Technical Appendix on Methods

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A: Appendix Table 1. Standardizing for age and sex: WHO World Standard Population[1]

Age group	WHO World Standard, adjusted to ages 15-85+ for DM study (weights, sum to 1)	Male	Female
15-19	0.114637194	0.057318597	0.0573186
20-24	0.111253725	0.055626862	0.05562686
25-29	0.107328684	0.053664342	0.05366434
30-34	0.102997464	0.051498732	0.05149873
35-39	0.096772097	0.048386049	0.04838605
40-44	0.089192801	0.0445964	0.0445964
45-49	0.081748898	0.040874449	0.04087445
50-54	0.072680279	0.03634014	0.03634014
55-59	0.061582121	0.03079106	0.03079106
60-64	0.050348569	0.025174285	0.02517428
65-69	0.040062768	0.020031384	0.02003138
70-74	0.029911006	0.014955503	0.0149555
75-79	0.020572956	0.010286478	0.01028648
80-84	0.012316695	0.006158347	0.00615835
85+	0.008594743	0.004297372	0.00429737

[1] Available at https://www.who.int/healthinfo/paper31.pdf.

Appendix Table 2: Prevalence, Deaths and Economic burden attributed to Diabetes in East Asia, the US and the Netherlands in 2017 and Projections of economic burden in 2045 (as per IDF estimates)

	Population in million, 2017	GDP per capita, 2017	Deaths due to diabetes, in 1000s (95% CI), 2017	Prevalence of diabetes in % (95% CI), 2017	Health expenditures per person with diabetes, US$,2017	Health expenditure of diabetes, million US$,2017	Health expenditures per person with diabetes, US$,2045*	Health expenditure of diabetes million US$,2045*
China	1,386	8,827	843 (775.5-1,006.5)	10.9 (9.9-14)	549.4	63,095.3	454.9	54,475.3
Hong Kong	7.4	46,193.6	N/A	11 (9.7-12.8)	N/A	N/A	N/A	N/A
Japan	126.8	38,430.3	70.3 (62.1-81)	7.7 (6.6-10.1)	3,925.4	28,217.1	3,560.7	22,655.4
South Korea	51.5	29,742.8	33.6 (25–39.5)	8.8 (6.7 - 11.1)	2,582.3	8,940.7	2,041.1	9,130.1
Taiwan	23.6	24,389.7	N/A	10.9 (8.1 - 14)	N/A	N/A	N/A	N/A
United States	325.1	59,927.9	176.7	13 (12.4-13.7)	11,638.3	348,273.7	10,470.1	372,221
Netherlands	17.1	48,482.8	4.8 (3.8-5.7)	7.8 (5.8-10.4)	7,038.8	6,498.1	5,793.6	6,155.1

All data represent annual costs, wages, or rates;
*projections for 2045: baseline scenario
Sources: International Diabetes Federation, IMF, World Bank

Appendix Table 3. Risk prediction models					
		Japan	The Netherlands	Hong Kong	Taiwan
	Risk Factor	JJRE	UKPDS (as applied by the Netherlands team)	HKU-SG Model	Taiwan Model
Demographics	Age	Y	Y	Y	Y
	Sex	Y	Y	Y	Y
Clinical Biomarkers	HbA1c	Y	Y	Y	Y
	Total cholesterol		Y		
	HDL cholesterol		Y		Y (HDL/LDL ratio)
	Non-HDL cholesterol	Y			
	LDL-cholesterol			Y	Y (HDL/LDL ratio)
	Serum creatinine				Y
	Systolic BP	Y		Y	
	Diastolic BP			Y	
	Hemoglobin				
	Duration of diabetes	Y	Y	Y	
	White blood cells				
Drug Use	Blood pressure-lowering drugs				Y (plus history of hypertension)
	Statins				Y
	Oral diabetes drugs				
Health behaviors and comorbidities	Atrial fibrillation	Y	Y	Y	
	Heart failure				
	Renal disease			Y	
	Leisure time physical activity	Y			
	BMI	Y	Y	Y	Y
	History of cancer				Y
	Diabetes complications				
	Tobacco smoking, current	Y	Y	Y	
	Cerebrovascular disease			Y	
	Ischaemic heart disease			Y	

Note: JJRE = the Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine (Tanaka et al. 2013)

B: Implementing the risk prediction models

For Japan: The "JJRE" Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine

Measurement of health outcomes, including all-cause mortality, is based on an extension of the 5-year risk of developing major complications and mortality as predicted by the Japan Diabetes Complications Study/the Japanese Elderly Diabetes Intervention Trial risk engine (JJRE) (Tanaka et al. 2013). The JJRE risk prediction model is similar to many other risk prediction models, such as the well-known Framingham cardiovascular disease risk model or the UK Prospective Diabetes Study (UKPDS) risk prediction model often used for estimating medium- and longer-term risks for individuals with diabetes. Such risk models use data from research studies to model how "risk factors" (or predictor variables), such as age, sex, and blood pressure, can predict specific health outcomes in the next 5 or 10 years. Most such models have been calibrated for non-Asian populations, and thus are not appropriate for our sample. The JJRE is specifically designed for predicting risks for a Japanese population. We are grateful to the JJRE authors for sharing their SAS program code with us.

The JJRE incorporates 11 risk factors to predict macro- and microvascular complications among Japanese patients with diabetes (without diabetes complications except mild retinopathy): sex, age, HbA_{1c}, years after diagnosis, BMI, systolic blood pressure, non-HDL cholesterol, albumin-to-creatinine ratio, atrial fibrillation, current smoker, and leisure-time physical activity. The model was developed based on data from 1,748 Japanese type 2 diabetic patients pooled from two clinical trials. The JJRE "separately calculates each risk of the first occurrence for five events: fatal and nonfatal CHD, fatal and nonfatal stroke, non-cardiovascular mortality, overt nephropathy, and progression of retinopathy" (Tanaka et al. 2013, p.1194).

We have used the JJRE code to calculate the risk of CHD, stroke, and non-cardiovascular mortality in our data. We do not estimate the net value of avoiding other complications such as overt nephropathy or progression of retinopathy.[2]

Defining JJRE input variables

We must use the JJRE default values for those values that we lack for our sample. For each risk factor used in one of the JJRE risk prediction equations, we code the risk factor as follows.

LTPA (Leisure Time Physical Activity) is defined from two questions asked at the health check-up: EXERCISE==1 if the patient answers yes to the question "Have you been exercising at least twice a week (at least 30 minutes per session of light sweating) for over one year?" and 2 otherwise; WALK==1 if answer yes to the question "Do you walk or exercise to a similar degree daily for at least one hour?" and 2 otherwise). The amount of LTPA fits at least the JJRE categories if the self-reported answer to either of these questions is "Yes."

Then the variable LTPA is coded as follows:

```
gen LTPA = .
replace LTPA = 1 if EXERCISE == 1 | WALKING == 1
replace LTPA = 0 if EXERCISE == 2 & WALKING == 2
```

Duration of diagnosis is defined as follows: In the JMDC dataset (4_diseases_x., where x signifies a year such as 2014), a variable named "FIRSTDX" (first diagnosis date) associated with each diagnosis code exists. We identified the first diagnosis year associated with diabetes for each patient in the cohort using data from 2005 to 2014. In the great majority of cases, this first diagnosis date remains constant throughout all diabetes-related visits in the data. However, where there are different values for FIRSTDX for a given patient over multiple visits, we took the earliest of the FIRSTDX variable. Duration of diabetes diagnosis in a given year is calculated as current year – min(FIRSTDX). Patients without two separate non-suspect (i.e. suspicion

[2] However, to run the JJRE SAS model requires inputting values for all risk factors and outputting all five predicted risks; therefore, we utilize the JJRE default values for the risk factors that are missing in the JMDC data.

flag[3]=0) diagnoses of diabetes in two or more years are assigned a duration of diagnosis of 0 in all years.

JMDC does not report ACR values. We therefore assigned ACR a value of 60 (the default value for a diagnosed diabetic in the JJRE) if a patient has two or more confirmed (non-suspect) diagnoses of diabetes in two separate years. Otherwise, a patient is assigned an ACR value of 30.

NHDL-C (Non-High Density Lipoprotein Cholesterol) was estimated from the JMDC checkup data on HDL, LDL, and triglycerides, using the Friedewald formula: If TG<400, NHDL=LDL+(TG/5); otherwise if TG>=400, NHDL is set to missing.

AF (Atrial Fibrillation) and DR (Diabetic Retinopathy) were coded based on JMDC's disease data files to determine whether an individual had a prior history of AF or DR. For each individual, we identified the earliest year he or she had a non-suspect diagnosis of AF (I48 Atrial fibrillation and flutter) and the earliest year the individual had a non-suspect diagnosis of DR (H36, E103, E113, E123, E133 or E143). Then, for each observation for which a JJRE risk calculation was conducted, we identified whether the earliest year of AF or DR is prior to the current year. If so, we set the dummy variables AF and/or DR to 1, and 0 otherwise.

BMI (Body Mass Index) was calculated based on height and weight in the JDMC checkup data and are reported in centimeter and kilograms. We calculated the BMI using the standard formula, weight (kg) / [height (m)]2 after converting height in centimeters to meters.

All other variables (age, female, systolic blood pressure, smoking status, and HbA1c) were taken directly from the patient demographic file or the checkup file.

We confirmed, for a random sample of patient IDs with check-up data, perfect congruence between our JJRE predicted risks (from applying the SAS code to our JMDC data) and the JJRE predicted risks output from the web engine of JJRE (www.biostatistics.jp/prediction/jjre).

[3] The JMDC claims data includes a "suspicion flag" to demarcate claims in which the physician may suspect a given condition but has not definitively diagnosed it, such as a diagnostic rule-out test for a given medical condition like diabetes. We use "non-suspect" to describe claims lacking this suspicion flag (i.e. SUSPECT==0).

For estimating all-cause mortality, we used the JJRE-estimated risk of non-cardiovascular mortality, plus the JJRE-estimated risks of major complications multiplied by the conditional probability of the complication being fatal (e.g. fatal stroke) based on the JMDC data in 2005-2012.

For Hong Kong: The HKU-SG risk model

We used the HKU-SG risk model to predict the probability of all-cause mortality in the next five years (Quan et al. 2019). This risk prediction score was specifically developed for ethnic Chinese individuals from detailed clinical data of over 1 million adults with type 2 diabetes in Hong Kong and Singapore over more than 6 million person-years of follow-up between 2006 and 2014. The HKU-SG risk score was developed using Cox proportional hazard models with data from 678,750 participants from Hong Kong, and then validated with data for 386,425 participants from Singapore.

The resulting HKU-SG risk score for mortality uses the following risk factors: age, duration of diabetes, gender, smoking, body mass index, systolic and diastolic blood pressure, HbA1c, LDL cholesterol and pre-existing conditions: atrial fibrillation, chronic kidney disease, ischemic heart disease and cerebrovascular disease (web engine: https://jquan.shinyapps.io/riskmodel).

Our Hong Kong sample data was drawn from the Hospital Authority's electronic health records (Clinical Management System) which covers the public health care system. We confirmed all cases of type 2 diabetes in our sample by lab glucose (HbA1c, fasting plasma glucose, oral glucose tolerance test (OGTT), random plasma glucose on two separate occasions); diagnosis code for diabetes (ICD-9 codes 250, 357.2, 366.41 and 362.01-362.0; or ICPC codes T89 and T90); or prescription of antihyperglycemic medication (including insulins, metformin, thiazolidinediones, sulfonylureas, incretin mimetics / glucagon-like peptide-1 analogues, glucosidase inhibitors, and dipeptidyl peptidase inhibitors).

Age, gender, smoking status, systolic and diastolic blood pressure (mmHg), HbA1c (%) and LDL cholesterol (mg/mmol) were taken directly from the patient health care records. Body mass index (BMI) was calculated based on height and weight in the electronic health records reported in centimeter and kilograms. Duration of diabetes was defined as the time from

diagnosis until cohort entry or the date of diabetes diagnosis if later. For example, an individual has a duration of 6 years if diagnosed in the year 2000 and a duration of zero years if diagnosed in 2006 or later.

The presence of pre-existing medical conditions (atrial fibrillation, chronic kidney disease, ischemic heart disease and cerebrovascular disease) was determined using the diagnosis codes recorded in the patient health records. Diagnoses were coded according to the International Classification of Disease 9th revision (ICD-9) for secondary care; and the International Classification of Primary Care 2nd Edition (ICPC-2) for primary care. For each individual, we identified the earliest year he or she had a diagnosis of atrial fibrillation (ICPC: K78; ICD: 427.3), chronic kidney disease (ICD: 585-587), ischemic heart disease (ICPC: K74-76; ICD: 410-414), cerebrovascular disease (ICPC: K90, ICD: 430-434, 436). Then, for each calculation of a risk score, we identified whether the earliest year of the respective medical condition is prior to the current year. If so, we set the dummy variables to 1, and 0 otherwise.

Taiwan

The Taiwan team developed a risk prediction model for all-cause mortality for type 2 diabetes mellitus (T2DM) patients with 7- and 10-year follow-up (Chiu at al. 2019). They incorporated data from one large-scale regional hospital with 1089 beds, located in Keelung, northern Taiwan, which provides an average of 175,000 outpatient visits annually. Records of outpatient visits and inpatient services between 1 Jan, 2007 and 31 Dec, 2013 were systematically retrieved from hospital-based information system. A total of 18,202 T2DM patients were recruited as our study population.

The study sample screening criteria was based on International Classification (ICD) version ICD-9-CM and 10 using code 250, but excluding Type I DM (coding 250.x1, 250.x3) for all inpatient and outpatient records. Those who were aged over 18 and coded with T2DM with ≥3 times within one year were defined as T2DM, otherwise as non-T2DM. Biochemical examination (HbA1c, cholesterol, HDL, creatinine, etc.), comorbidity history (hypertension, cancers, etc.), and drug use information (anti-hypertension, anti-hyperlipidemia, etc.), as well as basic patient information were all retrieved from the hospital information system.

Information on mortality, including date and cause of death, was obtained through linking with the death registry from the Health and Welfare Data Science Center (HWDC) using the unique national identification number for 2007-2013 and 2007-2016 for 7-year and 10-year risk prediction models, respectively. The median follow-up time and number of deaths were 4.81 years (2779 deaths) and 6.75 years (4561 deaths) for 7- and 10-year follow-up, respectively.

The Cox proportional hazards regression with univariate and multivariable models was employed to develop the risk prediction models. First, we conducted the stepwise approach to select those potential risk factors for multivariable analysis using both criteria of variable entrance and stay with $p<0.25$ and $p<0.1$, respectively. Second, the AIC (Akaike's Information Criterion) was adopted to select the parsimonious models for multivariable Cox proportional hazards regression. The model with lowest AIC was selected.

The full sample was used to construct the risk prediction model based on multivariable Cox regression. For model internal validation, the full sample was randomly divided into two groups, estimation sample (2/3 of the full sample) and validation sample (the remaining 1/3 of the full sample). A set of parameter estimates (risk factors identified from the full sample regression model) was derived from the regression using the estimation sample. Then we computed the predicted mortality for the validation sample using the parameter estimates from the estimation sample and compared the actual mortality and predicted mortality of the validation sample using Chi Square test. This procedure was repeated ten times in the validation process to assess internal validity and no significant difference with $p>0.05$ between actual and predictive mortality was observed in the validation process (Chiu et al. 2019).

C: Estimating net value

This part of the appendix describes the methods for net value analysis of health care for patients with type 2 diabetes mellitus (DM) based on longitudinal patient-level data on resource use and quality outcomes, as measured by clinical markers and predicted risk of complications and death.

The Stanford FSI Asia-Pacific Research Center's Asia Health Policy Program, directed by Karen Eggleston, coordinates a comparative research project on net value of diabetes management focusing on Asia in international comparative perspective. Participating research teams of health economists, epidemiologists and clinicians apply similar methods for assessing net value developed originally in Eggleston et al. (2009), a study with US Mayo Clinic data. Most samples in this collaboration include several thousand patients each year for at least 4 years between 2005 and 2019. Some of the studies, such as the Taiwan team, apply the method within a difference-in-difference framework to assess a pay-for-performance program, or combine with a regression discontinuity approach (Japan team) or other design to determining causal effects of specific programs. Four of the participating research teams contributed to this study. For more details, please see the full document published in *Healthy Aging in Asia* (edited by Karen Eggleston, Stanford University Walter H. Shorenstein Asia-Pacific Research Center series with Brookings Institution Press), which intends to inform researchers who are interested in estimating the value change in diabetes management in any country and any provider setting.

"Checklist" of sample characteristics to examine before specifying study cohort(s) and study period

- Number of diabetes cases per year – prevalence and incidence in the study population
- Availability of a risk prediction model appropriate for the study population with primary endpoint all-cause mortality. Examples include the UK Prospective Diabetes Study (UKPDS) risk equations, the Japan risk engine "JJRE" (Tanaka et al. 2013), and other tailored models such as those developed by our Hong Kong and Singapore teams (Quan et al. 2019).

- Number of deaths per year (to decide about using an available risk prediction model or the feasibility of developing such a model specific for the sample patient population)
- Average follow-up time per patient
- Completeness of clinical/biomarker data among the study population (e.g. blood pressure, HbA1c, other risk factors used in chosen risk prediction model)

Defining the study population

Inclusion criteria

- Diagnosis of type 2 diabetes (ICD 9 code: 250.*2, 250.*4 / ICD 10 code: E11.**, E14.**)—at least two outpatient visits, and/or one inpatient admission, with diabetes as the primary diagnosis
- > 18 years old (for Hong Kong, > 15 years old; only 0.03% (28/90891) age 15 to 19)
- Complete demographic and biomarker/laboratory data at baseline (or the time of diagnosis, for those newly diagnosed and entering the study sample during the study period)

Exclusion criteria

- Secondary diabetes (ICD 10 code: E08.*, E09.*, E13.*, unless many type 2 patients may be classified as ‘other specified diabetes’ during your study period)
- Type I diabetes (ICD 9 codes: 250.*1, 250.*3 / ICD 10 codes: E10.**). Or can exclude based on age<30 at diagnosis and taking insulin.
- Missing data at the baseline time window

These criteria identify type II diabetic patients who have been diagnosed and potentially obtained management over the defined study period. In order to group patients with similar duration of diabetes, the study population could be further stratified based on the year(s) since diagnosis (i.e., duration of diagnosis >10 years, 5-9 years, 3-4 years, 1-2 years before baseline period; incident cases in years 1-2; years 3-4; etc. (excluding incident cases in final study period because the method requires some follow-up period).

We code Elixhauser comorbidities (excluding diabetes) at baseline for all patients (see Quan et al. (2005) for coding algorithms).

Health Outcomes

We use a diabetes risk prediction model to estimate change in health outcomes of the sample population. Specifically, we measure the change in risk of all-cause mortality as the primary outcome. Other outcomes for sensitivity analyses include (1) major diabetes complications such as nonfatal and fatal coronary heart disease (CHD) and strokes, and (2) remaining life expectancy (LE) and quality-adjusted life years (QALYs) as estimated in models taking account of more sequelae, such as the UKPDS Outcomes Model 2. Previous studies in European countries and North America have used the UKPDS model both for predicting mortality and for applying the outcomes model; see appendix of Eggleston et al. (2009).

Extracting demographic and biomarker data from the data precedes their use as input for the risk prediction model(s). Types and details of required data vary according to the chosen model(s).

In calculating 5-year risks of mortality and diabetes complications, we will focus on "modifiable" risks by holding at the baseline value the patient's age and duration of diagnosis (the latter only for teams/samples that have the data). In this way, the net value analyses focus on the change in risks that are plausibly attributable to clinical care, rather than a natural part of the aging process and number of years the patient has lived with diabetes.

Data permitting, measured change in LEs and QALYs can capture the long-term effects of management among type 2 diabetes patients exposed to different treatment modes or changing technologies of treatment that may impact the development of complications including CVD, strokes, renal failure, amputation, and blindness.

Spending

1. Convert nominal spending into real spending in local currency units, using GDP deflator (base year was 2010 for this 4-system comparative study);
2. Include all spending for a given individual, with no attempt to isolate DM-specific spending;
3. Aggregate up to total annual spending, for each year in the study period (using fraction of year enrolled/observed, if individual only in sample part of a year);
4. However, in year of death for decedents, include total spending and count as a full year.

For samples that lack data at the patient level on actual spending in nominal or real currency (e.g. in whole or in part a national health service such as in Hong Kong, other parts of China, India), we use a standardized price vector applied to utilization data to calculate expenditures. For Hong Kong, statistics on bundled unit costs, as published in the Hospital Authority annual reports from

2006 to 2014, furnished inpatient cost per patient-day by specialty and cost per ambulatory visit by type of attendance. The unit cost of medications was provided by the Department of Pharmacy, Queen Mary Hospital, Hong Kong.

Net value analyses

Net value is estimated as the present discounted monetary value of improved survival (and, in a secondary analysis, improved survival plus avoided treatment spending for stroke and coronary heart disease), holding age and duration of diagnosis constant at baseline ("modifiable risk"), net of the increase in annual inflation-adjusted spending per patient. To do so, we will estimate two different risk predictions for each patient-year, for those who survive from the baseline through the final period: actual (non-modifiable) risk, and modifiable risk. The two measures coincide only for the initial observation (i.e., in the baseline period or at the year of cohort entry). In other words, for each year a DM patient is in sample from baseline period to final period, we compute actual risk and modifiable risk (holding age and duration of DM at their levels in baseline period, but allowing other risk factors to change between years/periods).

This cost-of-living approach is analogous to a cost-benefit analysis, or a cost-effectiveness analysis in which outcomes and costs for 2 interventions (e.g. medical care in the baseline period and in the final period) are compared, but instead of a threshold, we assign a monetary value to life-years gained as a result of improvements in health status between the 2 periods, and then subtract the added costs of care (see discussion in Eggleston et al. 2009, p.388).

Each team uses a lifetable most applicable to that population (i.e., national or regional/state life table estimates for a year within the study period, preferably 2010). None had access to lifetables

estimated for individuals with diagnosed diabetes, although in the future that would be a desired refinement of the net value estimates. Each research team applied the age- and sex-specific remaining life expectancy from that lifetable to the individual patient-level estimate of value, to estimate survival if the individual survives beyond the 5 years predicted by the mortality model.

We use the following approach:

I. Primary analyses:

   a. Baseline (or year of cohort entry) vs. final period;
   b. Among patients who survive to final period, change in modifiable predicted risk of all-cause mortality (i.e. holding age and duration of diagnosis at the same values as baseline);
   c. Spending in baseline and final periods, including all spending in year of death for decedents, and no attempt to isolate DM-specific spending;
   d. Value
      i. Estimate individual actual 5-year mortality risk using risk factors for baseline period, and then do same for final period;
      ii. Estimate individual *modifiable* mortality risk in final period, replacing the individual's actual age with the baseline period age (and duration of diagnosis);
      iii. In estimating value of (any) improved survival, use estimated modifiable all-cause mortality for next 5-year period based on risk model, and for survivors beyond that period, *assume remaining age- and sex-specific life expectancy from lifetable for that country/region/year*.
   e. Spending

i. Estimate GLM regression of medical spending for all patients in baseline period (empirical specification below);
ii. Predict each individual's medical spending in baseline period;
iii. Estimate medical spending for all patients in final period in same way;
iv. Predict each individual survivor's *modifiable* spending in final period by predicting spending from the final period regression BUT keeping age and duration of diagnosis at the same value as for that individual in the baseline period;
v. Change in spending is the additional annual spending between the baseline and final periods, i.e. the difference between predicted annual real spending in baseline period and predicted annual real *modifiable* spending in final period.

f. Net value
    i. Net Value 1:
        1. At individual patient level for each survivor, subtract change in spending from change in modifiable risk of all-cause mortality;
        2. Summarize net value by 5-year age group as specified in the reference populations;
    ii. Net Value 2: Age- and sex-standardized population, using World Health Organization world population standard reference population (modified for adult population 15 – 85+ years old)

1. Separately for men and for women, multiply the mean net value of each 5-year age group by the weight assigned to that group in the reference population;
2. Summarize the overall weighted average net value.

II. Secondary analyses: All-cause mortality, plus avoid treatment spending for stroke and CHD; and accounting for decedents, as described below.

PRIMARY ANALYSES: Protocol for survivor panel

Each team defines the relevant baseline and final periods. The baseline period may include 1, 2, or 3 years; the final period similarly. For large, short panels, 1 year is appropriate; for small, long panels, 3 years is appropriate. We will summarize in this document assuming two years in the baseline period (Baseline Year1 BY1 and Baseline Year 2 BY2) and two years in the final period (Final Year 1 FY1 and Final Year 2 FY2)

Denote the 5-year risk of all-cause mortality for individual *j* in period *t* as P_{jt}. We calculate the value of reductions in fatal risk as follows: Assuming a 3% annual real discount rate applied halfway through each year and a given value of 1 life-year (ranging from $50 000 to $150 000), estimate the present discounted value of remaining life for 2 time points: the baseline and final observation periods.

To do so, we approximate the predicted probability of death in the next 5 years by giving one fifth of the predicted probability ($0.2\ P_{jt}$) to each of the first 5 years, and assume that all patients surviving beyond year 5 (with probability $1- P_{jt}$) have the same age- and sex-specific remaining life expectancy as a general individual from the lifetable of that population. In calculating the

present discounted value of remaining life from the model simulations, we assume a 3% real annual discount rate.

We calculate a monetary value for changes in life expectancy for a given assumed value of 1 life-year (LE value) and calculate a net value for each individual *j* as follows: net $value_j$ = LE $value_j$ - cost $increase_j$, in which cost increase = C_{Final} - $C_{Baseline}$, with C_{Final} = (total predicted individual spending in Final Year1 and Final Year 2)/2 and $C_{Baseline}$ = (total predicted individual spending in Baseline Year1 and Baseline Year 2)/2.

We estimate predicted spending rather than actual spending to smooth variation in individual observations of actual spending, as well as to predict what individuals would probably spend if they had the same age and duration of diabetes they had at baseline. We estimated the total predicted medical spending by using administrative claims data for the first and last period of the study for each patient. To account for differences in how risk factors affect spending, we estimated a multivariate regression model by using generalized linear models as suggested by Manning and Mullahy. Using the modified Park test, as suggested by Manning and Mullahy, we assumed a log link and gamma distribution. All medical and pharmaceutical spending are included in the dependent variable: total 2-year spending for each patient. The independent variables in the model were age, sex, Elixhauser comorbid conditions except diabetes (included as a vector of indicator variables for the presence of each comorbidity at baseline). For teams/samples having information on duration of diabetes, duration (years with diagnosis) is included, as well as an interaction term of age with duration. For teams/samples lacking the duration of diabetes variable, age-squared is included in the regression model. By using the

estimated coefficients from the model, we predict total spending for each patient in the baseline and final periods, and then predict total spending while holding age (and duration of diagnosis) constant at their baseline values.

The increase in predicted spending between the baseline and final periods is then compared with the value of health status improvement to calculate the net value of additional spending.

We performed nonparametric bootstrapping with a large number of samples (e.g. 1000) to calculate 95% CIs (using the percentile method) for patient risk factors, spending, and net value.

Addendum

BY1 Baseline period Year1

BY2 Baseline period Year 2

FY1 Final period Year 1

FY2 Final period Year 2

E10 Insulin-dependent diabetes mellitus

E11 Non-insulin-dependent diabetes mellitus

E12 Malnutrition-related diabetes mellitus

E13 Other specified diabetes mellitus

E14 Unspecified diabetes mellitus

O24 Diabetes mellitus in pregnancy

Net value methods to account for selective survival and expense in last year of life

We started with method (1), the survivor panel. This section describes the methods for the method (2) robustness check including half a value of a life-year for every year survived by both decedents and survivors, using the example of 4 years of data (such as the Netherlands sample), with year 1 (Y1) as the baseline and Y4 as the final period.

We account for deaths using data on spending and mortality for those who died during our study period (i.e. decedents) in the following way:

Our analytic dataset includes a cohort that enters the data in the baseline year (Y1 cohort), some of whom survive to the end of the study period (e.g. Y4), and some of whom die during the study period. We ignore the incident cohorts who joint the sample after the baseline year, for lack of sufficient follow-up period.

Analysts do the net value analyses on the panel of survivors between the baseline and final periods, method (1). That yields the net value for the age-constant survivor panel (i.e. based on modifiable risk as predicted by biomarkers in the baseline and final years). Call this NV_S. This receives a weight in the overall net value that is proportional to the fraction of the baseline cohort that survives through the end of the study period.

Then we estimate the net value of decedents, NV_D; this receives a weight in the overall net value that is proportional to the fraction of the baseline cohort that dies before the end of the study period. NV_D is estimated in a different way from that of survivors, because it is based on cumulative spending and cumulative life-years, not subtracting baseline from final period values. As described in the main text, to this NV_D we added half the value of a life-year for every year

survived by individuals who survived to the final period, net of mean expenditures among survivors and weighted by the percentage survivors in the sample.

Denote the average total spending of the decedents in the year that they died as M^D_t. To do so, sum all the spending of all those who died at any point in the year, and divide by the number who died in that year. If there are data on spending and mortality in each of the four years, give the decedents the full assumed value for the years they actually survive and their spending up to the time they died. If the intermediate year data are not available but the year of death is known, given the decedents the average spending for survivors for the years they survive in full (can interpolate spending if necessary) and the average spending among decedents for the year they died. Assume they lived on average 0.5 years in the year they died, on the assumption of a uniform distribution for dates of death during the year. Give the decedents 0.5*(assumed value of life-year) for the year they died. With exact dates of death one can compute the average fraction of the year survived, which should be close to 0.5.

Using this method, we also explore sensitivity of net value to the assumption regarding how much of survival is attributable to medical care. One way to do so is to include a parameter α representing the fraction of a life-year attributable to medical care, with $0 < \alpha \leq 1$. Dubbed the "Cutler coefficient," the default is set to 0.5 following Cutler, Rosen, and Vijan (2006) in assuming that medical care accounts for half of health gains, with non-medical factors playing an equally important role in health improvement (Eggleston et al. 2019). We subtract decedents' actual (or, if not available, assumed average) spending, and express as a per-decedent net value ((Total value – total spending)/(# of decedents)). This gives the average net value of a life year for the decedents in a given year:

NV_{D1} = Per-decedent net value for decedents in Y1 = {(0.5LY)* α * $perLY}-$M^{D}_{b}$

For people who die in Y2, Y3 and Y4, give them 1.5, 2.5, and 3.5 years of life, respectively, and tabulate their expenses for each year ($M_{Y1,}$ $M_{Y2,}$ M_{Y3}). Then the average per-decedent net value for Y1 cohort decedents in Y2, Y3, and Y4 can be estimated as follows:

NV_{D2} = {(1.5LY)* α * $perLY}-$M_{Y1}$-$M^{D}_{Y2}$

NV_{D3} = {(2.5LY)* α * $perLY}-$M_{Y1}$- M_{Y2} -M^{D}_{Y3}

NV_{D4} = {(3.5LY)* α * $perLY}-$M_{Y1}$- M_{Y2} - M_{Y3} -M^{D}_{Y4}

Then compute a weighted average net value for decedents of the Y1 cohort as follows:

$$\mathrm{NV_D} = \sum_{t=1}^{4} \frac{D_{\mathrm{Yt}}}{D} * \mathrm{NV_{Dt}}$$

Where D = Total Y1 cohort decedents who died in the Y1-Y4 study period; and D_Y = Decedents in year Y, where D = D_{Y1} + D_{Y2} +D_{Y3} +D_{Y4}.

Finally, compute a weighted average net value for the panel of survivors and the decedents as follows:

$$\mathrm{NV} = \left(\frac{D}{S+D}\right)\mathrm{NV_D} + \left(\frac{S}{S+D}\right)[\mathrm{NV_S} + \frac{1}{2}\$QALY - mean\ spending]$$

Where S = Total Y1 cohort of survivors, the survivor panel.

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