be cost-saving. When these Website-related costs for the ODPP were even doubled, the ODPP was still favored, costing less than $55,000 per QALY gained (Table 9.6a and Figure 9.3a). Furthermore, enrolling more participants in the ODPP would reduce the costs of the ODPP, resulting in more favored ICERs. If the ODPP is implemented in a group of 16 participants or greater, the ODPP relative to usual care would cost less than $20,000 per QALY gained (Table 9.6b and Figure 9.3b). Results of the two-way sensitivity analysis on the overall Website-related costs of the ODPP and the number of participants enrolled in the ODPP are shown in Table 9.6c. When the

ODPP enrolled 100 participants or more, the ODPP was favored at a willingness-to-pay threshold of $20,000, $50,000, and $53,000 per QALY if the overall Website-related costs were ≤19%, 91%, and 100% higher than the base case costs, respectively.

A probabilistic sensitivity analysis of base case results is presented as a cost-effectiveness acceptability curve (Figure 9.4), showing the proportion of cost-effectiveness calculations that would be considered acceptable from a health care system and a societal perspective for various willingness-to-pay (or acceptability) thresholds. The ODPP was more likely to be favored with an acceptability threshold ≥$17,500 and $35,000 per QALY gained from a health care system and a societal perspective, respectively. At a threshold of $20,000, $50,000, and $100,000 per QALY gained, the ODPP was favored in 20-58%, 73-92%, and 95-99% of model iterations from a health care system and a societal perspective, respectively.

9.5 DISCUSSION

As the prevalence of obesity continues to rise, the need for practical, easily disseminated and effective weight control programs for overweight or obese people is increasingly important. Internet-based interventions may serve as an efficient and cost-effective approach to meet this growing public health need (31). Although start-up and sustainability costs may be high and require consideration in relation to a program's effectiveness, Internet-based interventions may be more economical in the long term (61). Our analysis showed that, from the perspective of a health care system and a society over 10 years, the ODPP delivered in the primary care setting compared with usual care was quite cost-effective, costing approximately $14,400 and $29,300 per QALY gained, respectively.

Among those nine sensitive parameters shown in Table 9.5, four of them are worth mention. First, the number of participants enrolled in the ODPP is one of the important considerations for keeping the ODPP cost-effective. Enrollment of 50 participants in the ODPP pilot study was very low. It is expected that as the program becomes more widely available in a routine practice clinic or community, the Website-related costs will be spread over a greater number of participants and thus total costs of the ODPP will reduce, which is most likely to produce a much more favored level of cost-effectiveness. Second, results were sensitive to the participant time required for technical support of the ODPP. If the online settings and functions of the ODPP were problematic frequently and substantially, it may become less cost-effective because of higher costs for technical support and potential for reduced intervention benefits. Hence, ensuring a stable and reliable online platform is quite important. Third, some well-organized orientation and training session(s) to enhance health coaches' ability to deliver counseling in a brief and efficient manner may further assure the cost-effectiveness of the ODPP. Lastly, an increasing number of weight management initiatives focus on employing coaches with minimal clinical training as a way to cut costs; however, the ODPP was effective for weight control using coaches with more clinical knowledge and was still be highly cost-effective despite high wages.

While the participant time spent in the in-person orientation session and the online sessions activities were considered, the ODPP still cost less than $30,000 per QALY gained. Time investment is necessary for behavior change (i.e., self-monitoring is one of the most effective tools to support behavior change, and sustained counseling is one of the best predictors of sustained weight loss), and thus it likely cannot be eliminated or even significantly minimized. Also, our model could not capture variations in the quality of participation time. For example,

with an online intervention, people can do their lifestyle counseling and behavioral support activities at the time/location that is convenient for them (vs. the original DPP where they had to make an appointment and travel to have a face-to-face meeting with a counselor), or people may feel more active and motivated (vs. the usual care without a lifestyle promotion plan), which could bias the analysis against the ODPP.

Cost per QALY gained and per disability-adjusted life-year (DALY) averted are the two most widely used measures in economic evaluations for combining morbidity and mortality into one common unit, allowing comparisons across studies. Four of the published reports (31,61-72) used these two measures to evaluate the cost-effectiveness of an Internet-based lifestyle weight management intervention and thus were selected for facilitating comparison with our findings. These studies suggested that the Internet-based intervention compared with usual care cost (in 2010 US$) $950-$2,000 (68), $30,400 (64), and $159,500 (70) per QALY gained, or $2,650-$8,830 per DALY averted (67). Our estimates of ODPP cost-effectiveness ranged from $7,777 to $29,331 per QALY gained, confirming most of these studies' observations that the Internet-based intervention is at a moderate to high level of cost-effectiveness.

Most new strategies in diabetes prevention or control are more effective but also costly, requiring more incremental resources per QALY gained (52,73). There are no absolute criteria for cost-effectiveness, and the long-cited benchmark of $50,000 per QALY gained is unsupported (74,75). However, in general, interventions costing less than $20,000 per QALY gained may be considered as having strong evidence for adoption; interventions costing $20,000 to $100,000 per QALY gained have moderate evidence; and those costing more than $100,000 per QALY gained have weaker evidence for adoption (75,76). In this regard, this study found

that the ODPP had strong evidence for implementation in the primary care setting, especially for a cohort of participants without diabetes.

Several limitations should be considered when interpreting these findings. First, interpretations of study results are contingent on data quality and model assumptions. Second, subjects in this analysis were representative of a primary care population in an academic general internal medicine practice, and may not be fully generalizable to other populations or health care settings. Third, a ten-year time frame was used to model the cost-effectiveness of the ODPP due to uncertainty in the empirical data for long-term effectiveness of weight change on diabetes risk (50,51). However, delaying or preventing type 2 diabetes will delay or prevent incurring the direct medical costs of diabetes, including the costs of diabetes education and nutritional counseling, glucose monitoring, treatment, surveillance for complications, and treatment of complications. Hence, adopting a ten-year time horizon may overestimate treatment costs and underestimate the benefits of the ODPP intervention.

Several conservative practice and assumptions were used and expected to negatively bias our findings. First, assuming an identical risk of disease progression to have diabetes-related complications for subjects with stable diabetes who achieved different magnitude of weight gain/loss was a conservative strategy. This is because our studies showed that the ODPP resulted in more participants with larger weight losses, and according to the Look AHEAD (Action for Health in Diabetes) study (77), the overweight/obese patients with type 2 diabetes with larger weight losses were associated with greater improvements in cardiovascular disease risk factors, which may reduce diabetes-related complications. Thus, this assumption potentially biases the model against the ODPP effect. Second, because there is no empirical utility or mortality data from the ODPP intervention, application of the same literature-based utility weights and the

same mortality risks to the four health states in the cohorts who achieved different magnitude of weight gain/loss may again underestimate the ODPP's potential to improve quality of life (78-80) and length of life (1,10). Third, the health- and cost-generating obesity-related conditions used in the current model were only limited to diabetes. Many other conditions known to be obesity-related, as illustrated by increased health and economic burden (4,81), were not considered, making our model conservative and biasing against the ODPP effect.

An Internet-based lifestyle intervention for weight management may offer a significant opportunity to reach individuals who may experience barriers to access interventions for addressing overweight or obesity and reducing chronic disease risk factors. Compared with usual care, the ODPP integrated into primary care practice provides greater health benefits at an attractive cost and, from the perspective of a financially prudent policy maker, it represents an intervention of choice.

9.6 LITERATURE CITED

1. NHLBI Obesity Education Initiative Expert Panel. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. Rockville, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity; October 2000; NIH Publication No. 00-4084. Available from http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf Accessed February 20, 2013.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. NCHS data brief, no 82. Hyattsville, MD: National Center for Health Statistics. 2012.
3. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA. 2012;307:491-497.
4. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.
5. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. Eur J Clin Nutr. 2010;64:16-22.
6. Emerging Risk Factors Collaboration; Wormser D, Kaptoge S, Di Angelantonio E, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011;377:1085-1095.

7. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. Lancet. 2011;378:815-825.

8. Rao G. Office-based strategies for the management of obesity. Am Fam Physician. 2010;81:1449-1456.

9. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. Arch Intern Med. 1999;159:837-843.

10. Prospective Studies Collaboration; Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083-1096.

11. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff (Millwood). 2009;28:w822-w831.

12. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. J Health Econ. 2012;31:219-230.

13. Robert Wood Johnson Foundation: F as in fat: how obesity threatens America's future, 2012 [article online]. Available from http://www.rwjf.org/en/research-publications/find-rwjf-research/2012/09/f-as-in-fat--how-obesity-threatens-america-s-future-2012.html Accessed February 20, 2013.

14. Tate DF, Wing RR, Winett RA. Using Internet technology to deliver a behavioral weight loss program. JAMA. 2001;285:1172-1177.

15. Norman JE, Bild D, Lewis CE, Liu K, West DS; CARDIA Study. The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. Int J Obes Relat Metab Disord. 2003;27:369-376.

16. Gillett M, Royle P, Snaith A, et al. Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: a systematic review and economic evaluation. Health Technol Assess. 2012;16:1-236.

17. Loveman E, Frampton GK, Shepherd J, et al. The clinical effectiveness and cost-effectiveness of long-term weight management schemes for adults: a systematic review. Health Technol Assess. 2011;15:1-182.

18. Johnson M, Jones R, Freeman C, et al. Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence. Diabet Med. 2013;30:3-15.

19. Ali MK, Echouffo-Tcheugui J, Williamson DF. How effective were lifestyle interventions in real-world settings that were modeled on the Diabetes Prevention Program? Health Aff (Millwood). 2012;31:67-75.

20. Pomeroy J, Palacios C. Translating findings from lifestyle intervention trials of cardiovascular disease and diabetes to the primary care setting. Curr Nutr Rep. 2012;1:215-221.

21. Johnston JD, Massey AP, Devaneaux CA. Innovation in weight loss programs: a 3-dimensional virtual-world approach. J Med Internet Res. 2012;14:e120.

22. Sherwood NE, Morton N, Jeffery RW, French SA, Neumark-Sztainer D, Falkner NH. Consumer preferences in format and type of community-based weight control programs. Am J Health Promot. 1998;13:12-18.

23. McTigue KM, Conroy MB. Use of the internet in the treatment of obesity and prevention of type 2 diabetes in primary care. Proc Nutr Soc. 2013;72:98-108.

24. Kodama S, Saito K, Tanaka S, et al. Effect of Web-based lifestyle modification on weight control: a meta-analysis. Int J Obes (Lond). 2012;36:675-685.

25. Manzoni GM, Pagnini F, Corti S, Molinari E, Castelnuovo G. Internet-based behavioral interventions for obesity: an updated systematic review. Clin Pract Epidemiol Ment Health. 2011;7:19-28.

26. Arem H, Irwin M. A review of web-based weight loss interventions in adults. Obes Rev. 2011;12:e236-e243.

27. Neve M, Morgan PJ, Jones PR, Collins CE. Effectiveness of web-based interventions in achieving weight loss and weight loss maintenance in overweight and obese adults: a systematic review with meta-analysis. Obes Rev. 2010;11:306-321.

28. Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res. 2010;12:e4.

29. Rao G, Burke LE, Spring BJ, et al; American Heart Association Obesity Committee of the Council on Nutrition, Physical Activity and Metabolism; Council on Clinical Cardiology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Stroke Council. New and emerging weight management strategies for busy ambulatory settings: a scientific statement from the American Heart Association endorsed by the Society of Behavioral Medicine. Circulation. 2011;124:1182-1203.

30. Kuehn BM. Online programs help with weight loss. JAMA. 2012;308:1079.

31. Wieland LS, Falzon L, Sciamanna CN, et al. Interactive computer-based interventions for weight loss or weight maintenance in overweight or obese people. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD007675. DOI: 10.1002/14651858.CD007675.pub2.

32. Boucher JL. The obesity and diabetes epidemics: how do we turn the tide? Diabetes Spectrum. 2011;24:123-125.

33. Krukowski RA, West DS, Harvey-Berino J. Recent advances in internet-delivered, evidence-based weight control programs for adults. J Diabetes Sci Technol. 2009;3:184-189.

34. Gortmaker SL, Swinburn BA, Levy D, et al. Changing the future of obesity: science, policy, and action. Lancet. 2011;378:838-847.

35. Lehnert T, Sonntag D, Konnopka A, Riedel-Heller S, König HH. The long-term cost-effectiveness of obesity prevention interventions: systematic literature review. Obes Rev. 2012;13:537-553.

36. Griffiths UK, Anigbogu B, Nanchahal K. Economic evaluations of adult weight management interventions: a systematic literature review focusing on methods used for determining health impacts. Appl Health Econ Health Policy. 2012;10:145-162.

37. Saha S, Gerdtham UG, Johansson P. Economic evaluation of lifestyle interventions for preventing diabetes and cardiovascular diseases. Int J Environ Res Public Health. 2010;7:3150-3195.

38. Cecchini M, Sassi F, Lauer JA, Lee YY, Guajardo-Barron V, Chisholm D. Tackling of unhealthy diets, physical inactivity, and obesity: health effects and cost-effectiveness. Lancet. 2010;376:1775-1784.

39. McTigue KM, Conroy MB, Hess R, et al. Using the internet to translate an evidence-based lifestyle intervention into practice. Telemed J E Health. 2009;15:851-858.

40. Diabetes Prevention Program (DPP) Research Group. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care. 2002;25:2165-2171.

41. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403.

42. Smith KJ, Hsu HE, Roberts MS, et al. Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005-2007. Prev Chronic Dis. 2010;7:A109.

43. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

44. U.S. Department of Labor; Bureau of Labor Statistics. Databases, tables, and calculators by subject. Available from http://www.bls.gov/data/ Accessed February 22, 2013.

45. Arias E. United States Life Tables, 2008. National Vital Statistics Reports; vol. 61 no. 3. Hyattsville, MD: National Center for Health Statistics. 2012.

46. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA. 2005;293:1861-1867.

47. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. Am J Public Health. 1991;81:1158-1162.

48. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia. 2001;44(Suppl 2):S54-S64.

49. McTigue KM, Conroy MB, Bigi L, Murphy C, McNeil M. Weight loss through living well: translating an effective lifestyle intervention into clinical practice. Diabetes Educ. 2009;35:199-204, 208.

50. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. J Epidemiol Community Health. 2000;54:596-602.

51. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of U.S. adults. Am J Epidemiol. 1997;146:214-22.

52. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. Ann Intern Med. 2005;142:323-332.

53. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: Risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. Stroke. 2002;33:1776-1781.

54. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-1847.

55. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care. 1998;36:778-792.

56. Coffey JT, Brandle M, Zhou H, et al. Valuing health-related quality of life in diabetes. Diabetes Care. 2002;25:2238-2243.

57. Zhou H, Isaman DJ, Messinger S, et al. A computer simulation model of diabetes progression, quality of life, and cost. Diabetes Care. 2005;28:2856-2863.

58. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2013 update: a report from the American Heart Association. Circulation. 2013;127:e6-e245.

59. Löthgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Econ. 2000;9:623-630.

60. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making. 1998;18(2 Suppl):S68-S80.

61. Rasu RS, Hunter CM, Peterson AL, Maruska HM, Foreyt JP. Economic evaluation of an Internet-based weight management program. Am J Manag Care. 2010;16:e98-e104.

62. Krukowski RA, Tilford JM, Harvey-Berino J, West DS. Comparing behavioral weight loss modalities: incremental cost-effectiveness of an internet-based versus an in-person condition. Obesity (Silver Spring). 2011;19:1629-1635.

63. Tate DF, Finkelstein EA, Khavjou O, Gustafson A. Cost effectiveness of internet interventions: review and recommendations. Ann Behav Med. 2009;38:40-45.

64. McConnon A, Kirk SF, Cockroft JE, et al. The Internet for weight control in an obese sample: results of a randomised controlled trial. BMC Health Serv Res. 2007;7:206.

65. Meenan RT, Stevens VJ, Funk K, et al. Development and implementation cost analysis of telephone- and Internet-based interventions for the maintenance of weight loss. Int J Technol Assess Health Care. 2009;25:400-410.

66. Sacks N, Cabral H, Kazis LE, et al. A web-based nutrition program reduces health care costs in employees with cardiac risk factors: before and after cost analysis. J Med Internet Res. 2009;11:e43.

67. Cobiac LJ, Vos T, Barendregt JJ. Cost-effectiveness of interventions to promote physical activity: a modelling study. PLoS Med. 2009;6:e1000110.

68. Hersey JC, Khavjou O, Strange LB, et al. The efficacy and cost-effectiveness of a community weight management intervention: a randomized controlled trial of the health weight management demonstration. Prev Med. 2012;54:42-49.

69. Robroek SJ, Polinder S, Bredt FJ, Burdorf A. Cost-effectiveness of a long-term Internet-delivered worksite health promotion programme on physical activity and nutrition: a cluster randomized controlled trial. Health Educ Res. 2012;27:399-410.

70. Miners A, Harris J, Felix L, Murray E, Michie S, Edwards P. An economic evaluation of adaptive e-learning devices to promote weight loss via dietary change for people with obesity. BMC Health Serv Res. 2012;12:190.

71. Archer E, Groessl EJ, Sui X, et al. An economic analysis of traditional and technology-based approaches to weight loss. Am J Prev Med. 2012;43:176-182.

72. Wylie-Rosett J, Swencionis C, Ginsberg M, et al. Computerized weight loss intervention optimizes staff time: the clinical and cost results of a controlled clinical trial conducted in a managed care setting. J Am Diet Assoc. 2001;101:1155-1162.

73. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care. 2010;33:1872-1894.

74. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med. 2003;163:1637-1641.

75. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care. 2008;46:349-356.

76. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ. 1992;146:473-481.

77. Wing RR, Lang W, Wadden TA, et all; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34:1481-1486.

78. Ackermann RT, Edelstein SL, Narayan KM, et al; Diabetes Prevention Program Research Group. Changes in health state utilities with changes in body mass in the Diabetes Prevention Program. Obesity (Silver Spring). 2009;17:2176-2181.

79. McDonough C, Dunkley AJ, Aujla N, Morris D, Davies MJ, Khunti K. The association between body mass index and health-related quality of life: influence of ethnicity on this relationship. Diabetes Obes Metab. 2013;15:342-348.

80. Bilger M, Finkelstein EA, Kruger E, Tate DF, Linnan LA. The effect of weight loss on health, productivity, and medical expenditures among overweight employees. Med Care. 2013 Apr 29. [Epub ahead of print]

81. Lenz M, Richter T, Mühlhauser I. The morbidity and mortality associated with overweight and obesity in adulthood: a systematic review. Dtsch Arztebl Int. 2009;106:641-648.

9.7 TABLES AND TABLE LEGENDS

Table 9.1 Parameters of cohort characteristics, probabilities, odds ratios, relative risks, utilities, costs and multipliers, and discount rates for the decision model: Base case values and ranges examined in sensitivity analyses

Parameter	Base case value		Range examined (PSA distribution)	Source
Cohort characteristics				
Starting age, years	53		27–79 (Uniform)	ODPP pilot study (39)
Female, %	76.0		7.2–100.0 (Beta)	
African American, %	8.0		2.1–17.0 (Beta)	
Angina, %	3.2		0.9–7.0 (Beta)	(58)
Hypertension, treated, %	64.0		9.2–99.3 (Beta)	ODPP pilot study (39)
History of cardiac arrest or MI, %	10.0		2.7–21.6 (Beta)	
History of stroke, %	2.0		0.5–4.4 (Beta)	
Peripheral vascular disease, %	0.0		Not varied	
Probabilities and incidence rates				
Probability of weight change status between baseline and the 12-month follow-up, %	Usual care	ODPP[a]		
Weight loss ≥2.0 kg	24.39	58.00	Not varied	ODPP pilot study (39); WiLLoW study (49)
Weight loss 1.5–<2.0 kg	3.66	4.00		
Weight loss 1.0–<1.5 kg	4.88	0.00		
Weight loss 0.5–<1.0 kg	1.22	10.00		
Weight loss 0.1–<0.5 kg	3.66	0.00		
Weight remained relatively stable (loss or gain <0.1 kg)	20.73	6.00		
Weight gain 0.1–<0.5 kg	4.88	0.00		
Weight gain 0.5–<1.0 kg	3.66	6.00		
Weight gain 1.0–<1.5 kg	4.88	2.00		
Weight gain 1.5–<2.0 kg	6.10	0.00		
Weight gain ≥2.0 kg	21.95	14.00		
Annual probability of developing diabetes in participants whose weight remained relatively stable, %	2.336		0.620–5.072 (Beta)	(50, 51)
Annual probability of progressing to complicated diabetes, %	7.500		1.931–16.661 (Beta)	(42, 52-54)
Odds ratios of developing diabetes				
Weight loss ≥2.0 kg	0.45		0.34–0.60 (Normal)	(50)
Weight loss 1.5–<2.0 kg	0.55		0.44–0.68 (Normal)	

Table 9.1 (Continued)

Weight loss 1.0–<1.5 kg	0.67	0.58–0.78 (Normal)	
Weight loss 0.5–<1.0 kg	0.82	0.76–0.88 (Normal)	
Weight loss 0.1–<0.5 kg	0.96	0.95–0.97 (Normal)	
Weight remained relatively stable (loss or gain <0.1 kg)	1.00	Not varied	
Weight gain 0.1–<0.5 kg	1.04	1.03–1.06 (Normal)	
Weight gain 0.5–<1.0 kg	1.22	1.13–1.31 (Normal)	
Weight gain 1.0–<1.5 kg	1.49	1.29–1.73 (Normal)	
Weight gain 1.5–<2.0 kg	1.82	1.46–2.27 (Normal)	
Weight gain ≥2.0 kg	2.22	1.66–2.98 (Normal)	
Relative risks of death			
No diabetes	1.26	1.14–1.39 (Log-normal)	(46)
Stable diabetes	2.00	1.81–2.21 (Log-normal)	(42, 47)
Complicated diabetes	2.40	2.18–2.65 (Log-normal)	(42, 48)
Utilities			
No diabetes	0.880	0.840–0.920 (Uniform)	(42, 55)
Stable diabetes	0.689	0.662–0.716 (Uniform)	(42, 52, 56, 57)
Complicated diabetes	0.593	0.505–0.681 (Uniform)	
Costs (in 2010 US$) and multipliers			
No diabetes (annual), $	780	Not varied	(42)
Base diabetes cost (annual), $	2,132	Not varied	(42, 52)
Multiplier for female	1.25	1.11–1.39 (Normal)	
Multiplier for African American	0.82	0.69–0.96 (Normal)	
Base complicated diabetes cost (annual), $	2,132	Not varied	
Multiplier for female	1.25	1.11–1.39 (Normal)	
Multiplier for African American	0.82	0.69–0.96 (Normal)	
Multiplier for angina	1.73	1.32–2.14 (Normal)	
Multiplier for hypertension, treated	1.24	1.09–1.40 (Normal)	
Multiplier for history of cardiac arrest or MI	1.90	1.66–2.16 (Normal)	
Multiplier for history of stroke	1.30	1.11–1.52 (Normal)	
Multiplier for peripheral vascular disease	1.31	1.15–1.48 (Normal)	
Discount rates			
Discount rate applied to cost and effectiveness, %	3.00	2.00–5.00[b]	Assumed

Abbreviations: MI, myocardial infarction; ODPP, Online adaptation of the Diabetes Prevention Program; PSA, probabilistic sensitivity analysis; WiLLoW, Weight Loss through Living Well.

[a]The probability was the number of participants who had complete weight data at any follow-up assessments in each of weight change categories divided by the total number of participants who had complete weight data at the baseline assessment. Data were obtained using a last observation carried forward approach.

[b]The parameter was not varied in the probabilistic sensitivity analysis.

Table 9.2 Direct cost of the one-year ODPP intervention for the decision model: Base case values and ranges examined in sensitivity analyses

Type of cost		Base case value[a]		Range examined (PSA distribution)	Source
		Amount, US$	Time, hour		
1) Orientation and training sessions for 2 health coaches				Not varied	ODPP pilot study (39)
Manuals (300 pages; $0.05 a page)		0.60	-		
2) Orientation session for the participants					
The dietary book detailing fat and calorie content of various foods		4.70	-		
Pedometer		3.76	-		
3) Greeting cards		2.10	-		
4) Posters/flyers		0.26	-		
5) Postage ($0.43 an USPS Forever stamp)		2.58	-		
6) Photocopies and printings ($0.05 a page)		0.50	-		
Total direct Web-unrelated costs of the ODPP intervention per participant		***14.5***	***-***	***7.25–21.75 (Triangular)***	
7) Website licensing, maintenance, and technical support[b]					
Total cost of hosting and maintaining the ODPP (annual)	***First year***	***3,000***	***-***	***0–6,000 (Triangular)***	
	Second year and afterward	***300***	***-***	***0–600 (Triangular)***	
Time required for technical support (annual)		***-***	***1.0***	***0.5–1.5 (Triangular)***	
Hourly cost of providing technical support (annual)		***63***	***-***	***0–126 (Triangular)***	

Abbreviations: ODPP, Online adaptation of the Diabetes Prevention Program; PSA, probabilistic sensitivity analysis.

[a]These base case values were per-participant values, except that the total annual costs of hosting and maintaining ODPP was for 50 participants enrolled in the ODPP pilot study. In sensitivity analyses, the number of participants enrolled in the ODPP was assumed to range from 5 to 500 with a Log-normal distribution.

[b]In base case analysis, the costs for "Website licensing, and maintenance, and technical support" were considered as a license purchase fee to distribute ODPP in a clinic or community and thus was included in the model, while in sensitivity analysis, the costs for "Website licensing, and maintenance, and technical support" were evaluated from 0 to the double of their base case values.

Table 9.3 Time cost of providing or partaking in the one-year ODPP intervention for the decision model: Base case values and ranges examined in sensitivity analyses

Activity of providing or partaking in the one-year ODPP intervention	Base case value		Range examined (PSA distribution)	Source
	Amount, US$	Time, hour[f]		
Health coach				ODPP pilot study (39)
1) Attend staff orientation and training session(s)	-	0.32	Not varied	
2) Conduct patient orientation session(s) by health coaches	-	0.16		
3) Review each patient's progress regularly (including, lesson completion, self-monitoring, and workbook entries)	-	6.80		
4) Write coaching notes to offer support and suggestions and send them to patients via secure emails (weekly during the core 16 lessons, and biweekly thereafter)				
5) Consult with a nutrition specialist as needed				
6) Consult with physician(s) as needed				
7) Consult with other professional(s) as needed				
8) Respond to and provide coaching advice to any patients' questions or concerns as needed via secure emails	-	0.68		
9) Conduct chat room sessions and answer patients' questions (1-2 chats/week)[a]	-	0.00		
10) Personalize the quarterly patient progress reports for primary care providers	-	0.10		
11) Notify and communicate with primary care providers if patients' health concerns arise	-	0.03		
12) Provide the reminder message to the potential inactive patient by making phone calls	-	0.19		
Total health coach time per participant for the one-year ODPP intervention	***-***	***8.28***	***4.14–12.42 (Triangular)***	
Hourly wage rate for the health coach[b]	***29.83***	***-***	***14.91–44.74 (Triangular)***	
Health coach assistant				
Total health coach assistant time per participant for the one-year ODPP intervention[c]	***-***	***1.128***	***0.564–1.692 (Triangular)***	
Hourly wage rate of the health coach assistant[d]	***22.47***	***-***	***11.23–33.70 (Triangular)***	
Participant				
Total time that the participant spent participating in the in-person orientation session and the online sessions activities related to the one-year ODPP	***-***	***33.675***	***16.837–50.512 (Triangular)***	
Hourly wage rate for the participant[e]	***18.33***	***-***	***9.165–27.495 (Triangular)***	(44)

Abbreviations: ODPP, Online adaptation of the Diabetes Prevention Program; PSA, probabilistic sensitivity analysis.

[a]Each chat lasted 45 minutes, but hardly anyone ever attended.

[b]The health coaches were paid at approximately the midpoint ($29.83 per hour in 2010 US$) for a Health Professional II job, not including benefits (http://www2.hr.pitt.edu/comp).

[c]First-line technical support, copying materials, and scheduling for participation for those sessions (when orientation sessions are happening) would be appropriate for a "coach helper", but this was no more than 1-2 hours per active week. On average, these were 37.6 active weeks over a year for 50 participants enrolled in the ODPP pilot study.
[d]The health coach assistant was paid at approximately the midpoint ($22.47 per hour in 2010 US$) for a Research IV job, not including benefits (http://www2.hr.pitt.edu/comp).
[e]Hourly wage rate for the participant was based on the average hourly wage of a US nonfarm production worker, i.e. $18.33 in 2010 US$.
[f]These base case values were per-participant time.

Table 9.4 Cost-effectiveness analysis results

Scenario		Strategy	Cost, US$	Increment cost (US$)	Effectiveness	Incremental effectiveness	ICER
Base case (health care system perspective)	Using QALY as the effectiveness measurement	Usual care	$12,007	-	6.5610 QALYs	-	-
		ODPP	$12,599	$591	6.6022 QALYs	0.0412 QALYs	$14,351 per QALY gained
	Using incidence of stable diabetes as the effectiveness measurement	Usual care	$12,007	-	15.77%	-	-
		ODPP	$12,599	$591	11.54%	-4.23%	$13,977 per case averted
	Using incidence of complicated diabetes as the effectiveness measurement	Usual care	$12,007	-	15.70%	-	-
		ODPP	$12,599	$591	14.47%	-1.23%	$47,889 per case averted
	Using deaths due to stable or complicated diabetes as effectiveness measurement	Usual care	$12,007	-	5.5506%	-	-
		ODPP	$12,599	$591	5.2168%	-0.3339%	$177,109 per death averted
Societal perspective[a]		Usual care	$12,007	-	6.5610 QALYs	-	-
		ODPP	$13,216	$1,209	6.6022 QALYs	0.0412 QALYs	$29,331 per QALY gained
Start of the model with a hypothetical cohort without diabetes[b]	Health care system perspective	Usual care	$8,173	-	7.1305 QALYs	-	-
		ODPP	$8,631	$458	7.1894 QALYs	0.0589 QALYs	$7,777 per QALY gained
	Societal perspective[a]	Usual care	$8,173	-	7.1305 QALYs	-	-
		ODPP	$9,248	$1,075	7.1894 QALYs	0.0589 QALYs	$18,263 per QALY gained

Abbreviations: ICER, incremental cost-effectiveness ratio; ODPP, Online adaptation of the Diabetes Prevention Program; QALY(s), quality-adjusted life-year(s).

[a]In addition to direct medical costs, the cost of time that the participant spent participating in the in-person orientation session and the online sessions activities related to ODPP was included to assess the cost-effectiveness from a societal perspective.

[b]The study cohort was assumed to have no stable or complicated diabetes at the start of the model.

Table 9.5 One-way sensitivity analyses: Nine parameters whose variations changed the base case incremental cost-effectiveness ratio by 20% or greater

	Base case value	**Range of base case values (low range value / high range value)**	**ICER (ODPP vs. Usual care), $ per QALY gained (ICER at low range value / ICER at high range value)**
Base case analysis			14,351
Annual probability of developing stable diabetes in our overweight/obese study cohort whose weight remained relatively stable after the ODPP intervention, %	2.336	0.620 / 5.072	67,201 / 4,263
Hourly cost of providing technical support for the ODPP (annual), $	63	0 / 126	1,703 / 26,999
Number of participants enrolled in the ODPP, persons	50	5 / 500	37,206 / 12,065
Time required for technical support of the ODPP (annual, per participant), hour	1.0	0.5 / 1.5	8,027 / 20,675
Odds ratio of developing stable diabetes for individuals with annual weight loss ≥2.0 kg	0.45	0.34 / 0.60	11,989 / 18,557
Hourly wage rate of the health coach, $	29.83	14.91 / 44.74	11,353 / 17,347
Health coach time of providing the ODPP intervention (per participant), hour	8.28	4.14 / 12.42	11,354 / 17,348
Odds ratio of developing stable diabetes for individuals with annual weight gain ≥2.0 kg	2.22	1.66 / 2.98	17,222 / 11,601
Utility of overweight/obese individuals without diabetes	0.88	0.84 / 0.92	17,552 / 12,137

Abbreviations: ICER, incremental cost-effectiveness ratio; ODPP, Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

Table 9.6a One-way sensitivity analysis on the costs for Website licensing, maintenance, and technical support

Multiplier for Website-related costs[a]	Annual total cost of hosting and maintaining ODPP, $		Per-participant time required for technical support (annual), hour	Hourly cost of providing technical support (annual), $	ICER (ODPP vs. Usual care), $ per QALY gained
	First year	Second year and afterward			
0.00	0	0	0	0	Cost-saving
0.17	510	51	0.17	10.71	Cost-saving
0.18	540	54	0.18	11.34	30
0.50	1,500	150	0.50	31.50	3,595
1.00 (base case value)	3,000	300	1.00	63.00	14,351
1.18	3,540	354	1.18	74.34	19,771
1.19	3,570	357	1.19	74.97	20,096
1.90	5,700	570	1.90	119.70	49,648
1.91	5,730	573	1.91	120.33	50,155
2.00	6,000	600	2.00	126.00	54,835

Abbreviations: ICER, incremental cost-effectiveness ratio; ODPP, Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

[a]The Website-related costs included (1) annual total costs of hosting and maintaining ODPP, (2) annual per-participant time required for technical support, and (3) annual hourly cost of providing technical support. The multiplier for Website-related costs was assumed to range from 0 to be double.

Table 9.6b One-way sensitivity analysis on the number of participants enrolled in the ODPP

Number of participants enrolled in the ODPP, persons	**ICER (ODPP vs. Usual care), $ per QALY gained**
5	37,206
10	24,509
20	18,160
30	16,044
40	14,986
50 (base case value)	14,351
100	13,081
200	12,446
300	12,235
400	12,129
500	12,065

Abbreviations: ICER, incremental cost-effectiveness ratio; ODPP, Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

Table 9.6c Two-way sensitivity analysis on the overall costs for Website licensing, maintenance, and technical support and the number of participants enrolled in the ODPP[a]

ICER (ODPP vs. Usual care), $ per QALY gained		Number of participants enrolled in the ODPP, persons										
		5	10	20	30	40	50 (base case value)	100	200	300	400	500
Multiplier for Website-related costs[b]	0.00	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
	0.17	3,846	1,687	608	248	68	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
	0.18	4,144	1,858	716	335	144	30	Cost-saving	Cost-saving	Cost-saving	Cost-saving	Cost-saving
	0.50	15,023	8,674	5,499	4,441	3,912	3,595	2,960	2,643	2,537	2,484	2,452
	1.00 (base case value)	37,206	24,509	18,160	16,044	14,986	14,351	13,081	12,446	12,235	12,129	12,065
	1.18	46,740	31,757	24,266	21,769	20,520	19,771	18,273	17,524	17,274	17,149	17,074
	1.19	47,294	32,184	24,629	22,111	20,852	20,096	18,585	17,830	17,578	17,452	17,376
	1.90	93,073	68,948	56,886	52,865	50,854	49,648	47,236	46,029	45,627	45,426	45,306
	1.91	93,809	69,557	57,431	53,389	51,368	50,155	47,730	46,518	46,113	45,911	45,790
	2.00	100,546	75,151	62,453	58,221	56,105	54,835	52,295	51,026	50,602	50,391	50,264

Abbreviations: ICER, incremental cost-effectiveness ratio; ODPP, Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

[a]Compared with usual care, green-highlighted cells indicated that the ODPP was cost-saving; blue-highlighted cells indicated that the ODPP cost less than $20,000 per QALY gained; yellow-highlighted cells indicated that the ODPP cost less than $50,000 per QALY gained; orange-highlighted cells indicated that the ODPP cost less than $100,000 per QALY gained; and pink-highlighted cells indicated that the ODPP cost higher than $100,000 per QALY gained.

[b]The Website-related costs for each multiplier were detailed in Table 9.6a.

9.8 FIGURES

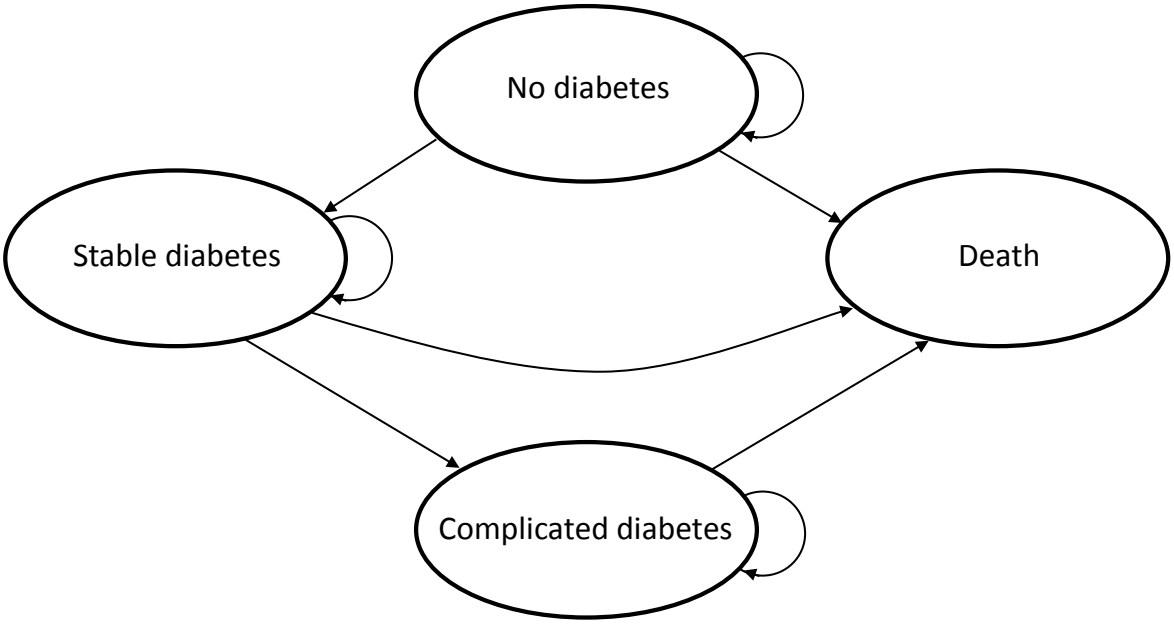

Figure 9.1 Markov-state diagram for the basic model structure

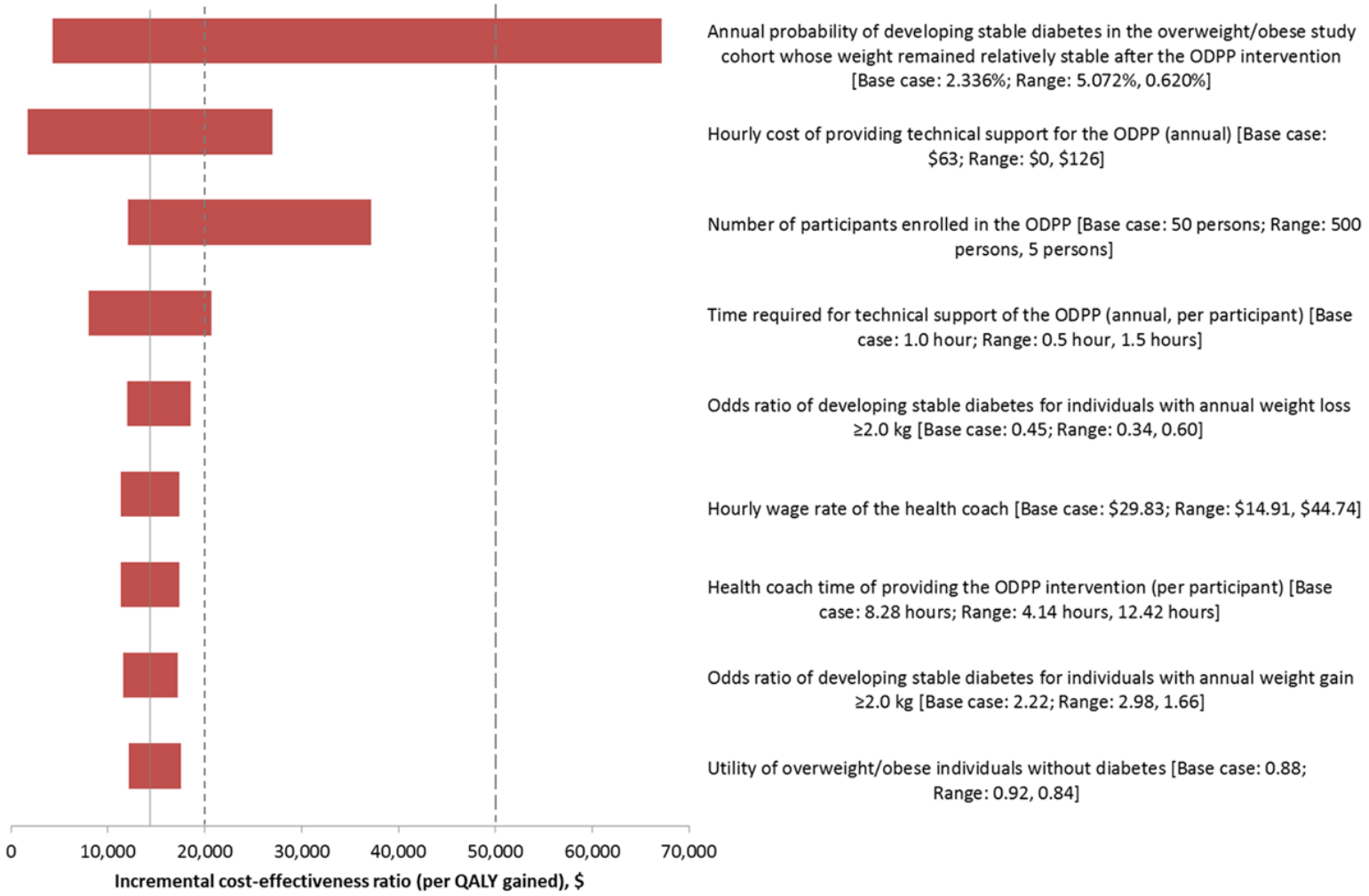

Figure 9.2 Tornado diagram from one-way sensitivity analyses for the ODPP compared with usual care

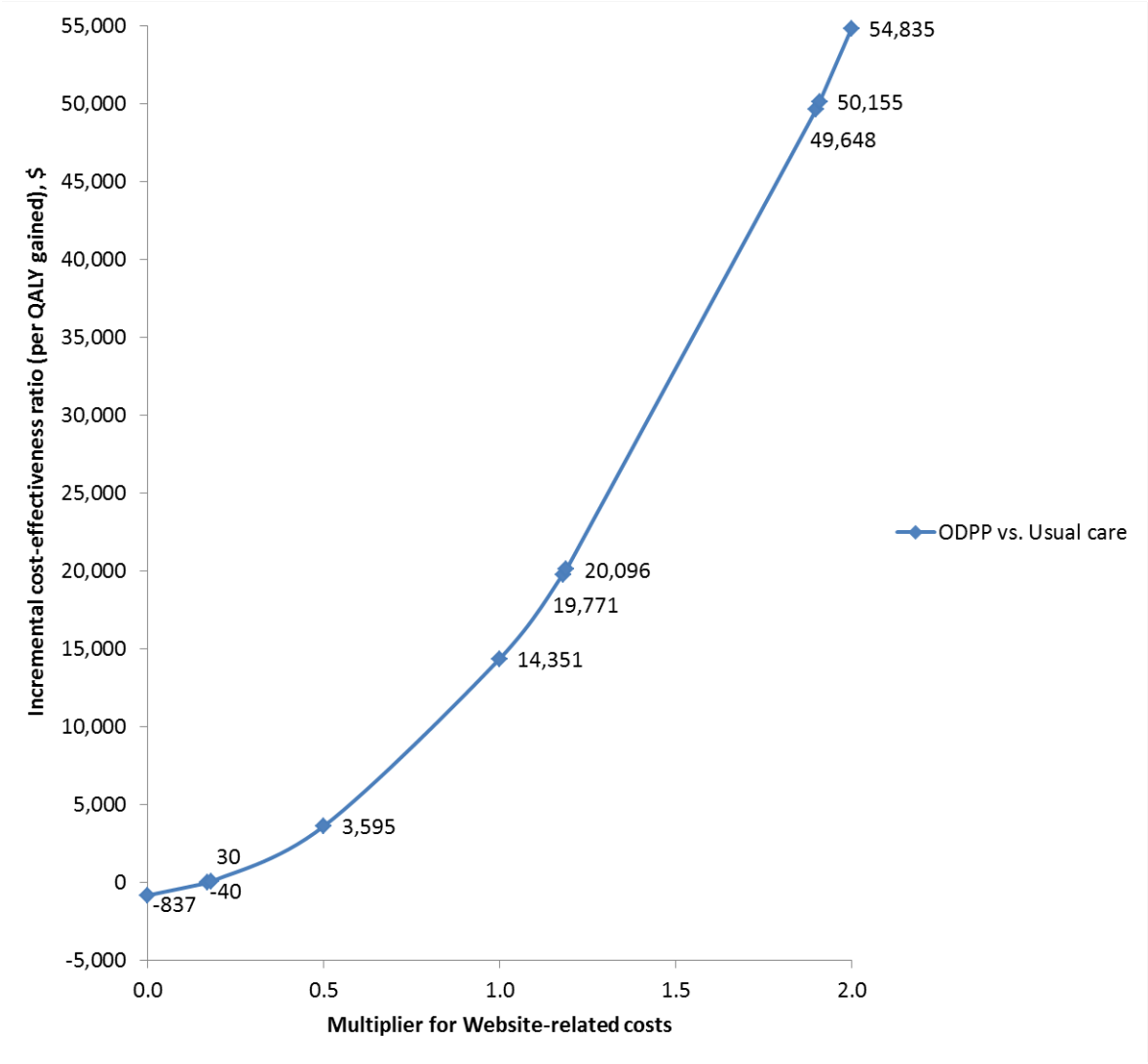

Figure 9.3a One-way sensitivity analysis on the multiplier for Website-related costs

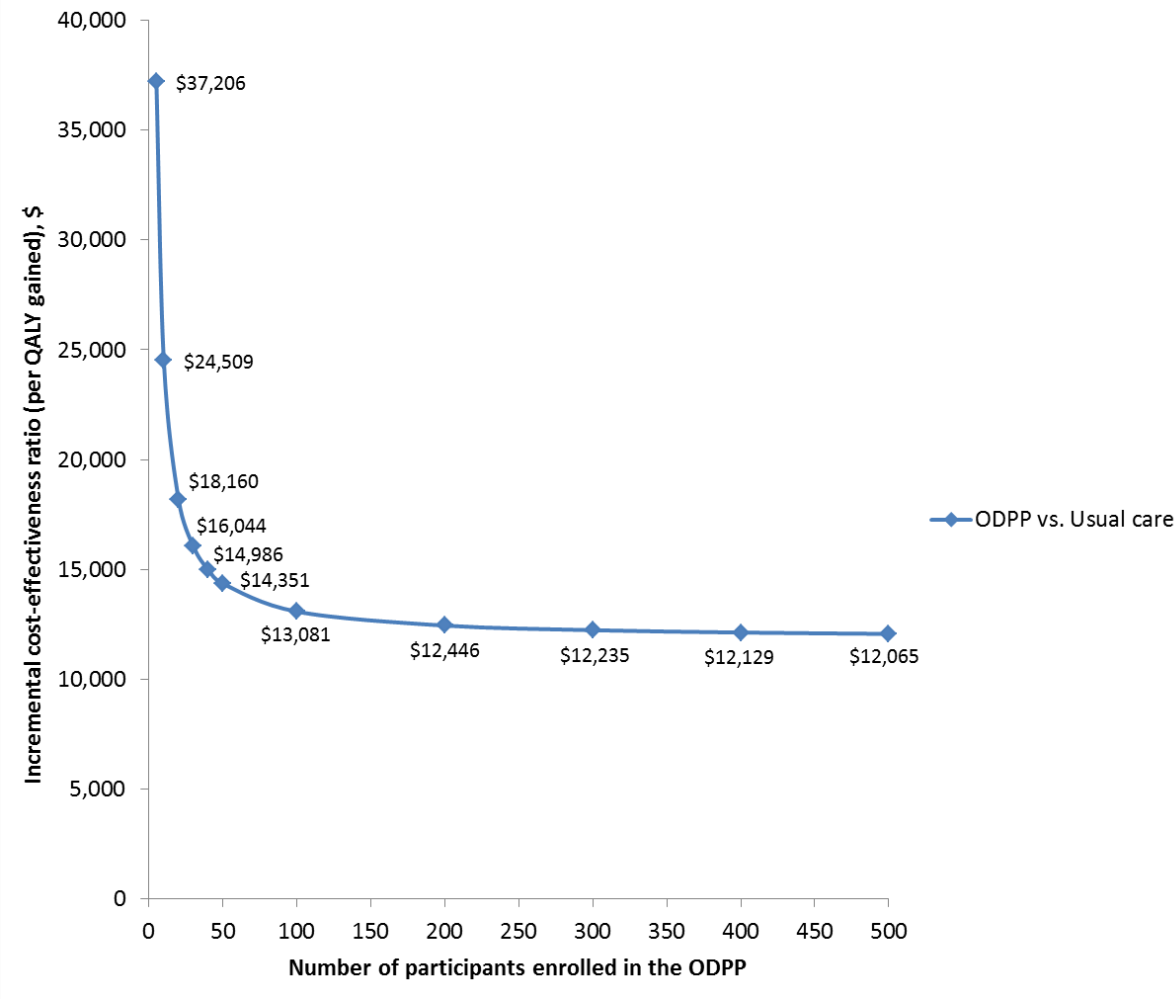

Figure 9.3b One-way sensitivity analysis on the number of participants enrolled in the ODPP

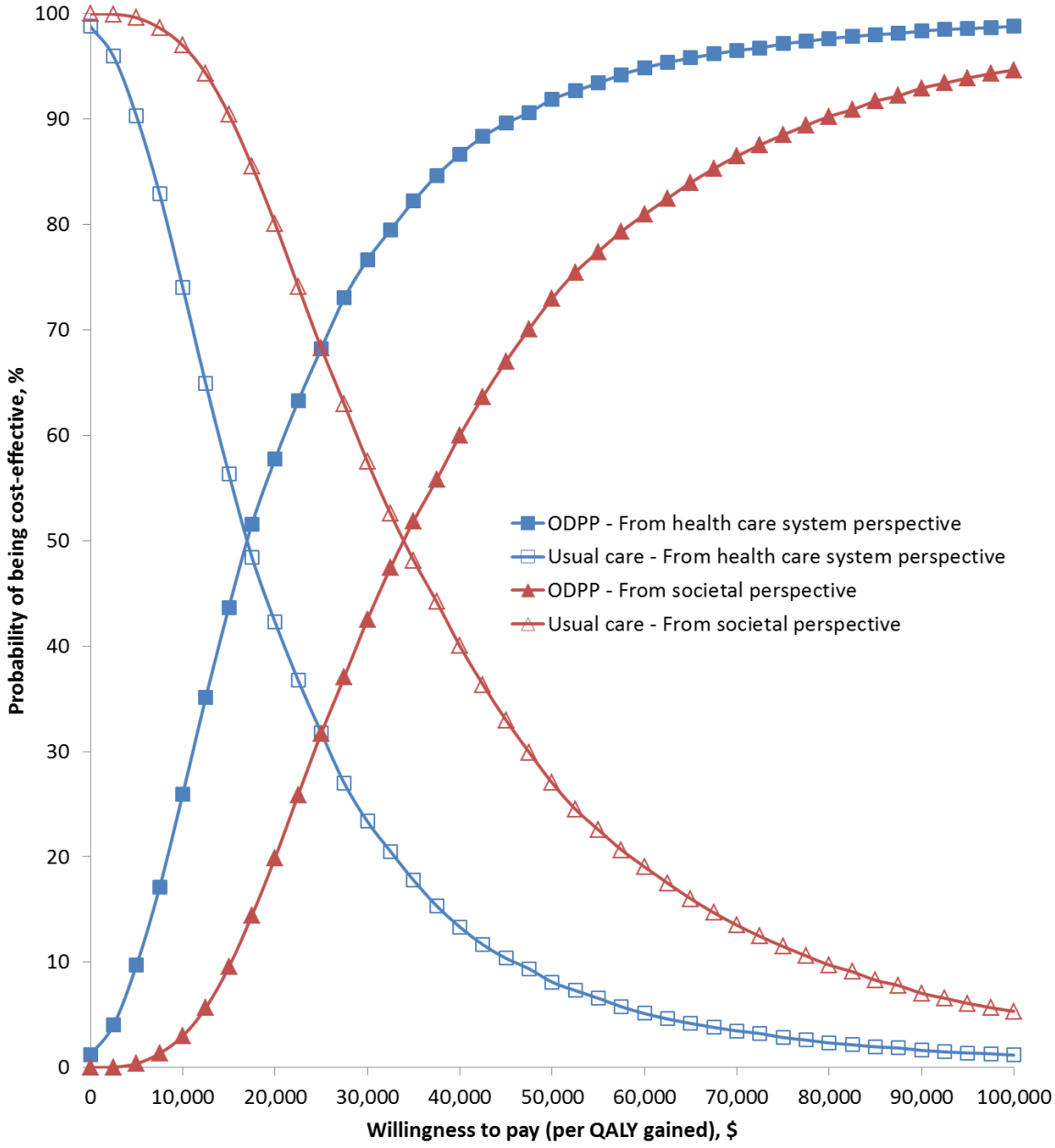

Figure 9.4 Probabilistic sensitivity analysis for the ODPP compared with usual care

9.9 FIGURE LEGENDS

Figure 9.1 Markov-state diagram for the basic model structure

Ovals indicate health states. Subjects may remain within a health state (short curved arrow) or may move to a different health state (straight arrow or long curved arrow) during each model cycle.

Figure 9.2 Tornado diagram from one-way sensitivity analyses for the ODPP compared with usual care

One-way sensitivity analyses included the model parameters whose variations changed the base case incremental cost-effectiveness ratio (ICER) (x axis) by 20% or greater. Horizontal bars depicted the range of ICERs corresponding to the values shown in each parameter. The vertical solid line depicted the base case ICER of $14,351 per quality-adjusted life-year (QALY) gained, the vertical dash line depicted the ICER of $20,000 per QALY gained, and the vertical long dash line depicted the ICER of $50,000 per QALY gained. Variation of all other model parameters not shown in the figure did not increase the ICER to be $20,000 per QALY gained or greater.

Figure 9.3a One-way sensitivity analysis on the multiplier for Website-related costs

The Website-related costs included (1) annual total cost of hosting and maintaining ODPP, (2) annual per-participant time required for technical support, and (3) annual hourly cost of providing technical support. Results were shown as the incremental cost-effectiveness ratio of comparing the ODPP with usual care by the multiplier for considering the Website-related costs

as a whole. ODPP indicated Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

Figure 9.3b One-way sensitivity analysis on the number of participants enrolled in the ODPP

Results were shown as the incremental cost-effectiveness ratio (ICER) of comparing the ODPP with usual care by the number of participants enrolled in the ODPP. When 20 or more participants were enrolled in the ODPP, the model revealed the ICER of less than $20,000 per QALY gained under the base case assumptions and values for all other model parameters. ODPP indicated Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

Figure 9.4 Probabilistic sensitivity analysis for the ODPP compared with usual care

Results were shown as a cost-effectiveness acceptability curve the ODPP. The y-axis showed the likelihood that strategies would be considered cost-effective for a given cost-effectiveness willingness to pay (or acceptability) threshold in the x-axis. ODPP indicated Online adaptation of the Diabetes Prevention Program; QALY, quality-adjusted life-year.

10.0 DISCUSSION

10.1 SUMMARY OF STUDY FINDINGS

This dissertation assessed long-term cost-effectiveness of implementing interventions to control and prevent diabetes in the community and military settings. Three specific aims of this dissertation were to: 1) evaluate cost-effectiveness of implementing the Chronic Care Model (CCM) intervention for diabetes control relative to a provider continuing medical education (PROV) intervention and to usual care (UC) in an underserved community population in Pittsburgh, PA; 2) estimate cost-effectiveness of implementing the CCM intervention through the Diabetes Outreach Clinic (DOC) for diabetes control relative to UC in a military population in San Antonio, TX; and 3) examine cost-effectiveness of implementing an Online adaptation of the Diabetes Prevention Program lifestyle intervention (ODPP) compared with UC (or do nothing) to reduce metabolic risk in the primary care patients with high cardiovascular risk in Pittsburgh, PA.

For the first aim, analyses showed that compared with the PROV and UC strategies over a 3-year period, the CCM strategy reduced the incidence of diabetes with either microvascular or macrovascular complications by an absolute 41.3 (from 86.2% to 44.9%) and 3.9 (from 48.7% to 44.9%) percentage points, respectively. From a health care system perspective, the costs over 3 years for the CCM strategy compared with the UC strategy were $70,317 per QALY gained and $29,573 per diabetes complication averted; the CCM strategy dominated the PROV strategy in both analyses. Over 10 years, the costs per QALY gained from a health care system and a societal perspective for the CCM strategy compared with the UC strategy were $42,179 and

$113,280, respectively. In the probabilistic sensitivity analysis, the PROV was unlikely to be favored over CCM or UC; using a willingness-to-pay threshold of $50,000/QALY, the CCM was favored in 45% of model iterations (compared with 50% for UC and 5% for PROV); with a threshold of $100,000/QALY, the CCM was favored in 51%. This study suggested that application of the comprehensive six-element CCM for diabetes care in an underserved community is a sound and cost-saving investment compared with the provider continuing medical education intervention, and is economically reasonable relative to usual care.

For the second aim, analyses showed that from a health care system perspective, the DOC compared with UC cost $45,495 per QALY gained; from a societal perspective, the DOC compared with UC cost $42,051 per QALY gained (when the model started with the uncomplicated diabetes cohort), $61,243 per QALY gained (when the model started with the DOC cohort), or $61,813 per QALY gained (when the model started with the UC cohort). In one-way sensitivity analyses, results were most sensitive to the yearly costs for specialty care visits. In the probabilistic sensitivity analysis, the DOC was favored in 51% of model iterations using an acceptability threshold of $50,000/QALY and in 72% at a threshold of $100,000/QALY. This study suggested that the DOC strategy for diabetes care, performed with the CCM methodology in a military population, appears to be economically reasonable compared with UC.

For the third aim, analyses showed that compared to UC, the ODPP performed in the pilot study cohort (30% with diabetes) cost $14,351 and $29,331 per QALY gained from a health care system and a societal perspective, respectively. In a hypothetical cohort without diabetes, the ODPP cost $7,777 and $18,263 per QALY gained, respectively. Results were robust in sensitivity analyses, but enrolling cohorts with lower annual risk of developing diabetes (≤1.8%),

enrolling fewer participants (≤15), or increasing the hourly cost (≥$91.2) or the annual per-participant time required (≥1.45 hours) for ODPP technical support could increase the ODPP to cost >$20,000 per QALY gained. In the probabilistic sensitivity analysis, the ODPP was cost-effective in 20-58% of model iterations using an acceptability threshold of $20,000/QALY, 73-92% at $50,000/QALY, and 95-99% at $100,000/QALY. This study suggested that the ODPP delivered in the primary care settings for weight management appears to be an economically reasonable intervention.

10.2 CONTRIBUTION TO THE LITERATURE

The findings of this dissertation are significant and help fill the gap in the literature by providing evidence of revealing the economic value in the effective interventions for diabetes control and prevention. Full economic evaluation (i.e., cost-effectiveness analysis, cost-utility analysis, or cost-benefit analysis) is quite limited in the CCM for diabetes care and in the Internet-based lifestyle intervention for diabetes prevention and risk reduction. The first study that is incorporated into this dissertation provides supporting evidence that performing the full six-element CCM as a secondary and tertiary prevention strategy for diabetes care (i.e., treating diabetes to prevent complications or death) in an underserved community-based population is cost-effective compared with the PROV or UC strategy. To our knowledge, our study provides the first comprehensive attempt to determine the cost-effectiveness of implementing the full CCM for diabetes care in an underserved community-based population. Also, our study confirms Huang et al.'s study (314) that was the only published, full economic evaluation of comparing the costs of implementing the partial CCM to the benefits of improved health

outcomes in people with diabetes in US Federally Qualified Health Centers, and found that CCM reduced lifetime risk of blindness, ESRD, and coronary artery disease, resulting in an increase in health benefits at a cost of $33,386 per QALY gained. Despite discrepancies in study population/design and model setups/assumptions, both of these studies suggest that community-based efforts to implement the CCM are economically reasonable.

The second study that is incorporated into this dissertation provides the finding that implementing the CCM through the DOC for secondary and tertiary prevention of diabetes care in a military population is cost-effective compared with the UC strategy. We believe that this is the first study to evaluate the cost-effectiveness of implementing the CCM in a military population. Although there are differences in study population/design and model setups/assumptions, the first two studies of this dissertation and the study published by Huang et al. (314) indicate that implementation of the CCM compared with UC is economically reasonable in the community and military settings.

The third study that is incorporated into this dissertation provides positive results that compared with UC, the Internet-based weight management intervention delivered as a primary prevention strategy for the primary care population at a high risk of diabetes is at a high level of cost-effectiveness. Research on the cost-effectiveness of this intervention modality is relatively sparse. Among the published reports, four studies that were viewed as a full economic evaluation with a cost-effectiveness outcome of either cost per QALY gained or cost per disability-adjusted life-year (DALY) averted were selected for facilitating comparison with our findings. These studies suggested that the Internet-based weight management intervention compared with UC cost $950-$2,000 (315), $30,400 (316), and $159,500 (317) per QALY gained, or $2,650-$8,830 per DALY averted (318). Although there is a difference in study

population and design between this third study and the published reports, our estimates of ODPP cost-effectiveness ranged from $7,777 to $29,331 per QALY gained, confirming most of these four published studies' observations that the Internet-based weight management intervention is at a moderate to high level of cost-effectiveness.

10.3 STUDY LIMITATIONS

Like all modeling efforts (319), the computational models developed here have several limitations. First, interpretations of study results are contingent on data quality and model assumptions. The source data that were selected and used in all analyses of this dissertation were based on empirical data, pivotal studies, commonly cited references, or the published studies at a nationally representative level, which would ensure the quality of input data. Second, subjects in three studies incorporated into this dissertation are representative of different populations and settings, and thus extrapolation to other populations or health care settings requires caution.

In the first study, we restricted our long-term simulations about costs, quality of life, and clinical outcomes to 3 and 10 years because we employed the empirically observed data on complications directly from Piatt et al.'s clinical trial with 12-month follow-up data. Indeed, to have longer length of simulated follow-up and more robust predicted rates of complications, we would consider using one of the publicly available epidemiological models of diabetes complications which would allow accounting for improvements in intermediate risk factors attributable to the CCM. In addition, because of the short-term follow-up period of Piatt et al.'s clinical trial, we conservatively assumed identical mortality and incidence of ESRD for all three intervention strategies, perhaps biasing the model against the CCM. Lastly, due to lack of utility

data, we applied the same literature-based utility weights to all three intervention strategies, and again, this is a conservative response that may underestimate the CCM's potential to improve quality of life.

In the second study, the effectiveness data were not from a randomized controlled trial, resulting in differences in baseline characteristics; hence, the analyses adjusted for significant differences in demographics and clinical characteristics at baseline. In addition, assuming an identical risk of disease progression for DOC and UC patients who have had diabetes complications is a conservative strategy that potentially biases the model against the CCM effect. Lastly, because there is no empirical utility data, we applied the same literature-based utility weights to both strategies, which again may underestimate the CCM's potential to improve quality of life.

In the third study, a ten-year time frame was used to simulate the cost-effectiveness of the ODPP due to uncertainty in the empirical data for long-term effectiveness of weight change on diabetes risk (113,299). However, delaying or preventing type 2 diabetes will delay or prevent incurring the direct medical costs of diabetes, including the costs of diabetes education and nutritional counseling, glucose monitoring, treatment, surveillance for complications, and treatment of complications. Hence, adopting a ten-year time horizon may overestimate treatment costs and underestimate the benefits of the ODPP intervention. In addition, assuming an identical risk of developing diabetes-related complications for participants with stable diabetes who achieved different magnitude of weight gain or loss is a conservative strategy. This is because according to the Look AHEAD (Action for Health in Diabetes) study (320), the overweight/obese patients with type 2 diabetes with larger weight losses were associated with greater improvements in cardiovascular disease risk factors, which may reduce diabetes-related

complications. Thus, this assumption potentially biases the model against the ODPP effect. Furthermore, because there is no empirical utility or mortality data from the ODPP intervention, application of the same literature-based utility weights and the same mortality risks to the four health states in the cohorts who achieved different magnitude of weight gain or loss may again underestimate the ODPP's potential to improve quality of life and length of life. Lastly, the health- and cost-generating obesity-related conditions used in the current model were only limited to diabetes. Many other conditions known to be obesity-related, as illustrated by increased health and economic burden, were not considered, making our model conservative and biasing against the ODPP effect.

10.4 PUBLIC HEALTH SIGNIFICANCE

Diabetes is common, serious, and costly, representing not only a major clinical care concern but also an immense and growing public health challenge. In 2010, diabetes affected 25.8 million Americans – 8.3 percent of the US population – including 18.8 million people with diagnosed diabetes and 7.0 million people with undiagnosed diabetes (268). Another seventy-nine million (35%) American adults aged 20 years or older with prediabetes were at high risk of developing the disease over the next decade (268). One in three American children born in 2000 is likely to develop diabetes over their lifetimes (32). The percentage of the population with diagnosed diabetes continues to rise, with one study projecting that as many as one in three US adults could have diabetes by 2050 if current trends continue (269).

Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness among adults; a major cause of heart disease and stroke; and the

seventh leading cause of death in the US (268). Financially, diabetes imposes a substantial burden on the US economy in terms of increased direct medical costs and indirect costs from work-related absenteeism, reduced productivity at work and at home, reduced labor force participation from chronic disability, and premature mortality. Additionally, diabetes imposes high intangible costs on society in terms of reduced quality of life as well as pain and suffering of individuals with diabetes, their families, and friends (231). The total estimated cost of diagnosed diabetes in 2012 reached $245 billion (including $176 billion in direct medical costs and $69 billion in reduced productivity), a 41% increase from the previous estimate of $174 billion in 2007 (231).

Overweight and obesity also rank prominently among current major clinical care and public health problems since they are common, serious, and costly as well as the major predisposing factor for insulin resistance and type 2 diabetes. Approximately 69% of US adults aged 20 years or older were overweight or obese in 2009-2010, and 36% (over 78 million) were obese (321,322). Overweight and obesity are the major risk factors for morbidity from a wide range of medical conditions, social conditions, psychological conditions, and impaired quality of life (323). Higher body weights are also associated with an increase in mortality from all causes (323). Financially, medical costs associated with adult obesity in the US are estimated to range from $147 billion to nearly $210 billion per year (324,325). People who are classified as obese spend $1,429 (42 percent) more on health care costs compared to those of normal-weight. The additional costs attributable to obesity are almost entirely a result of costs generated from treating the diseases that obesity promotes (324,326).

Considering the increasing prevalence of diabetes and the burgeoning cost of managing patients with this disease, improving the efficiency of diabetes management is an important goal.

Many interventions can reduce the health and financial burden of diabetes and overweight/obesity; however, health care resources are limited. Hence, interventions for diabetes prevention and control should be prioritized (260). Indeed, the rapid rate of growth in health care expenditures in the US raises both public and private decision makers' great concerns about the financial sustainability of the US health care system. Now, an increasing number of people believe that, in deciding whether to cover a particular treatment or prevention strategy, employer or other health care payers are justified in asking whether the net benefits of the strategy are worth its costs (261). Costs are already a consideration in establishment of public health priorities or recommendations for clinical practices in much of the world (261); in other words, efforts to control expenditures should focus on seeking the value of health care interventions, reflecting health benefits that justify their costs (271). This dissertation report compared the effectiveness and costs of various interventions in order to identify those that are the most effective for a lower cost. The cost-effectiveness analysis conducted in the three studies presented demonstrates that this is a useful tool for this purpose. Such analyses consist of compiling the incremental cost-effectiveness ratio (e.g., cost per QALY gained), which is calculated as a ratio of the difference in costs to the difference in effectiveness between the intervention of interest and the comparison intervention, and can provide a key measure of the value of a health care intervention (260,271).

There are no absolute criteria for cost-effectiveness; however, in general, interventions costing less than $20,000 per QALY gained may be considered as having strong evidence for adoption; interventions costing $20,000 to $100,000 per QALY gained have moderate evidence; and those costing more than $100,000 per QALY gained have weaker evidence for adoption (312,327). Hence, the findings of the three studies in this dissertation (see Section 10.1) suggest

that compared with usual care, the CCM intervention (delivered in either an underserved community population or a military population) appears to be a good-value secondary and tertiary prevention strategy for diabetes, and likewise, the ODPP intervention (delivered in a primary care population with high cardiovascular risk) for primary diabetes prevention provides both health benefits and good use of health care resources. Policy makers should consider giving these interventions a higher priority.

Epidemiology (or clinical epidemiology) is an integral part of a cost-effectiveness analysis. This is because epidemiology is a set of methods and techniques that are used to create and interpret scientific observations in medicine and public health problems. These methods and techniques are used to study the natural history and prognosis of disease, and evaluate the role of both existing and newly developed preventive and therapeutic measures and modes of health care delivery as determinants of health-related states or events (328,329). Specifically, epidemiology can be used to measure and value the impact of health care interventions either under ideal conditions (efficacy) or in real-life situation (effectiveness), which is one of crucial elements in a cost-effectiveness analysis.

The findings in this dissertation using the economic evaluation (i.e., cost-effectiveness analysis) of interventions for diabetes prevention and control are of public health significance. The rationale for economic evaluation is simple: Resources are always limited; not everything worth doing can be done, and not everything that can be done is worth doing (330). Economic evaluation is an increasingly used tool which aims to provide a formal, explicit and transparent framework for informing decisions about allocating public funds in the health care sector (331). By utilizing economic evaluation in the fields of clinical care and public health, questions about the efficiency of allocating resources to fund interventions aimed at improving clinical care and

public health can be addressed. In other words, the basic economic principle of establishing the opportunity cost of devoting resources to a particular intervention, i.e. whether the benefits of devoting resources to a particular intervention exceed the benefits that could have been achieved with an alternative use of those resources, can be used to ensure that public funds are directed to the most valuable interventions (331).

Public health is the art and science of preventing disease, prolonging life, and promoting health through organized community efforts. It is made up of systematic efforts to identify health needs and to organize comprehensive health services within a well-defined population base. Thus, planning of and prioritizing clinical services are integral parts of public health (330). An important area where economic evaluation seems to play a major role is in insurance coverage decisions, especially those concerning pharmaceutical coverage (330). For example, in the UK, the National Institute for Health and Clinical Excellence (NICE) assumed responsibility for the development of indicators for the pay-for-performance program to ensure that cost-effectiveness is taken into account and to increase transparency and independence (332). To encourage use of good-value services or treatments, in the USA, the insurers commonly reduce cost sharing (user charges) when patients use preferred providers (e.g., those offering higher quality care) or cost-effective prescription drugs and preventive services. Through the work of NICE and the planned introduction of value-based pricing for drugs in 2014 in England, initiatives already exist to encourage cost-effective prescribing (332). In addition, economic evaluation could help identify the interventions which may potentially reduce the overall costs of health care, which is one of the major public health concerns and one of the goals contained in the Patient Protection and Affordable Care Act in the US (332).

Indeed, to achieve state and national objectives for improved clinical care and public health, more widespread adoption of evidence-based strategies has been recommended. It has been argued that increased focus on evidence-based medicine and public health practice has numerous direct and indirect benefits, including access to more and higher-quality information on what works, a higher likelihood of successful programs and policies being implemented, greater workforce productivity, and more efficient use of public and private resources (333). Economic evaluation is one of the critical analytic tools which can be useful in accelerating the uptake of evidence-based medicine and public health practice, and it can provide information to help assess the relative value of alternative expenditures on public health programs/policies and has become an increasingly important tool for researchers, practitioners, and policy makers (333). Also, it has been argued that both clinical epidemiology and public health share the view that efficacy, effectiveness, and cost-effectiveness are all important in defining the impact of clinical and public health care strategies on health disparities (329).

10.5 FUTURE RESEARCH

When facing increasing demand for limited resources from the growing number of new effective interventions available, translational research with full economic evaluations is vital to inform changes in the health care delivery systems that would improve diabetes management, and even to guide enhanced public health efforts and community-based programs for diabetes prevention.

Indeed, evidence on the cost-effectiveness of the chronic care model (CCM) for diabetes care is still very limited, and more research is needed to understand the costs and benefits to practices, payers, and patients. Furthermore, there is no published available comparative

effectiveness research with full economic analysis among different effective quality improvement strategies on diabetes management, e.g. CCM, team changes, and case management. Since several of these strategies may be marginally beneficial relative to other strategies and the resource intensity of the different strategies varied significantly (253), further exploration of the relative cost-effectiveness of these quality improvement strategies is needed. Public or private policy decision makers might also consider how they value the expected benefits before widely implementing such quality improvement strategies. Moreover, among different modalities of quality improvement strategies for delivering secondary and tertiary diabetes prevention, further research is warranted to identify which interventions and combination of quality improvement strategies will optimally improve important outcomes in patients with diabetes at an acceptable cost to aid health-system planning.

In addition, there is a paucity of full economic evaluations for a successful Internet-delivered weight management program in comparison with the in-person delivery of a comparable program. Such a comparison would inform policy decisions about the cost-effectiveness of different modalities of disseminating effective weight management as the primary diabetes prevention strategies to a large population of overweight and obese individuals.

BIBLIOGRAPHY

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33(Suppl 1):S62-S69.

2. Centers for Disease Control and Prevention. *National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008. Accessed March 15, 2010, at http://www.cdc.gov/diabetes/pubs/factsheet07.htm.

3. American Diabetes Association. Standards of medical care in diabetes-2010. *Diabetes Care* 2010;33(Suppl 1):S11-S61.

4. Leu JP, Zonszein J. Diagnostic criteria and classification of diabetes. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 107-115.

5. de Courten M. Classification of diabetes. In: Herman WH, Kinmonth AL, Wareham NJ, Williams R, eds. *The Evidence Base for Diabetes Care*. 2nd ed. West Sussex: Wiley-Blackwell; 2010: 9-24.

6. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047-1053.

7. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4-14.

8. Roglic G, Unwin N. Mortality attributable to diabetes: estimates for the year 2010. *Diabetes Res Clin Pract* 2010;87:15-19.

9. Zhang P, Zhang X, Brown J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:293-301.

10. Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. ABC of arterial and venous disease: vascular complications of diabetes. *BMJ* 2000;320:1062-1066.

11. Davies MJ, Tringham JR, Troughton J, Khunti KK. Prevention of Type 2 diabetes mellitus. A review of the evidence and its application in a UK setting. *Diabet Med* 2004;21:403-414.

12. Centers for Disease Control and Prevention National Center for Chronic Disease Prevention and Health Promotion. *Diabetes-successes and opportunities for population-based prevention and control: At a Glance 2009*. Accessed March 15, 2010, at http://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/diabetes.pdf.

13. Hoerger TJ, Zhang P, Segel JE, Gregg EW, Narayan KM, Hicks KA. Improvements in risk factor control among persons with diabetes in the United States: evidence and implications for remaining life expectancy. *Diabetes Res Clin Pract* 2009;86:225-232.

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

15. Hogan P, Dall T, Nikolov P. American Diabetes Association. Economic costs of diabetes in the US in 2002. *Diabetes Care* 2003;26:917-932.

16. Huang ES, Basu A, O'Grady MJ, Capretta JC. Using clinical information to project federal health care spending. *Health Aff (Millwood)* 2009;28:w978-w990.

17. Engelgau MM, Geiss LS, Saaddine JB, et al. The evolving diabetes burden in the United States. *Ann Intern Med* 2004;140:945-950.

18. Zhang P, Engelgau MM, Norris SL, Gregg EW, Narayan KM. Application of economic analysis to diabetes and diabetes care. *Ann Intern Med* 2004;140:972-977.

19. Detsky AS, Laupacis A. Relevance of cost-effectiveness analysis to clinicians and policy makers. *JAMA* 2007;298:221-224.

20. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990;113:147-154.

21. Wranik D. Using economic evidence as a support tool for policy decisions: Herculean or Sisyphean effort? *Expert Rev Pharmacoecon Outcomes Res* 2008;8:329-332.

22. Torgerson DJ. Cost-effectiveness analysis and health policy. *Nestle Nutr Workshop Ser Clin Perform Programme* 2009;12:95-104.

23. Zajac J, Shrestha A, Patel P, Poretsky L. The main events in the history of diabetes mellitus. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 3-16.

24. Bennett PH, Knowler WC. Definition, diagnosis, and classification of diabetes mellitus and glucose homeostasis. In: Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ, eds. *Joslin's Diabetes Mellitus*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2005: 331-339.

25. Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. *Diabetes Care* 2006;29:2114-2116.

26. Geiss LS, Pan L, Cadwell B, Gregg EW, Benjamin SM, Engelgau MM. Changes in incidence of diabetes in U.S. adults, 1997-2003. *Am J Prev Med* 2006;30:371-377.

27. Centers for Disease Control and Prevention. State-specific incidence of diabetes among adults-participating states, 1995-1997 and 2005-2007. *MMWR* 2008;57:1169-1173.

28. Roglic G, Unwin N, Bennett PH, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care* 2005;28:2130-2135.

29. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care* 1998;21:1138-1145.

30. Gregg EW, Gu Q, Cheng YJ, Narayan KM, Cowie CC. Mortality trends in men and women with diabetes, 1971 to 2000. *Ann Intern Med* 2007;147:149-155.

31. Chamany S, Tabaei BP. Epidemiology. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 117-127.

32. Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. *JAMA* 2003;290:1884-1890.

33. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183-1197.

34. Ali O. Type 1 diabetes mellitus: epidemiology, genetics, pathogenesis, and clinical manifestations. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 181-201.

35. Trevisan R, Vedovato M, Tiengo A. The epidemiology of diabetes mellitus. *Nephrol Dial Transplant* 1998;13(Suppl 8):2-5.

36. Stene LC, Tuomilehto J, Rewers M. Global epidemiology of type 1 diabetes. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 355-383.

37. Triplitt CL, Reasner, II CA, Isley WL. Diabetes mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York: McGraw-Hill Medical; 2008: 1205-1242.

38. LaPorte RE, Matsushima M, Chang YF. Prevalence and incidence of insulin-dependent diabetes. In: Harris MI, Cowie CC, Reiber G, Boyko E, Stern M, Bennett P, eds. *Diabetes in America*. 2nd ed. Washington D.C.: U.S. Department of Health and Human Services; 1995:37-46. NIH publication no. 95-1468.

39. SEARCH for Diabetes in Youth Study Group, Liese AD, D'Agostino RB Jr, Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics* 2006;118:1510-1518.

40. Dall TM, Mann SE, Zhang Y, et al. Distinguishing the economic costs associated with type 1 and type 2 diabetes. *Popul Health Manag* 2009;12:103-110.

41. Dokheel TM for Pittsburgh Diabetes Epidemiology Research Group. An epidemic of childhood diabetes in the United States? Evidence from Allegheny County, PA. *Diabetes Care* 1993;16:1606-1611.

42. Melton LJ 3rd, Palumbo PJ, Chu CP. Incidence of diabetes mellitus by clinical type. *Diabetes Care* 1983;6:75-86.

43. The Writing Group for the SEARCH for Diabetes in Youth Study Group, Dabelea D, Bell RA, D'Agostino RB Jr, et al. Incidence of diabetes in youth in the United States. *JAMA* 2007;297:2716–2724.

44. Krolewski AS, Warram JH, Rand LI, Kahn CR. Epidemiologic approach to the etiology of type I diabetes mellitus and its complications. *N Engl J Med* 1987;317:1390-1398.

45. Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. *Pediatr Clin North Am* 2005;52:1553-1578.

46. Barr ELM, Zimmet PZ, Shaw JE. Mortality and life expectancy associated diabetes. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 603-625.

47. Entmacher PS, Root HF, Marks HH. Longevity of diabetic patients in recent years. *Diabetes* 1964;13:373-377.

48. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. *Diabetes* 2006;55:1463-1469.

49. Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ. Mortality trends in type 1 diabetes. The Allegheny County (Pennsylvania) Registry 1965-1999. *Diabetes Care* 2001;24:823-827.

50. Portuese E, Orchard T. Mortality in insulin-dependent diabetes. In: Harris MI, Cowie CC, Reiber G, Boyko E, Stern M, Bennett P, eds. *Diabetes in America*. 2nd ed. Washington D.C.: U.S. Department of Health and Human Services; 1995:221-232. NIH publication no. 95-1468.

51. Diabetes Epidemiology Research International Mortality Study Group. Major cross-country differences in risk of dying for people with IDDM. *Diabetes Care* 1991;14:49-54.

52. Florkowski CM, Scott RS, Graham PJ, Han DY, Moir CL. Cause-specific and total mortality in the Canterbury (New Zealand) insulin-treated Diabetic Registry population: a 15-year follow-up study. *Diabet Med* 2003;20:191-197.

53. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med* 1999;16:466-471.

54. Green A, Jensen OM. Frequency of cancer among insulin-treated diabetic patients in Denmark. *Diabetologia* 1985;28:128-130.

55. Alberti KG. Insulin dependent diabetes mellitus: a lethal disease in the developing world. *BMJ* 1994;309:754-755.

56. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782-787.

57. The Eurodiab Ace Study Group and The Eurodiab Ace Substudy 2 Study Group. Familial risk of type I diabetes in European children. *Diabetologia* 1998;41:1151-1156.

58. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR. Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *N Engl J Med* 1984;311:149-152.

59. Tuomilehto J, Podar T, Tuomilehto-Wolf E, Virtala E. Evidence for importance of gender and birth cohort for risk of IDDM in offspring of IDDM parents. *Diabetologia* 1995;38:975-982.

60. Harjutsalo V, Reunanen A, Tuomilehto J. Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. *Diabetes* 2006;55:1517-1524.

61. Kyvik KO, Green A. Genetic epidemiology of type 1 diabetes mellitus. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 403-412.

62. Hyttinen V, Kaprio J, Kinnunen L, Koskenvuo M, Tuomilehto J. Genetic liability of type 1 diabetes and the onset age among 22,650 young Finnish twin pairs: a nationwide follow-up study. *Diabetes* 2003;52:1052-1055.

63. Kyvik KO, Green A, Beck-Nielsen H. Concordance rates of insulin dependent diabetes mellitus: a population based study of young Danish twins. *BMJ* 1995;311:913-917.

64. Degnbol B, Green A. Diabetes mellitus among first- and second-degree relatives of early onset diabetics. *Ann Hum Genet* 1978;42:25-47.

65. Tillil H, Köbberling J. Age-corrected empirical genetic risk estimates for first-degree relatives of IDDM patients. *Diabetes* 1987;36:93-99.

66. Concannon P, Erlich HA, Julier C, et al. Type 1 diabetes: evidence for susceptibility loci from four genome-wide linkage scans in 1,435 multiplex families. *Diabetes* 2005;54:2995-3001.

67. Undlien DE, Lie BA, Thorsby E. HLA complex genes in type 1 diabetes and other autoimmune diseases. Which genes are involved? *Trends Genet* 2001;17:93-100.

68. Thorsby E, Rønningen KS. Particular HLA-DQ molecules play a dominant role in determining susceptibility or resistance to type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1993;36:371-377.

69. Pugliese A, Miceli D. The insulin gene in diabetes. *Diabetes Metab Res Rev* 2002;18:13-25.

70. Barratt BJ, Payne F, Lowe CE, et al. Remapping the insulin gene/IDDM2 locus in type 1 diabetes. *Diabetes* 2004;53:1884-1889.

71. Davies JL, Kawaguchi Y, Bennett ST, et al. A genome-wide search for human type 1 diabetes susceptibility genes. *Nature* 1994;371:130-136.

72. Wong AH, Gottesman II, Petronis A. Phenotypic differences in genetically identical organisms: the epigenetic perspective. *Hum Mol Genet* 2005;14(Spec No 1):R11-R18.

73. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999;281:2005-2012.

74. Carlisle BA, Kroon LA, Koda-Kimble MA. Diabetes mellitus. In: Koda-Kimble MA, Young LY, Alldredge BK, Corelli RL, Guglielmo BJ, Kradjan WA, Williams BR, eds. *Applied Therapeutics: The Clinical Use of Drugs*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2008: 50-1-50-86.

75. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Reiber G, Boyko E, Stern M, Bennett P, eds. *Diabetes in America*. 2nd ed. Washington D.C.: U.S. Department of Health and Human Services; 1995:47-68. NIH publication no. 95-1468.

76. Warram JH, Krolewski AS. Epidemiology of diabetes mellitus. In: Kahn CR, Weir GC, King GL, Jacobson AM, Moses AC, Smith RJ, eds. *Joslin's Diabetes Mellitus*. 14th ed. Philadelphia: Lippincott Williams & Wilkins; 2005: 341-354.

77. Fonseca V, John-Kalarickal J. Type 2 diabetes mellitus: epidemiology, genetics, pathogenesis, and clinical manifestations. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 203-220.

78. Saaddine JB, Cadwell B, Gregg EW, et al. Improvements in diabetes processes of care and intermediate outcomes: United States, 1988-2002. *Ann Intern Med* 2006;144:465-474.

79. Dodd AH, Colby MS, Boye KS, Fahlman C, Kim S, Briefel RR. Treatment approach and HbA1c control among US adults with type 2 diabetes: NHANES 1999-2004. *Curr Med Res Opin* 2009;25:1605-1613.

80. Leibson CL, O'Brien PC, Atkinson E, Palumbo PJ, Melton LJ 3rd. Relative contributions of incidence and survival to increasing prevalence of adult-onset diabetes mellitus: a population-based study. *Am J Epidemiol* 1997;146:12-22.

81. Centers for Disease Control and Prevention. *National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2005*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2005. Accessed April 08, 2010, at http://www.cdc.gov/diabetes/pubs/factsheet05.htm.

82. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care* 2006;29:1263-1268.

83. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care* 2009;32:287-294.

84. American Diabetes Association. Type 2 diabetes in children and adolescents. *Diabetes Care* 2000;23:381-389.

85. Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 2000;136:664-672.

86. Fagot-Campagna A, Narayan KM, Imperatore G. Type 2 diabetes in children. *BMJ* 2001;322:377-378.

87. Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth. *Diabetes Care* 1999;22:345-354.

88. Goran MI, Ball GD, Cruz ML. Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab* 2003;88:1417-1427.

89. Geiss LS, Wang J, Gregg EW, Engelgau MM. Epidemiology of type 2 diabetes in North America. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 241-254.

90. McBean AM, Li S, Gilbertson DT, Collins AJ. Differences in diabetes prevalence, incidence, and mortality among the elderly of four racial/ethnic groups: Whites, Blacks, Hispanics, and Asians. *Diabetes Care* 2004;27:2317-2324.

91. Burke JP, O'Brien P, Ransom J, et al. Impact of case ascertainment on recent trends in diabetes incidence in Rochester, Minnesota. *Am J Epidemiol* 2002;155:859-865.

92. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med* 1999;159:1450-1456.

93. Green C, Blanchard JF, Young TK, Griffith J. The epidemiology of diabetes in the Manitoba-registered First Nation population: current patterns and comparative trends. *Diabetes Care* 2003;26:1993-1998.

94. Pinhas-Hamiel O, Dolan LM, Daniels SR, Standiford D, Khoury PR, Zeitler P. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr* 1996;128(5 Pt 1):608-615.

95. Geiss LS, Herman WH, Smith PJ. Mortality in non-insulin-dependent diabetes. In: Harris MI, Cowie CC, Reiber G, Boyko E, Stern M, Bennett P, eds. *Diabetes in America*. 2nd ed. Washington D.C.: U.S. Department of Health and Human Services; 1995:233-258. NIH publication no. 95-1468.

96. Collins VR, Dowse GK, Ram P, Cabealawa S, Zimmet PZ. Non-insulin-dependent diabetes and 11-year mortality in Asian Indian and Melanesian Fijians. *Diabet Med* 1996;13:125-132.

97. Shaw JE, Hodge AM, de Courten M, Chitson P, Zimmet PZ. Isolated post-challenge hyperglycaemia confirmed as a risk factor for mortality. *Diabetologia* 1999;42:1050-1054.

98. Nakagami T; DECODA Study Group. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* 2004;47:385-394.

99. Buse JB, Polonsky KS, Burant CF. Type 2 diabetes mellitus. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: Saunders Elsevier; 2008: 1329-1389.

100. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005;365:1333-1346.

101. Stumvoll M, Goldstein BJ, van Haeften TW. Pathogenesis of type 2 diabetes. *Endocr Res* 2007;32:19-37.

102. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: pathogenesis and treatment. *Lancet* 2008;371:2153-2156.

103. Froguel P, Velho G. Genetic determinants of type 2 diabetes. *Recent Prog Horm Res* 2001;56:91-105.

104. Zimmet PZ. Kelly West Lecture 1991. Challenges in diabetes epidemiology-from West to the rest. *Diabetes Care* 1992;15:232-252.

105. Narayan KM, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U.S. *Diabetes Care* 2007;30:1562-1566.

106. Clark DO. Physical activity efficacy and effectiveness among older adults and minorities. *Diabetes Care* 1997;20:1176-1182.

107. Alberti KG. Impaired glucose tolerance: what are the clinical implications? *Diabetes Res Clin Pract* 1998;40(Suppl):S3-S8.

108. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.

109. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 1992;15:815-819.

110. Harris MI. Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 1993;16:642-652.

111. Harris MI, Eastman RC. Early detection of undiagnosed diabetes mellitus: a US perspective. *Diabetes Metab Res Rev* 2000;16:230-236.

112. Harris MI, Hadden WC, Knowler WC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20-74 yr. *Diabetes* 1987;36:523-534.

113. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol* 1997;146:214-222.

114. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the U.S.: 1990-1998. *Diabetes Care* 2000;23:1278-1283.

115. Kahn R, Alperin P, Eddy D, et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* 2010;375:1365-1374.

116. Genuth S, Alberti KG, Bennett P, et al; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160-3167.

117. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003;26(Suppl 1):S5-S20.

118. Nathan DM, Davidson MB, DeFronzo RA, et al; American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007;30:753-759.

119. Forouhi NG, Balkau B, Borch-Johnsen K, et al; EDEG. The threshold for diagnosing impaired fasting glucose: a position statement by the European Diabetes Epidemiology Group. *Diabetologia* 2006;49:822-827.

120. World Health Organization. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation*. Geneva: WHO; 2006.

121. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980-1985 World Health Organization diagnostic criteria. *Diabetes Care* 1997;20:1859-1862.

122. Borch-Johnsen K, Colagiuri S, Balkau B, et al. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. *Diabetologia* 2004;47:1396-1402.

123. International Diabetes Federation. The global burden. In: Unwin N, Gan D, Mbanya JC, et al, eds. *IDF Diabetes Atlas*. 4th ed. Brussels: International Diabetes Federation; 2009:21-37.

124. Abdul-Ghani MA, DeFronzo RA. Pathophysiology of prediabetes. *Curr Diab Rep* 2009;9:193-199.

125. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care* 1998;21:518-524.

126. Benjamin SM, Valdez R, Geiss LS, Rolka DB, Narayan KM. Estimated number of adults with prediabetes in the US in 2000: opportunities for prevention. *Diabetes Care* 2003;26:645-649.

127. Davidson MB, Landsman PB, Alexander CM. Lowering the criterion for impaired fasting glucose will not provide clinical benefit. *Diabetes Care* 2003;26:3329-3330.

128. Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005-2006. *Diabetes Care* 2009;32:342-347.

129. Hanna-Moussa A, Gardner MJ, Kurukulasuriya LR, Sowers JR. Dysglycemia/prediabetes and cardiovascular risk factors. *Rev Cardiovasc Med* 2009;10:202-208.

130. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006;29:1130-1139.

131. Abdul-Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. *Diabetes* 2006;55:1430-1435.

132. Hanefeld M, Koehler C, Fuecker K, Henkel E, Schaper F, Temelkova-Kurktschiev T; Impaired Glucose Tolerance for Atherosclerosis and Diabetes study. Insulin secretion and insulin sensitivity pattern is different in isolated impaired glucose tolerance and impaired fasting glucose: the risk factor in Impaired Glucose Tolerance for Atherosclerosis and Diabetes study. *Diabetes Care* 2003;26:868-874.

133. Festa A, D'Agostino R Jr, Hanley AJ, Karter AJ, Saad MF, Haffner SM. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. *Diabetes* 2004;53:1549-1555.

134. Santaguida PL, Balion C, Hunt D, et al. *Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose*. Summary, Evidence Report/Technology Assessment No. 128. (Prepared by the McMaster Evidence-based Practice Center under Contract No. 290-02-0020). AHRQ Pub. No. 05-E026-1. Rockville, MD: Agency for Healthcare Research and Quality; August 2005.

135. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 2010;55:1310-1317.

136. Alberti KG. The clinical implications of impaired glucose tolerance. *Diabet Med* 1996;13:927-937.

137. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003;46:3-19.

138. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 2001;161:397-405.

139. Williams DE, Cadwell BL, Cheng YJ, et al. Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999-2000. *Pediatrics* 2005;116:1122-1126.

140. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;346:802-810.

141. Cali AM, Bonadonna RC, Trombetta M, Weiss R, Caprio S. Metabolic abnormalities underlying the different prediabetic phenotypes in obese adolescents. *J Clin Endocrinol Metab* 2008;93:1767-1773.

142. Cali AM, Man CD, Cobelli C, et al. Primary defects in beta-cell function further exacerbated by worsening of insulin resistance mark the development of impaired glucose tolerance in obese adolescents. *Diabetes Care* 2009;32:456-461.

143. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med* 2003;157:821-827.

144. Weiss R, Taksali SE, Tamborlane WV, Burgert TS, Savoye M, Caprio S. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care* 2005;28:902-909.

145. Garber AJ, Handelsman Y, Einhorn D, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risks of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract* 2008;14:933-946.

146. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J Am Coll Cardiol* 2006;47:1093-1100.

147. Hoerger TJ, Ahmann AJ. The impact of diabetes and associated cardiometabolic risk factors on members: strategies for optimizing outcomes. *J Manag Care Pharm* 2008;14(1 Suppl C):S2-S14.

148. Fowler M. Hyperglycemic crisis in adults: pathophysiology, presentation, pitfalls, and prevention. *Clin Diabetes* 2009;27:19-23.

149. Wang J, Williams DE, Narayan KM, Geiss LS. Declining death rates from hyperglycemic crisis among adults with diabetes, U.S., 1985-2002. *Diabetes Care* 2006;29:2018-2022.

150. Centers for Disease Control and Prevention: National Diabetes Surveillance System. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2009. Accessed April 27, 2010, at http://www.cdc.gov/diabetes/statistics/complications_national.htm.

151. Kuo S, Fleming BB, Gittings NS, et al. Trends in care practices and outcomes among Medicare beneficiaries with diabetes. *Am J Prev Med* 2005;29:396-403.

152. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009;32:1335-1343.

153. Rewers AB. Epidemiology of acute complications: diabetic ketoacidosis, hyperglycemic hyperosmolar state and hypoglycemia. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 577-602.

154. Feng Y, Fleckman AM. Acute hyperglycemic syndromes: diabetic ketoacidosis and the hyperosmolar state. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 281-295.

155. Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. *Diabetes Care* 1997;20:349-354.

156. Agency for Healthcare Research and Quality: HCUP Statistical Briefs Chronological. Rockville, MD: Agency for Healthcare Research and Quality, 2010. Accessed April 30, 2010, at http://www.hcup-us.ahrq.gov/reports/statbriefs.jsp.

157. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005;28:1245-1249.

158. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902-1912.

159. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272-2279.

160. Alsahli M, Gerich JE. Hyperglycemia in diabetes mellitus. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 297-312.

161. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. *JAMA* 2002;287:2511-2518.

162. Levine BS, Anderson BJ, Butler DA, Antisdel JE, Brackett J, Laffel LM. Predictors of glycemic control and short-term adverse outcomes in youth with type 1 diabetes. *J Pediatr* 2001;139:197-203.

163. Fowler MJ. Hypoglycemia. *Clin Diabetes* 2008;26:170-173.

164. International Diabetes Federation. What is diabetes? In: Unwin N, Gan D, Mbanya JC, et al, eds. *IDF Diabetes Atlas*. 4th ed. Brussels: International Diabetes Federation; 2009:15-19.

165. Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clin Diabetes* 2008;26:77-82.

166. Laud K, Shabto U. Diabetic retinopathy. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 331-346.

167. Wong TY, Klein R. The epidemiology of eye diseases in diabetes. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 475-497.

168. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003;26:2653-2664.

169. Fong DS, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care* 2004;27:2540-2553.

170. Garg S, Davis RM. Diabetic retinopathy screening update. *Clin Diabetes* 2009;27:140-145.

171. Crawford TN, Alfaro DV 3rd, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. *Curr Diabetes Rev* 2009;5:8-13.

172. Saaddine JB, Narayan KM, Engelgau MM, Aubert RE, Klein R, Beckles GL. Prevalence of self-rated visual impairment among adults with diabetes. *Am J Public Health* 1999;89:1200-1205.

173. Lloyd CE, Klein R, Maser RE, Kuller LH, Becker DJ, Orchard TJ. The progression of retinopathy over 2 years: the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. *J Diabetes Complications* 1995;9:140-148.

174. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol* 1994;112:1217-1228.

175. Mimoun L, Massin P, Steg G. Retinal microvascularisation abnormalities and cardiovascular risk. *Arch Cardiovasc Dis* 2009;102:449-456.

176. Boulton AJ, Vinik AI, Arezzo JC, et al; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005;28:956-962.

177. Boulton AJM. Epidemiology of diabetic neuropathy. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 565-576.

178. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care* 2004;27:1458-1486.

179. Chin RL, Rubin M. Diabetic neuropathy. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 357-370.

180. Blézquez-Medela AM, López-Novoa JM, Martínez-Salgado C. Mechanisms involved in the genesis of diabetic nephropathy. *Curr Diabetes Rev* 2010;6:68-87.

181. Molitch ME, DeFronzo RA, Franz MJ, et al; American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004;27(Suppl 1):S79-S83.

182. Burrows NR, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continues to decline. Diabetes Care 2010;33:73-77.

183. Candido R, Cooper ME, Jandeleit-Dahm KAM. The pathogenesis of macrovascular complications including atherosclerosis in diabetes. In: Holt RIG, Cockram CS, Flyvbjerg A, Goldstein BJ, eds. *Textbook of Diabetes*. 4th ed. West Sussex: Wiley-Blackwell; 2010: 637-656.

184. Barrett-Connor E. Epidemiology of large-vessel disease in diabetes: coronary heart disease and stroke. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 519-538.

185. International Diabetes Federation. Glossary, acronyms & references. In: Gan D, Mbanya JC, Allgot B, et al, eds. *IDF Diabetes Atlas*. 3rd ed. Brussels: International Diabetes Federation; 2006:350-375.

186. International Diabetes Federation. Diabetes and impaired glucose tolerance: complications of diabetes. In: Gan D, Mbanya JC, Allgot B, et al, eds. *IDF Diabetes Atlas*. 3rd ed. Brussels: International Diabetes Federation; 2006:111-149.

187. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229-234.

188. Calcutt NA, Cooper ME, Kern TS, Schmidt AM. Therapies for hyperglycaemia-induced diabetic complications: from animal models to clinical trials. *Nat Rev Drug Discov* 2009;8:417-429.

189. Boyle PJ. Diabetes mellitus and macrovascular disease: mechanisms and mediators. *Am J Med* 2007;120(9 Suppl 2):S12-S17.

190. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570-2581.

191. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care* 2004;27:1879-1884.

192. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation* 2001;103:2668-2673.

193. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699-703.

194. Singh N, Wheeler S, Boyko EJ. The epidemiology of peripheral vascular disease. In: Ekoé J-M, Rewers M, Williams R, Zimmet P, eds. *The Epidemiology of Diabetes Mellitus*. 2nd ed. West Sussex: Wiley-Blackwell; 2008: 539-563.

195. Sillesen HH. Peripheral vascular disease. In: Holt RIG, Cockram CS, Flyvbjerg A, Goldstein BJ, eds. *Textbook of Diabetes*. 4th ed. West Sussex: Wiley-Blackwell; 2010: 710-724.

196. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: Harris MI, Cowie CC, Reiber G, Boyko E, Stern M, Bennett P, eds. *Diabetes in America*. 2nd ed. Washington D.C.: U.S. Department of Health and Human Services; 1995:429-448. NIH publication no. 95-1468.

197. Wilson PW, Cupples LA, Kannel WB. Is hyperglycemia associated with cardiovascular disease? The Framingham Study. *Am Heart J* 1991;121:586-590.

198. Laws A, Marcus EB, Grove JS, Curb JD. Lipids and lipoproteins as risk factors for coronary heart disease in men with abnormal glucose tolerance: the Honolulu Heart Program. *J Intern Med* 1993;234:471-478.

199. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 1991;151:1141-1147.

200. Seeman T, Mendes de Leon C, Berkman L, Ostfeld A. Risk factors for coronary heart disease among older men and women: a prospective study of community-dwelling elderly. *Am J Epidemiol* 1993;138:1037-1049.

201. Orchard TJ, Olson JC, Erbey JR, et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 2003;26:1374-1379.

202. Soedamah-Muthu SS, Chaturvedi N, Toeller M, et al; EURODIAB Prospective Complications Study Group. Risk factors for coronary heart disease in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. *Diabetes Care* 2004;27:530-537.

203. Zhou L, Deng W, Zhou L, et al. Prevalence, incidence and risk factors of chronic heart failure in the type 2 diabetic population: systematic review. *Curr Diabetes Rev* 2009;5:171-184.

204. Thrainsdottir IS, Rydén L. Congestive heart failure. In: Holt RIG, Cockram CS, Flyvbjerg A, Goldstein BJ, eds. *Textbook of Diabetes*. 4th ed. West Sussex: Wiley-Blackwell; 2010: 684-697.

205. Uusitupa MI, Niskanen LK, Siitonen O, Voutilainen E, Pyörälä K. 5-year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level, and abnormalities in lipoprotein composition in non-insulin-dependent diabetic and nondiabetic subjects. *Circulation* 1990;82:27-36.

206. Pignone M, Alberts MJ, Colwell JA, et al; American Diabetes Association; American Heart Association; American College of Cardiology Foundation. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. *Diabetes Care* 2010;33:1395-1402.

207. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-2222.

208. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;332:73-78.

209. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med* 2002;162:1737-1745.

210. Giorda CB, Avogaro A, Maggini M, et al; DAI Study Group. Incidence and risk factors for stroke in type 2 diabetic patients: the DAI study. *Stroke* 2007;38:1154-1160.

211. Howard BV, Best LG, Galloway JM, et al. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care* 2006;29:391-397.

212. Devereux RB. Coronary artery disease and cardiomyopathy. In: Poretsky L, ed. *Principles of Diabetes Mellitus*. 2nd ed. New York: Springer; 2010: 499-513.

213. Laakso M, Lehto S. Epidemiology of macrovascular disease in diabetes. *Diabetes Rev* 1997;5:294-315.

214. Almeda-Valdes P, Cuevas-Ramos D, Mehta R, Gomez-Perez FJ, Aguilar-Salinas CA. UKPDS Risk Engine, decode and diabetes PHD models for the estimation of cardiovascular risk in patients with diabetes. *Curr Diabetes Rev* 2010;6:1-8.

215. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-952.

216. Nilsson PM, Viljoen A, Wierzbicki AS. Cardiovascular risk factors. In: Holt RIG, Cockram CS, Flyvbjerg A, Goldstein BJ, eds. *Textbook of Diabetes*. 4th ed. West Sussex: Wiley-Blackwell; 2010: 657-683.

217. Zgibor JC, Piatt GA, Ruppert K, Orchard TJ, Roberts MS. Deficiencies of cardiovascular risk prediction models for type 1 diabetes. *Diabetes Care* 2006;29:1860-1865.

218. Libby P, Nathan DM, Abraham K, et al; National Heart, Lung, and Blood Institute; National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Cardiovascular Complications of Type 1 Diabetes Mellitus. *Circulation* 2005;111:3489-3493.

219. Zgibor JC, Ruppert K, Orchard TJ, et al. Development of a coronary heart disease risk prediction model for type 1 diabetes: The Pittsburgh CHD in Type 1 Diabetes Risk Model. *Diabetes Res Clin Pract* 2010;88:314-321.

220. Rosamond W, Flegal K, Friday G, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007;115:e69-e171.

221. Stephens JM, Botteman MF, Hay JW. Economic impact of antidiabetic medications and glycemic control on managed care organizations: a review of the literature. *J Manag Care Pharm* 2006;12:130-142.

222. Finkelstein EA, Fiebelkorn IC, Wang G. National medical spending attributable to overweight and obesity: how much, and who's paying? *Health Aff (Millwood)* 2003;Suppl W3:219-226.

223. Ali MK, Weber MB, Narayan KMV. The global burden of diabetes. In: Holt RIG, Cockram CS, Flyvbjerg A, Goldstein BJ, eds. *Textbook of Diabetes*. 4th ed. West Sussex: Wiley-Blackwell; 2010: 69-84.

224. Killilea T. Long-term consequences of type 2 diabetes mellitus: economic impact on society and managed care. *Am J Manag Care* 2002;8(16 Suppl):S441-S449.

225. Evans JM, MacDonald TM, Leese GP, Ruta DA, Morris AD. Impact of type 1 and type 2 diabetes on patterns and costs of drug prescribing: a population-based study. *Diabetes Care* 2000;23:770-774.

226. Centers for Disease Control Diabetes in Managed Care Work Group. Diabetes mellitus in managed care: complications and resource utilization. *Am J Manag Care* 2001;7:501-508.

227. Dall TM, Zhang Y, Chen YJ, Quick WW, Yang WG, Fogli J. The economic burden of diabetes. *Health Aff (Millwood)* 2010;29:297-303.

228. Zhang Y, Dall TM, Mann SE, et al. The economic costs of undiagnosed diabetes. *Popul Health Manag* 2009;12:95-101.

229. Zhang Y, Dall TM, Chen Y, et al. Medical cost associated with prediabetes. *Popul Health Manag* 2009;12:157-163.

230. Chen Y, Quick WW, Yang W, et al. Cost of gestational diabetes mellitus in the United States in 2007. *Popul Health Manag* 2009;12:165-174.

231. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013;36:1033-1046.

232. Huang ES, Basu A, O'Grady M, Capretta JC. Projecting the future diabetes population size and related costs for the U.S. *Diabetes Care* 2009;32:2225-2229.

233. Ramsey S, Summers KH, Leong SA, Birnbaum HG, Kemner JE, Greenberg P. Productivity and medical costs of diabetes in a large employer population. *Diabetes Care* 2002;25:23-29.

234. Tao B, Pietropaolo M, Atkinson M, Schatz D, Taylor D. Estimating the cost of type 1 diabetes in the U.S.: a propensity score matching method. *PLoS One* 2010;5:e11501.

235. Caro JJ, Ward AJ, O'Brien JA. Lifetime costs of complications resulting from type 2 diabetes in the U.S. *Diabetes Care* 2002;25:476-481.

236. Gilmer TP, O'Connor PJ, Rush WA, et al. Predictors of health care costs in adults with diabetes. *Diabetes Care* 2005;28:59-64.

237. Fitch K, Iwasaki K, Pyenson B. *Milliman client report: improved management can help reduce the economic burden of type 2 diabetes: a 20-year actuarial projection*. New York, NY: Milliman, Inc., 2010. Accessed July 27, 2010, at http://publications.milliman.com/publications/health-published/pdfs/improved-management-can-help.pdf.

238. Cheung BM, Ong KL, Cherny SS, Sham PC, Tso AW, Lam KS. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. *Am J Med* 2009;122:443-453.

239. Davidson MB. The effectiveness of nurse- and pharmacist-directed care in diabetes disease management: a narrative review. *Curr Diabetes Rev* 2007;3:280-286.

240. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335-342.

241. Grant RW, Buse JB, Meigs JB; University HealthSystem Consortium (UHC) Diabetes Benchmarking Project Team. Quality of diabetes care in U.S. academic medical centers: low rates of medical regimen change. *Diabetes Care* 2005;28:337-442.

242. McFarlane SI, Jacober SJ, Winer N, et al. Control of cardiovascular risk factors in participants with diabetes and hypertension at urban academic medical centers. *Diabetes Care* 2002;25:718-723.

243. Kemp TM, Barr EL, Zimmet PZ, et al. Glucose, lipid, and blood pressure control in Australian adults with type 2 diabetes: the 1999-2000 AusDiab. *Diabetes Care* 2005;28:1490-1492.

244. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care* 2013 Feb 15. [Epub ahead of print]

245. American Diabetes Association. Standards of medical care in diabetes-2013. *Diabetes Care* 2013;36(Suppl 1):S11-S66.

246. Gillies CL, Abrams KR, Lambert PC, et al.Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* 2007;334:299.

247. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008;371:1783-1789.

248. Lindström J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;368:1673-1679.

249. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374:1677-1686.

250. Ackermann RT, Finch EA, Brizendine E, Zhou H, Marrero DG. Translating the Diabetes Prevention Program into the community. The DEPLOY Pilot Study. *Am J Prev Med* 2008;35:357-363.

251. Narayan KM, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F. Diabetes-a common, growing, serious, costly, and potentially preventable public health problem. *Diabetes Res Clin Pract* 2000;50 Suppl 2:S77-S84.

252. Shojania KG, Ranji SR, McDonald KM, et al. Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. *JAMA* 2006;296:427-440.

253. Tricco AC, Ivers NM, Grimshaw JM, et al. Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis. *Lancet* 2012;379:2252-2261.

254. Coleman K, Austin BT, Brach C, Wagner EH. Evidence on the chronic care model in the new millennium. *Health Aff (Millwood)* 2009;28:75-85.

255. Stellefson M, Dipnarine K, Stopka C. The Chronic Care Model and diabetes management in US primary care settings: a systematic review. *Prev Chronic Dis* 2013;10:120180. DOI: http://dx.doi.org/10.5888/pcd10.120180

256. Neumann PJ. *Using Cost-Effectiveness Analysis to Improve Health Care: Opportunities and Barriers*. New York: Oxford University Press; 2004.

257. Pizzi LT, Lofland JH, eds. *Economic Evaluation in U.S. Health Care: Principles and Applications*. Sudbury: Jones and Bartlett Publishers; 2005.

258. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

259. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. New York: Oxford University Press; 2005.

260. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. *Diabetes Care* 2010;33:1872-1894.

261. Li R, Zhang P. Cost-effectiveness of interventions for the prevention and control of diabetes. In: Herman WH, Kinmonth AL, Wareham NJ, Williams R, eds. *The Evidence Base for Diabetes Care*. 2nd ed. West Sussex: Wiley-Blackwell; 2010: 449-470.

262. Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. *Diabetes Care* 2000;23:390-404.

263. Raikou M, McGuire A. The economics of screening and treatment in type 2 diabetes mellitus. *Pharmacoeconomics* 2003;21:543-564.

264. Vijgen SM, Hoogendoorn M, Baan CA, de Wit GA, Limburg W, Feenstra TL. Cost effectiveness of preventive interventions in type 2 diabetes mellitus: a systematic literature review. *Pharmacoeconomics* 2006;24:425-441.

265. CDC Diabetes Cost-Effectiveness Study Group. The cost-effectiveness of screening for type 2 diabetes. *JAMA* 1998;280:1757-1763.

266. Hoerger TJ, Harris R, Hicks KA, Donahue K, Sorensen S, Engelgau M. Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. *Ann Intern Med* 2004;140:689-699.

267. van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil* 2010;17(Suppl 1):S3-S8.

268. Centers for Disease Control and Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011*. Atlanta, GA:

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. Accessed February 15, 2011, at http://www.cdc.gov/diabetes/pubs/factsheet11.htm.

269. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr* 2010;8:29.

270. Nathan DM. Time for clinically relevant comparative effectiveness studies in type 2 diabetes. *Ann Intern Med* 2011;154:131-132.

271. Owens DK, Qaseem A, Chou R, Shekelle P; for the Clinical Guidelines Committee of the American College of Physicians. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. *Ann Intern Med* 2011;154:174-180.

272. Ratner R, Goldberg R, Haffner S, et al; Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care* 2005;28:888-894.

273. Orchard TJ, Temprosa M, Goldberg R, et al; Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med* 2005;142:611-619.

274. American Diabetes Association. Standards of medical care in diabetes-2011. *Diabetes Care* 2011;34(Suppl 1):S11-S61.

275. Piatt GA, Orchard TJ, Emerson S, et al. Translating the chronic care model into the community: results from a randomized controlled trial of a multifaceted diabetes care intervention. *Diabetes Care* 2006;29:811-817.

276. Siminerio LM, Kuo SS, Zgibor JC, Wolf D, Crail T, True M. Applying the chronic care model in the US Air Force (USAF): lessons learned from a Diabetes Outreach Clinic [Abstract]. *Diabetes* 2010;59(Suppl 1):A345.

277. McTigue KM, Conroy MB, Hess R, et al. Using the internet to translate an evidence-based lifestyle intervention into practice. *Telemed J E Health* 2009;15:851-858.

278. Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5-Working with Markov processes. *Med Decis Making* 1997;17:152-159.

279. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17:479-500.

280. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322-338.

281. Smith KJ, Hsu HE, Roberts MS, et al. Cost-effectiveness analysis of efforts to reduce risk of type 2 diabetes and cardiovascular disease in southwestern Pennsylvania, 2005-2007. *Prev Chronic Dis* 2010;7:A109.

282. United States Renal Data System. Annual Data Report Atlas of End-Stage Renal Disease in the United States, 2008. Minneapolis, MN: USRDS Coordinating Center. http://www.usrds.org/; Accessed May 16, 2009.

283. Arias E. United States life tables, 2004. National Vital Statistics Reports; vol 59, no 9. Hyattsville, MD: National Center for Health Statistics; 2007.

284. Medicare Fee-for-Service Payment. Baltimore, MD: Centers for Medicare & Medicaid Services; 2009. Accessed November 19, 2009, at http://www.cms.hhs.gov/home/medicare.asp.

285. US Bureau of Labor Statistics; 2009. Accessed November 19, 2009, at http://www.bls.gov/data/.

286. CDC Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA* 2002;287:2542-2551.

287. Thomson Healthcare. *Red Book 2008 (Red Book Drug Topics)*. Montvale, NJ: Thomson Healthcare; 2008.

288. Smith KJ, Cook RL, Ness RB. Cost comparisons between home- and clinic-based testing for sexually transmitted diseases in high-risk young women. *Infect Dis Obstet Gynecol* 2007;2007:62467.

289. Coffey JT, Brandle M, Zhou H, et al. Valuing health-related quality of life in diabetes. *Diabetes Care* 2002;25:2238-2243.

290. US Consumer Price Index. NE Washington, DC: US Bureau of Labor Statistics; 2009. Accessed November 19, 2009, at http://www.bls.gov/data/.

291. Coleman RL, Stevens RJ, Aldington SJ, Holman RR. Estimating risk of clinically evident retinopathy in type 2 diabetes. *Diabetes* 2006;55(Suppl 1):A53.

292. Coleman RL, Stevens RJ, Holman RR. Estimating risk of clinically evident neuropathy in type 2 diabetes: a UKPDS risk equation. *Diabet Med* 2006;23(Suppl 2):51.

293. Coleman RL, Stevens RJ, Holman RR. Incident nephropathy in type 2 diabetes: a UKPDS risk equation. *Diabetologia* 2005;48(Suppl 1):A32.

294. Stevens RJ, Kothari V, Adler AI, Stratten IM, Holman RR. UKPDS 56: The UKPDS Risk Engine: a model for the risk of coronary heart disease in type 2 diabetes. *Clin Sci* 2001;101:671-679.

295. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: Risk of stroke in type 2 diabetes estimated by the UKPDS Risk Engine. *Stroke* 2002;33:1776-1781.

296. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. UKPDS 66: Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes. *Diabetes Care* 2004;27:201-207.

297. Zoungas S, de Galan BE, Ninomiya T, et al. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. *Diabetes Care* 2009;32:2068-2074.

298. McTigue KM, Conroy MB, Bigi L, Murphy C, McNeil M. Weight loss through living well: translating an effective lifestyle intervention into clinical practice. *Diabetes Educ* 2009;35:199-204, 208.

299. Resnick HE, Valsania P, Halter JB, Lin X. Relation of weight gain and weight loss on subsequent diabetes risk in overweight adults. *J Epidemiol Community Health* 2000;54:596-602.

300. Herman WH, Hoerger TJ, Brandle M, et al. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;142:323-332.

301. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-1847.

302. Lenz M, Richter T, Mühlhauser I. The morbidity and mortality associated with overweight and obesity in adulthood: a systematic review. *Dtsch Arztebl Int* 2009;106:641-648.

303. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991;81:1158-1162.

304. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001;44(Suppl 2):S54-S64.

305. Brandle M, Zhou H, Smith BR, et al. The direct medical cost of type 2 diabetes. *Diabetes Care* 2003;26:2300-2304.

306. Zhou H, Isaman DJ, Messinger S, et al. A computer simulation model of diabetes progression, quality of life, and cost. *Diabetes Care* 2005;28:2856-2863.

307. Trueman P, Haynes SM, Felicity Lyons G, et al; Counterweight Project Team. Long-term cost-effectiveness of weight management in primary care. *Int J Clin Pract* 2010;64:775-783.

308. Petitti DB. *Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. 2nd ed. New York: Oxford University Press; 2000.

309. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making* 1985;5:157-177.

310. Löthgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. *Health Econ* 2000;9:623-630.

311. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18(Suppl 2):S68-S80.

312. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? *Med Care* 2008;46:349-356.

313. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med* 2003;163:1637-1641.

314. Huang ES, Zhang Q, Brown SE, Drum ML, Meltzer DO, Chin MH. The cost-effectiveness of improving diabetes care in U.S. federally qualified community health centers. *Health Serv Res* 2007;42(6 Pt 1):2174-2193; discussion 2294-2323.

315. Hersey JC, Khavjou O, Strange LB, et al. The efficacy and cost-effectiveness of a community weight management intervention: a randomized controlled trial of the health weight management demonstration. *Prev Med* 2012;54:42-49.

316. McConnon A, Kirk SF, Cockroft JE, et al. The Internet for weight control in an obese sample: results of a randomised controlled trial. *BMC Health Serv Res* 2007;7:206.

317. Miners A, Harris J, Felix L, Murray E, Michie S, Edwards P. An economic evaluation of adaptive e-learning devices to promote weight loss via dietary change for people with obesity. *BMC Health Serv Res* 2012;12:190.

318. Cobiac LJ, Vos T, Barendregt JJ. Cost-effectiveness of interventions to promote physical activity: a modelling study. *PLoS Med* 2009;6:e1000110.

319. Herman WH. Diabetes modeling. *Diabetes Care* 2003;26:3182-3183.

320. Wing RR, Lang W, Wadden TA, et all; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481-1486.

321. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. NCHS data brief, no 82. Hyattsville, MD: National Center for Health Statistics. 2012.

322. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012;307:491-497.

323. NHLBI Obesity Education Initiative Expert Panel. The practical guide: identification, evaluation, and treatment of overweight and obesity in adults. Rockville, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity; October 2000; NIH Publication No. 00-4084. Available from http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf Accessed May 5, 2013.

324. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff (Millwood)* 2009;28:w822-w831.

325. Cawley J, Meyerhoefer C. The medical care costs of obesity: an instrumental variables approach. *J Health Econ* 2012;31:219-230.

326. Robert Wood Johnson Foundation: F as in fat: how obesity threatens America's future, 2012 [article online]. Available from http://www.rwjf.org/en/research-publications/find-rwjf-research/2012/09/f-as-in-fat--how-obesity-threatens-america-s-future-2012.html Accessed May 5, 2013.

327. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992;146:473-481.

328. Gordis L. *Epidemiology*. 4th ed. Philadelphia: Saunders; 2009.

329. Anderson GM, Bronskill SE, Mustard CA, Culyer A, Alter DA, Manuel DG. Both clinical epidemiology and population health perspectives can define the role of health care in reducing health disparities. *J Clin Epidemiol* 2005;58:757-762.

330. Banta HD, de Wit GA. Public health services and cost-effectiveness analysis. *Annu Rev Public Health* 2008;29:383-397.

331. Griffin S, Rice N, Sculpher M. Economic evaluation of public health interventions. In: Killoran A, Kelly MP, eds. *Evidence-based Public Health: Effectiveness and Efficiency*. 1st ed. New York: Oxford University Press; 2010: 111-127.

332. Blumenthal D, Dixon J. Health-care reforms in the USA and England: areas for useful learning. *Lancet* 2012;380:1352-1357.

333. Brownson RC, Fielding JE, Maylahn CM. Evidence-based public health: a fundamental concept for public health practice. *Annu Rev Public Health* 2009;30:175-201.