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(54) **DIABETES RISK ENGINE AND METHODS THEREOF FOR PREDICTING DIABETES PROGRESSION AND MORTALITY**

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G16H 50/50	(2006.01)

(52) **U.S. Cl.**

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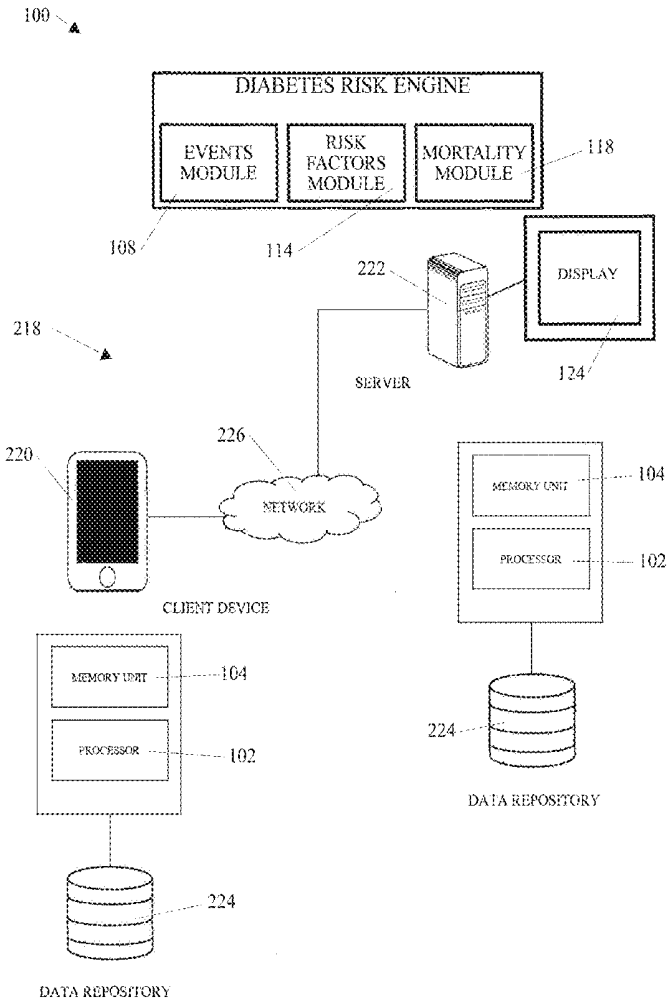
(57) **ABSTRACT**

The present disclosure provides for diabetes risk engine systems and methods for predicting diabetes progression and mortality in a patient with type 2 diabetes mellitus, for the U.S. population, including the building, relating, assessing, and validating outcomes (BRAVO) risk engine. The BRAVO risk engine includes a diabetes-related events module to predict an occurrence of one or more events, a risk factors module to predict a progression of risk factors, a mortality module to predict an occurrence of mortality, and a display interface configured to display the predicted risk of diabetes-related events or mortality. Risk equations for predicting diabetes-related microvascular and macrovascular events, hypoglycemia, mortality, and progression of diabetes risk factors were estimated using the data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. The BRAVO risk engine preferably includes risk factors including severe hypoglycemia and common U.S. racial/ethnicity categories, compared to the UKPDS risk engine.



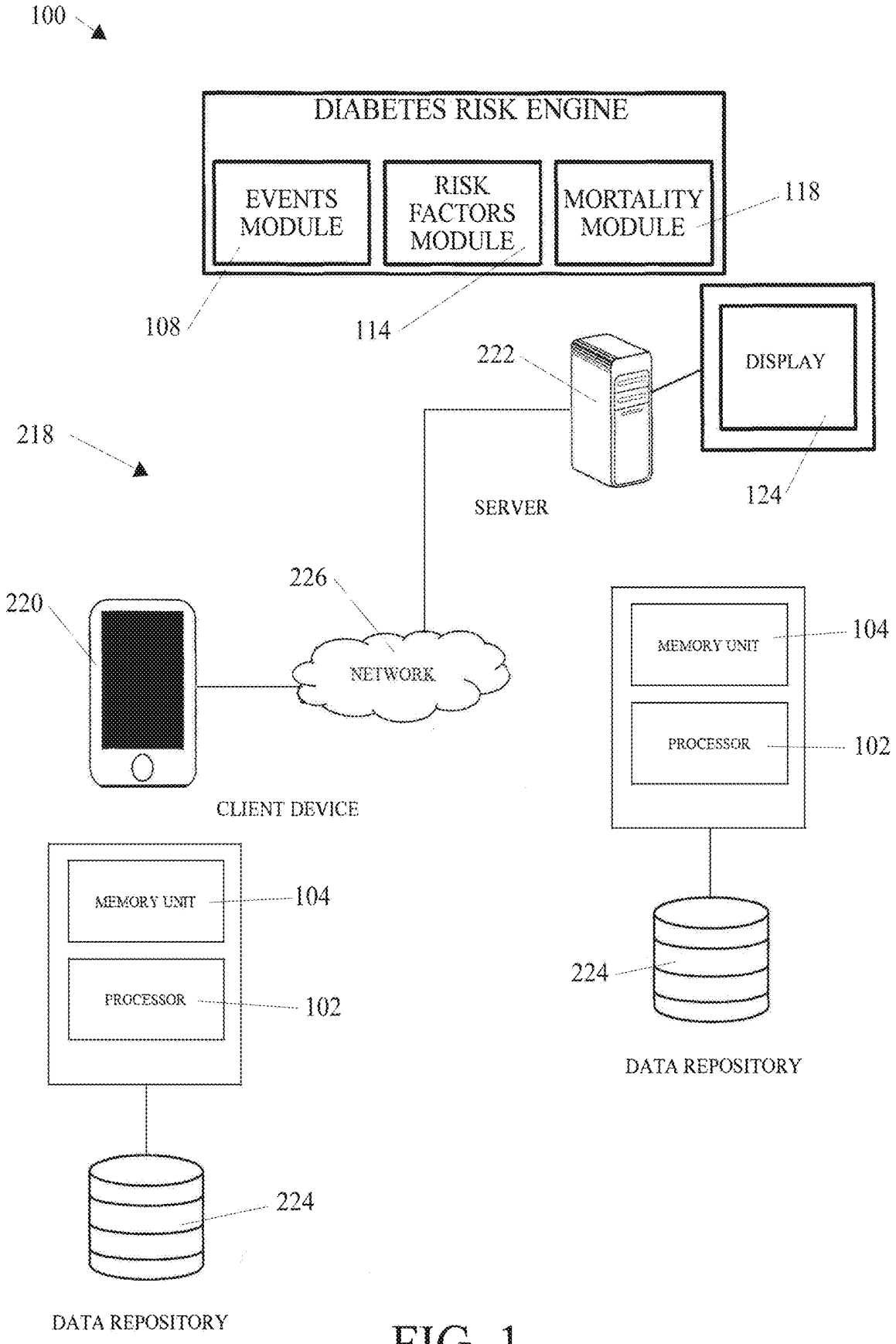

100
DIABETES RISK ENGINE
EVENTS MODULE
RISK FACTORS MODULE
MORTALITY MODULE
118
108
114
222
DISPLAY
218
SERVER
124
226
220
NETWORK
MEMORY UNIT
104
PROCESSOR
102
CLIENT DEVICE
MEMORY UNIT
104
PROCESSOR
102
224
DATA REPOSITORY
224
DATA REPOSITORY

FIG. 1

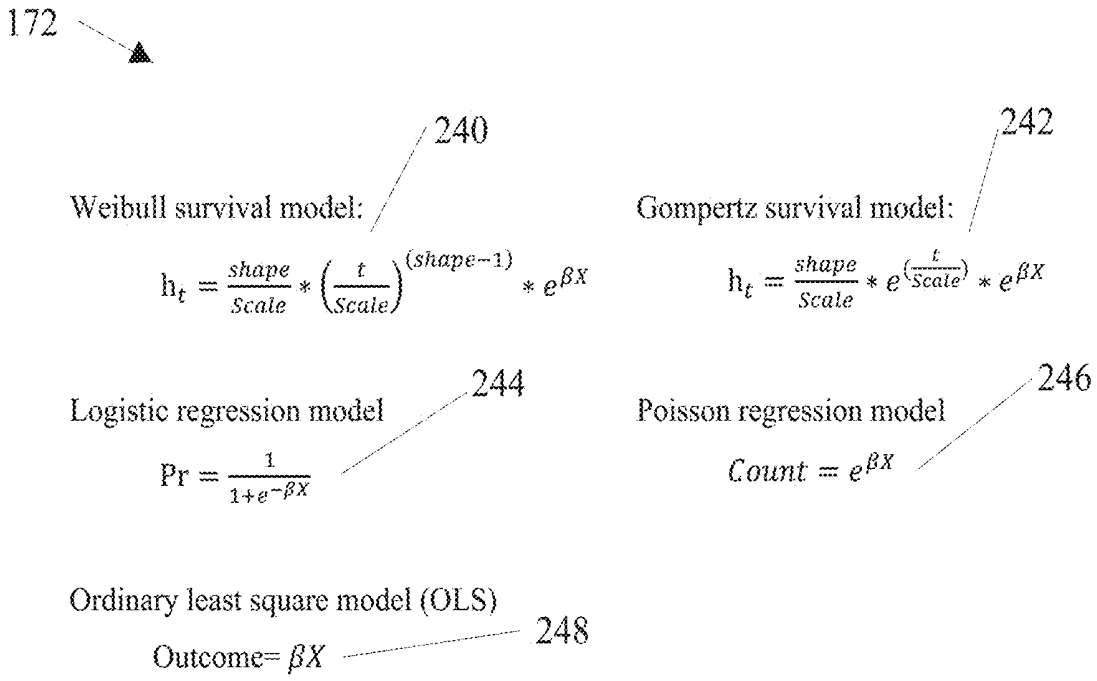

172
240
Weibull survival model:
$h_t = \frac{shape}{Scale} * \left(\frac{t}{Scale}\right)^{(shape-1)} * e^{\beta X}$
242
Gompertz survival model:
$h_t = \frac{shape}{Scale} * e^{\left(\frac{t}{Scale}\right)} * e^{\beta X}$
244
Logistic regression model
$Pr = \frac{1}{1+e^{-\beta X}}$
246
Poisson regression model
$Count = e^{\beta X}$
Ordinary least square model (OLS)
Outcome= βX
248

FIG. 2

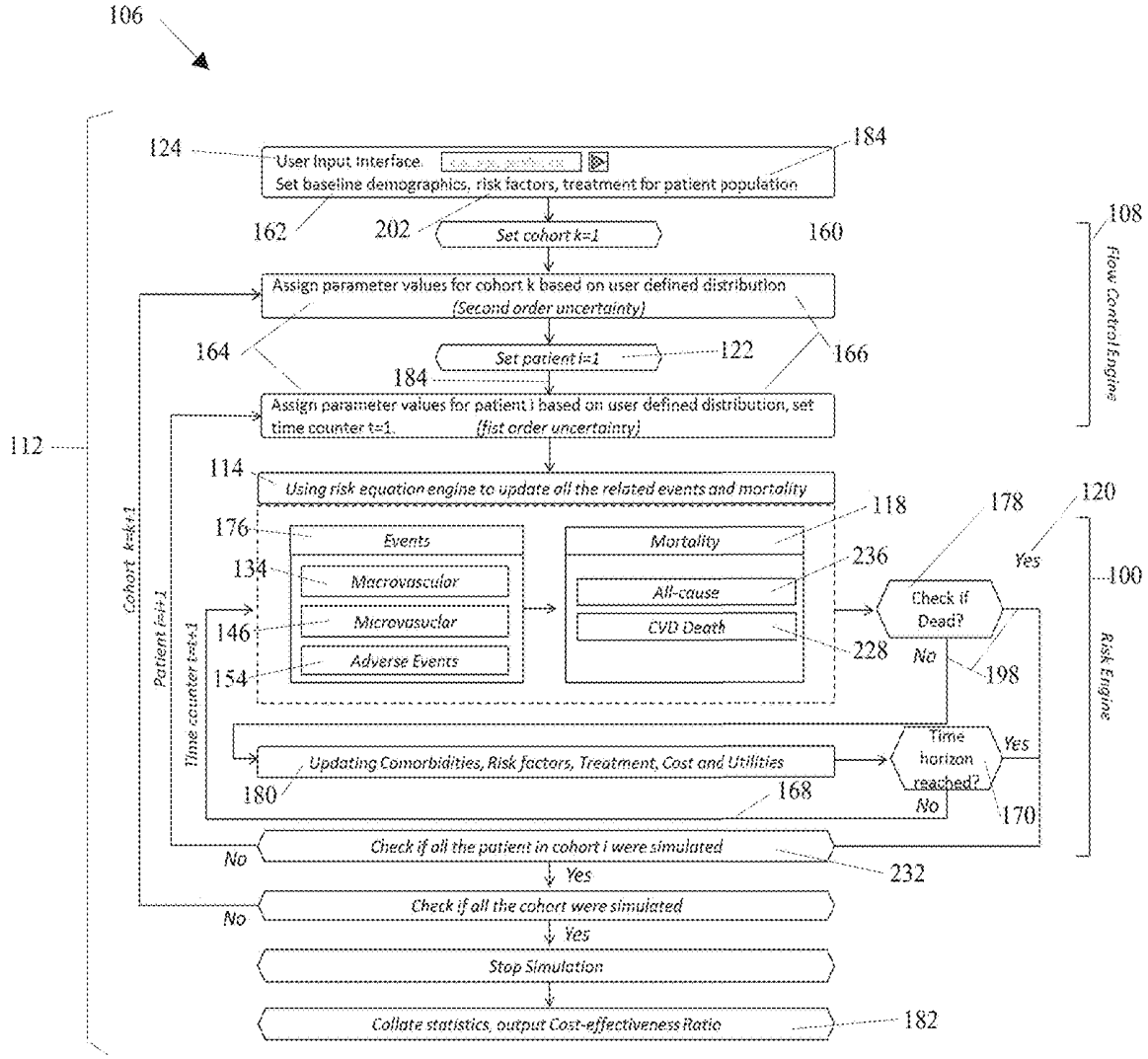

106
112
124
User Input Interface
Set baseline demographics, risk factors, treatment for patient population
184
162
202
Set cohort k=1
160
108
Flow Control Engine
Assign parameter values for cohort k based on user defined distribution
(Second order uncertainty)
164
Set patient i=1
122
166
184
Assign parameter values for patient i based on user defined distribution, set time counter t=1
(first order uncertainty)
114
Using risk equation engine to update all the related events and mortality
118
178
120
176
Events
Mortality
236
Yes
134
Macrovascular
All-cause
100
Check if Dead?
146
Microvascular
CVD Death
228
No
198
154
Adverse Events
Risk Engine
Time horizon reached?
Yes
Updating Comorbidities, Risk factors, Treatment, Cost and Utilities
180
168
No
170
Check if all the patient in cohort i were simulated
No
232
Yes
Check if all the cohort were simulated
No
Yes
Stop Simulation
Collate statistics, output Cost-effectiveness Ratio
182
Cohort k=k+1
Patient i=i+1
Time counter t=t+1

FIG. 3

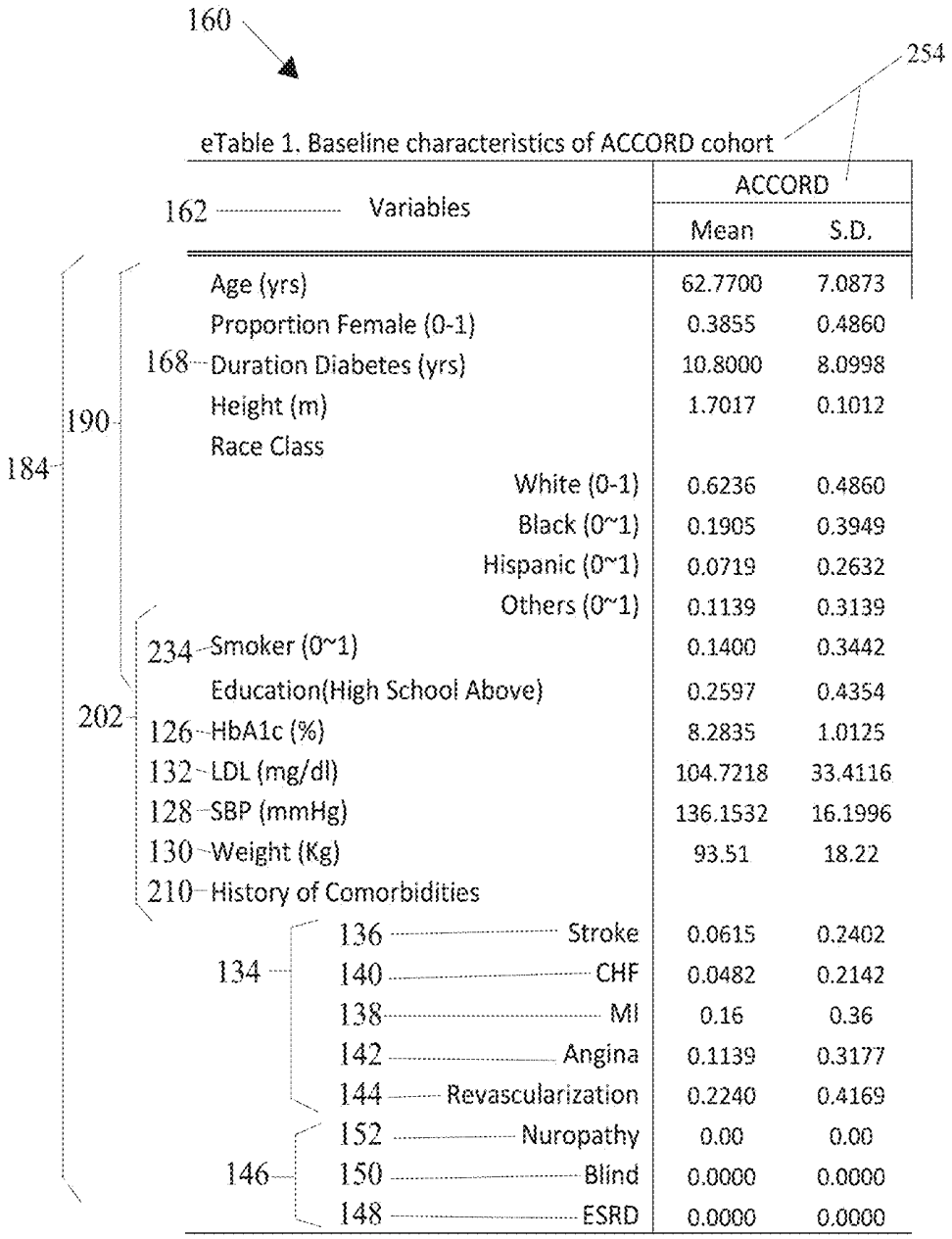
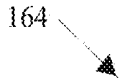

160
254
eTable 1. Baseline characteristics of ACCORD cohort
162
Variables
ACCORD
Mean
S.D.
184
190
202
168
234
126
132
128
130
210
134
136
140
138
142
144
146
152
150
148
Age (yrs) 62.7700 7.0873
Proportion Female (0-1) 0.3855 0.4860
Duration Diabetes (yrs) 10.8000 8.0998
Height (m) 1.7017 0.1012
Race Class
White (0-1) 0.6236 0.4860
Black (0~1) 0.1905 0.3949
Hispanic (0~1) 0.0719 0.2632
Others (0~1) 0.1139 0.3139
Smoker (0~1) 0.1400 0.3442
Education(High School Above) 0.2597 0.4354
HbA1c (%) 8.2835 1.0125
LDL (mg/dl) 104.7218 33.4116
SBP (mmHg) 136.1532 16.1996
Weight (Kg) 93.51 18.22
History of Comorbidities
Stroke 0.0615 0.2402
CHF 0.0482 0.2142
MI 0.16 0.36
Angina 0.1139 0.3177
Revascularization 0.2240 0.4169
Nuropathy 0.00 0.00
Blind 0.0000 0.0000
ESRD 0.0000 0.0000

FIG. 4



eTable 2. Variables included in the risk engine

	Abbreviations	Definitions	Units
188 Biomedical Factors			
	HbA1c 126	Glycated hemoglobin	%
	SBP 128	Systolic blood pressure	mmHg
	LDL 132	Low-density lipoprotein	mg/dl
	Body Weight 130	Weight measurement	kg
	BMI 130	BMI measurement	kg/m^2
190 Demographic	Age	Age at time of the event	Years
	Age_at_diagnosis	Age when T2DM was diagnosed	Years
	Duration 168	Duration of T2DM	Years
	Female	1 for female, 0 for male	1/0 (Yes/No)
	Education	1 for above college, 0 for below college	1/0 (Yes/No)
	Smoking 234	If current smoker	1/0 (Yes/No)
	Race Class (ref=Af. Am)		
	White	1 for white	1/0 (Yes/No)
	Hispanic	1 for Hispanic	1/0 (Yes/No)
	Others	1 for others besides white, Hispanic, Asian and African American	1/0 (Yes/No)
210 Complications	MI History 138	Myocardial infarction before this year	1/0 (Yes/No)
	MI Events 138	MI this year	1/0 (Yes/No)
134	CHF History 140	Congestive heart failure before this year	1/0 (Yes/No)
	CHF Events 140	CHF this year	1/0 (Yes/No)
	Stroke History 136	Stroke before this year	1/0 (Yes/No)
	Stroke Events 136	Stroke this year	1/0 (Yes/No)
	Angina History 142	Angina before this year	1/0 (Yes/No)
	Angina Events 142	Angina this year	1/0 (Yes/No)
	Revascularization History 144	Revascularization surgery before this year	1/0 (Yes/No)
	Revascularization Events 144	Revascularization surgery this year	1/0 (Yes/No)
146	Blindness History 150	Blindness before this year	1/0 (Yes/No)
	Blindness Events 150	Blindness this year	1/0 (Yes/No)
	ESRD History 148	ESRD before this year	1/0 (Yes/No)
	ESRD Events 148	ESRD this year	1/0 (Yes/No)
	SPSL History 152	Severe pressure sensation loss before this year	1/0 (Yes/No)
	SPSL Events 152	SPSL this year	1/0 (Yes/No)

FIG. 5

172

eTable 3. Prediction equations for time varying risk factors

	HbA1c (126)	SBP (128)	LDL (132)	Weight (130)	Severe Hypoglycemia (156)	Symptomatic Hypoglycemia (158)	Smoking (234)
Intercept	3.330	69.935	38.185	6.126	-2.954	-5.845	-1.572
L1-HbA1c[1]	-0.459						
L1-SBP[1]		0.476					
L1-LDL[1]			0.590				
L1-Weight[1]				0.982			
L1-Smoking							3.623
L2-Smoking							2.113
Log(Duration)	0.082		-1.159				
Age				-0.064	0.039		-0.032
HbA1c					-1.009	0.163	
HbA1c^2					0.072		
BMI							-0.016
Diabetes Duration					0.047	0.045	
Education(Above College)							-0.246
Female						0.285	-0.083
Race							
Hispanic					-0.311		-0.286
Others					-1.033		-0.349
White					-0.663		-0.162
Functional Form	Linear	Linear	Linear	Linear	Poisson	Poisson	Logistic

250 246 244

[1] "L" denotes lagged value (1=last year, 2= two years ago)

170

FIG. 6

252 100

eTable 4. Differences between RECODE risk equations and BRAVO risk equations

	RECODE	BRAVO
Infer clinical decision (e.g. risk stratification, and patient heterogeneity)	Yes	Yes
174 • Short-term outcomes prediction (<=10 years)	Yes	Yes
174 • Long-term or lifetime outcomes prediction		Yes
Support discrete-time event simulation and cost-effectiveness analysis		Yes
• Allow 1st (stochastic) order uncertainty		Yes
• Allow 2nd order uncertainty		Yes
202 • Allow time-varying risk factors		Yes
208 • Allow inter-related diabetes complications		Yes
Need to make assumptions on baseline hazards	Yes*	

*The requirement is a weakness

FIG. 7

164 172 100

eTable 5. Parameter estimates of risk equations in the BRAVO risk engine

Abbreviations	Stroke (136)	CHF (140)	MI (138)	Angina (142)	Revasc (144)	ESRD (148)	Blindness (150)	SPSL (152)	All-cause Mortality (236)	CVD Death (228)
HbA1c	0.302	0.103	0.165	0.189	0.068	0.121	0.174	0.284	-0.669	0.260
HbA1c^2									0.047	
SBP	0.029	0.017			0.006	0.014	0.015	0.010		0.014
LDL	0.009		0.007	0.004			0.004	0.002		
BMI		0.058		0.027	0.167				0.017	0.034
BMI^2					-0.002					
Age_at_Diagnosis	0.046	0.056	0.031				0.021	0.024		
Severe Hypoglycemia		0.683	0.827	0.634			0.417			
Female			-0.292		-0.313			-0.321	-0.551	
Education		-0.547	-0.384				-0.300		-0.321	
Smoking			0.178						0.568	
RaceClass (ref=Black)										
White			0.523		0.381		0.078	0.202		
Hispanic			0.237		0.104		0.531	-0.166		
Others			0.246		0.166		0.165	-0.594		
MI_History	0.613	0.600	0.487	0.379					0.202	0.767
CHF_History		1.246	0.217			0.514			0.777	0.763
Stroke_History	1.125		0.472		0.320				0.328	0.729
Angina_History				0.515	0.342				0.417	
Revasc_History		0.794		1.191	0.845					
Blindness_History						0.689		0.312		
Stroke_Event									1.218	2.009
CHF_Event									1.738	1.783
Log(duration)									1.738	0.223
Log(Scale)	10.028	8.029	6.311	7.986	7.093	6.945	6.431	6.399	2.452	-5.959
Log(Shape)	0.586	0.728	0.538	0.065	0.264	0.259	0.592	0.501	-6.336	
Function	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Gompertz	Logistic

240 242 244

FIG. 8

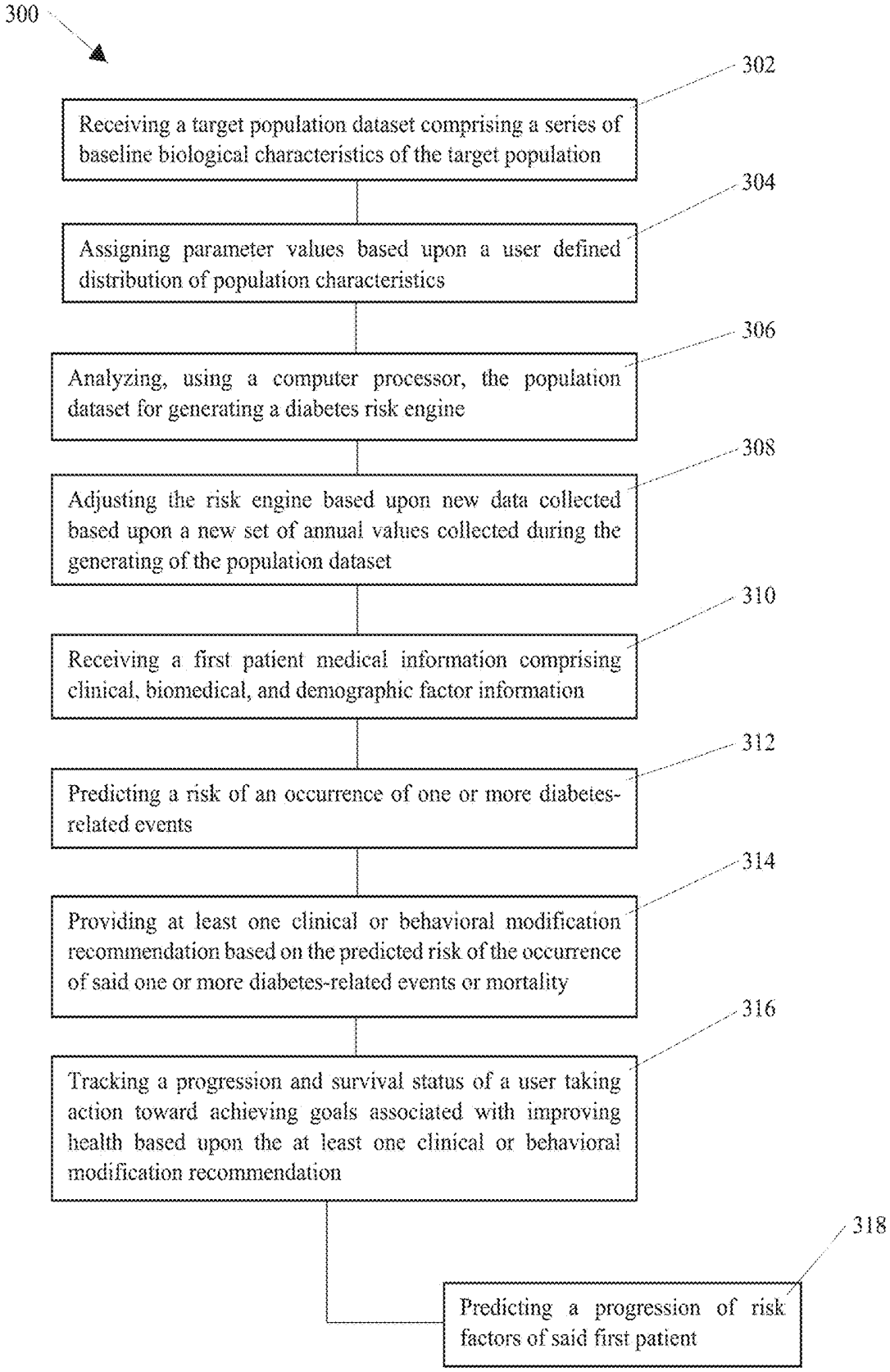

300
302
Receiving a target population dataset comprising a series of baseline biological characteristics of the target population
304
Assigning parameter values based upon a user defined distribution of population characteristics
306
Analyzing, using a computer processor, the population dataset for generating a diabetes risk engine
308
Adjusting the risk engine based upon new data collected based upon a new set of annual values collected during the generating of the population dataset
310
Receiving a first patient medical information comprising clinical, biomedical, and demographic factor information
312
Predicting a risk of an occurrence of one or more diabetes-related events
314
Providing at least one clinical or behavioral modification recommendation based on the predicted risk of the occurrence of said one or more diabetes-related events or mortality
316
Tracking a progression and survival status of a user taking action toward achieving goals associated with improving health based upon the at least one clinical or behavioral modification recommendation
318
Predicting a progression of risk factors of said first patient

FIG. 9

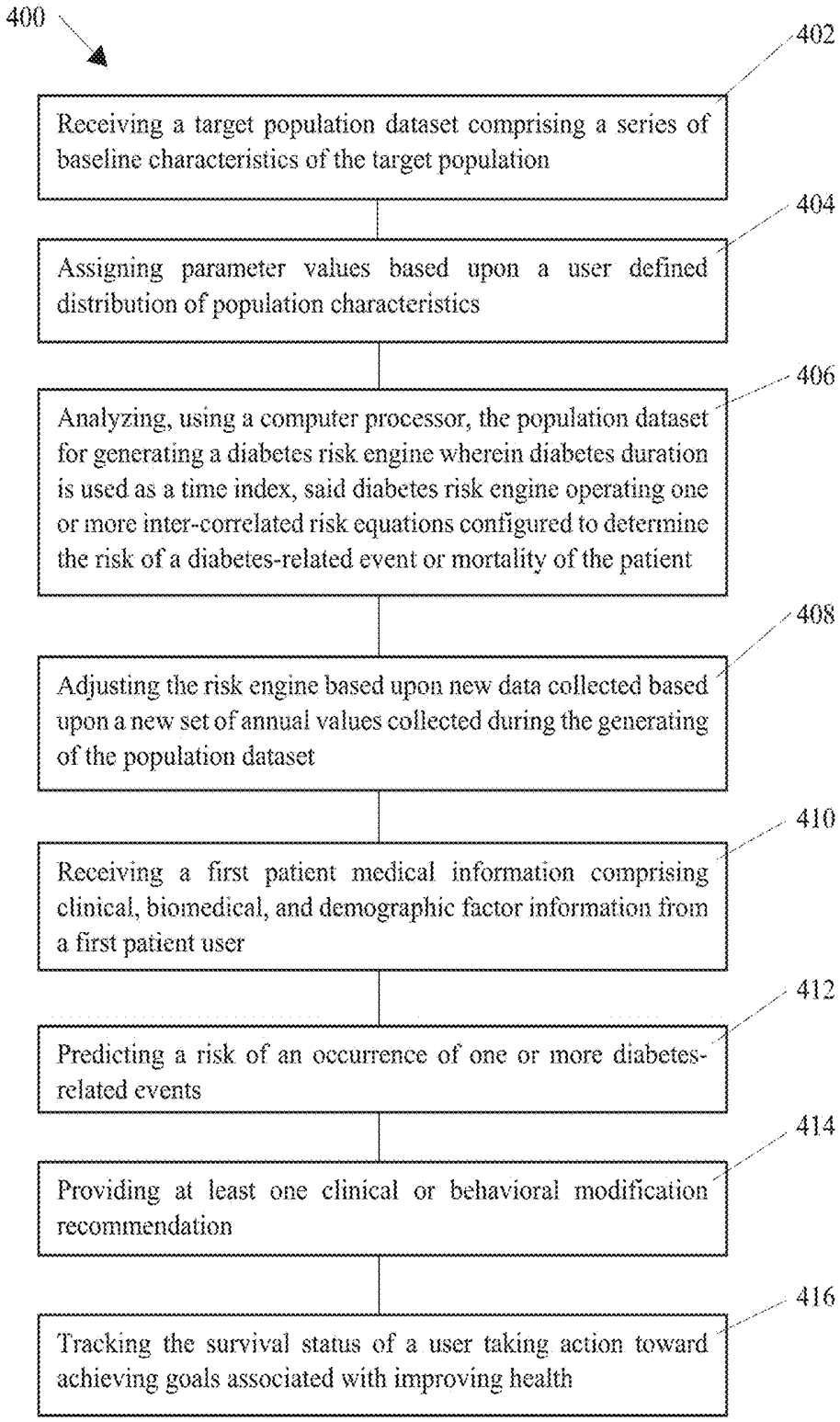

400
402
Receiving a target population dataset comprising a series of baseline characteristics of the target population
404
Assigning parameter values based upon a user defined distribution of population characteristics
406
Analyzing, using a computer processor, the population dataset for generating a diabetes risk engine wherein diabetes duration is used as a time index, said diabetes risk engine operating one or more inter-correlated risk equations configured to determine the risk of a diabetes-related event or mortality of the patient
408
Adjusting the risk engine based upon new data collected based upon a new set of annual values collected during the generating of the population dataset
410
Receiving a first patient medical information comprising clinical, biomedical, and demographic factor information from a first patient user
412
Predicting a risk of an occurrence of one or more diabetes-related events
414
Providing at least one clinical or behavioral modification recommendation
416
Tracking the survival status of a user taking action toward achieving goals associated with improving health

FIG. 10

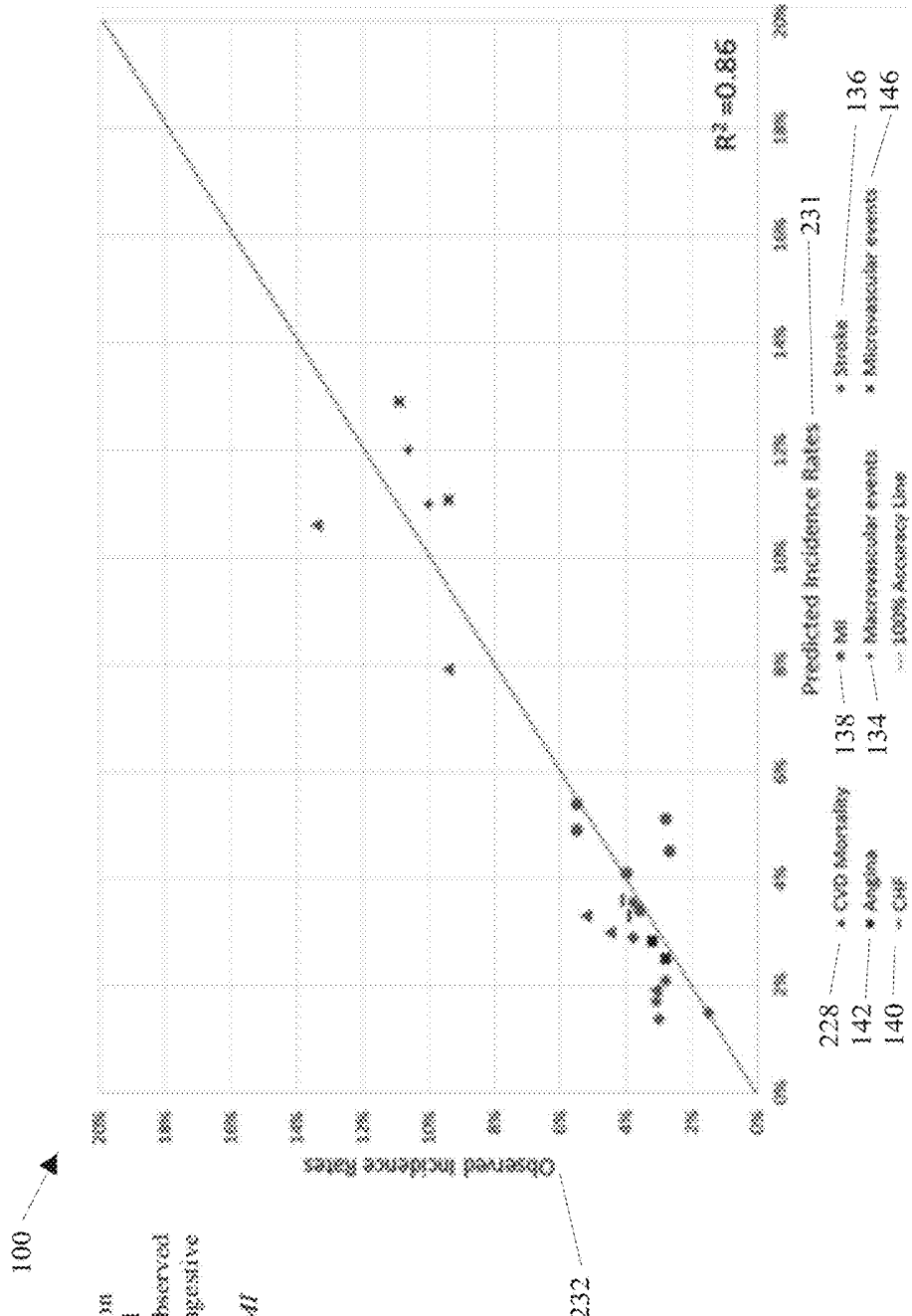


Fig. 2 External validation results plotting predicted incidence rates against observed incidence rates. *CHF* congestive heart failure, *CVD* cardiovascular disease, *MI* myocardial infarction

FIG. 11

164

100

Table 3. Definitions of variables included in the risk engine

	Abbreviations	Definitions	Units
126	HbA1c	2 years moving average of yearly value	%
128	SBP	2 years moving average of yearly value	mmHg
132	LDL	2 years moving average of yearly value	mg/dl
130	BodyWeights	2 years moving average of yearly value	kg
	BMI	2 years moving average of yearly value	kg/m^2
	Age	Age at time of the event	
168	Age_at_Diagnosis	Age at diagnose of T2DM	
	Duration	Number of Years after diagnose of T2DM	Years
	Female	1 for female, 0 for male	
	Education	1 for above college, 0 for below college	
234	Smoking	1 for current smoker, 0 for non-smoker	
	RaceClass (ref=Black)		
	White	1 for white	1/0 (Yes/No)
	Hispanic	1 for Hispanic	1/0 (Yes/No)
	Others	1 for others besides white, hispanic and black	1/0 (Yes/No)
138	MI_History	Encounterd MI before this year	1/0 (Yes/No)
	MI_events	Encounterd MI this year	1/0 (Yes/No)
140	CHF_History	Encounterd CHF before this year	1/0 (Yes/No)
	CHF_events	Encounterd CHF this year	1/0 (Yes/No)
136	Stroke_History	Encounterd Stroke before this year	1/0 (Yes/No)
	Stroke_events	Encounterd Stroke this year	1/0 (Yes/No)
142	Angina_History	Encounterd Angina before this year	1/0 (Yes/No)
	Angina_events	Encounterd Angina this year	1/0 (Yes/No)
144	Revasc_History	Encounterd Revascularization surgery before this year	1/0 (Yes/No)
	Revasc_events	Encounterd Revascularization surgery this year	1/0 (Yes/No)
150	Blindness_History	Encounterd Blindness before this year	1/0 (Yes/No)
	Blindness_events	Encounterd Blindness this year	1/0 (Yes/No)
148	ESRD_History	Encounterd ESRD before this year	1/0 (Yes/No)
	ESRD_events	Encounterd ESRD this year	1/0 (Yes/No)
152	Neuropathy_History	Encounterd Neuropathy before this year	1/0 (Yes/No)
	Neuropathy_events	Encounterd Neuropathy this year	1/0 (Yes/No)

FIG. 12

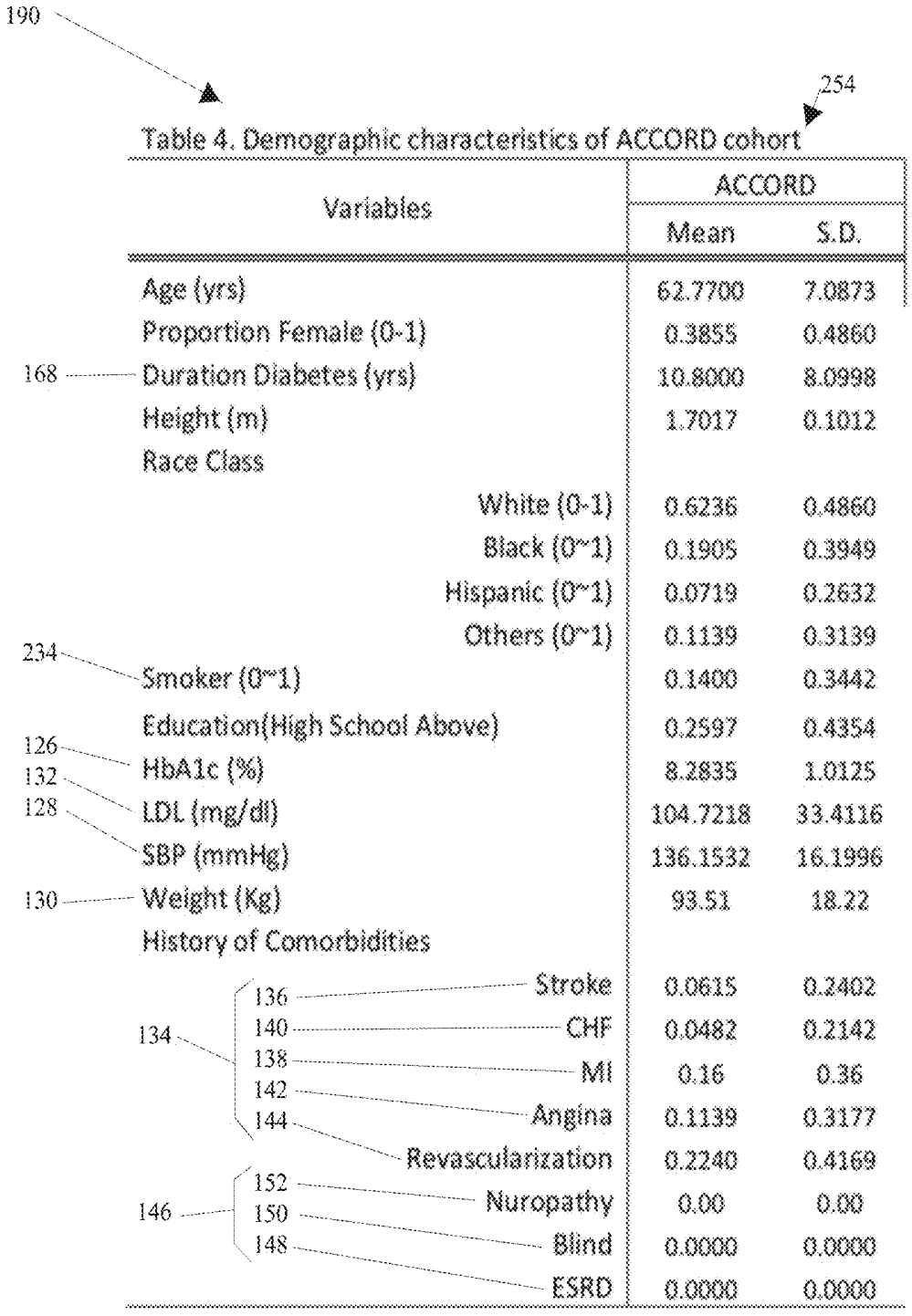

190
254
Table 4. Demographic characteristics of ACCORD cohort
Variables
ACCORD
Mean
S.D.
Age (yrs) 62.7700 7.0873
Proportion Female (0-1) 0.3855 0.4860
168 Duration Diabetes (yrs) 10.8000 8.0998
Height (m) 1.7017 0.1012
Race Class
White (0-1) 0.6236 0.4860
Black (0~1) 0.1905 0.3949
Hispanic (0~1) 0.0719 0.2632
Others (0~1) 0.1139 0.3139
234 Smoker (0~1) 0.1400 0.3442
Education(High School Above) 0.2597 0.4354
126 HbA1c (%) 8.2835 1.0125
132 LDL (mg/dl) 104.7218 33.4116
128 SBP (mmHg) 136.1532 16.1996
130 Weight (Kg) 93.51 18.22
History of Comorbidities
134
136 Stroke 0.0615 0.2402
140 CHF 0.0482 0.2142
138 MI 0.16 0.36
142 Angina 0.1139 0.3177
144 Revascularization 0.2240 0.4169
146
152 Nuropathy 0.00 0.00
150 Blind 0.0000 0.0000
148 ESRD 0.0000 0.0000

FIG. 13

172 136

Table 5. Prediction equation for Stroke

Variables	Coefficient	S.E.	OR	95% CI	
				Lower	Upper
126 HbA1c	0.302	0.076	1.353	1.165	1.570
128 SBP	0.029	0.005	1.029	1.019	1.040
132 LDL	0.009	0.002	1.009	1.005	1.013
Age_At_Diagonose	0.046	0.011	1.047	1.025	1.070
138 MI History	0.613	0.178	1.846	1.302	2.617
136 Stroke History	1.125	0.207	3.080	2.053	4.622
Log(Scale)	10.028	0.708			
Log(Shape)	0.586	0.100			

FIG. 14

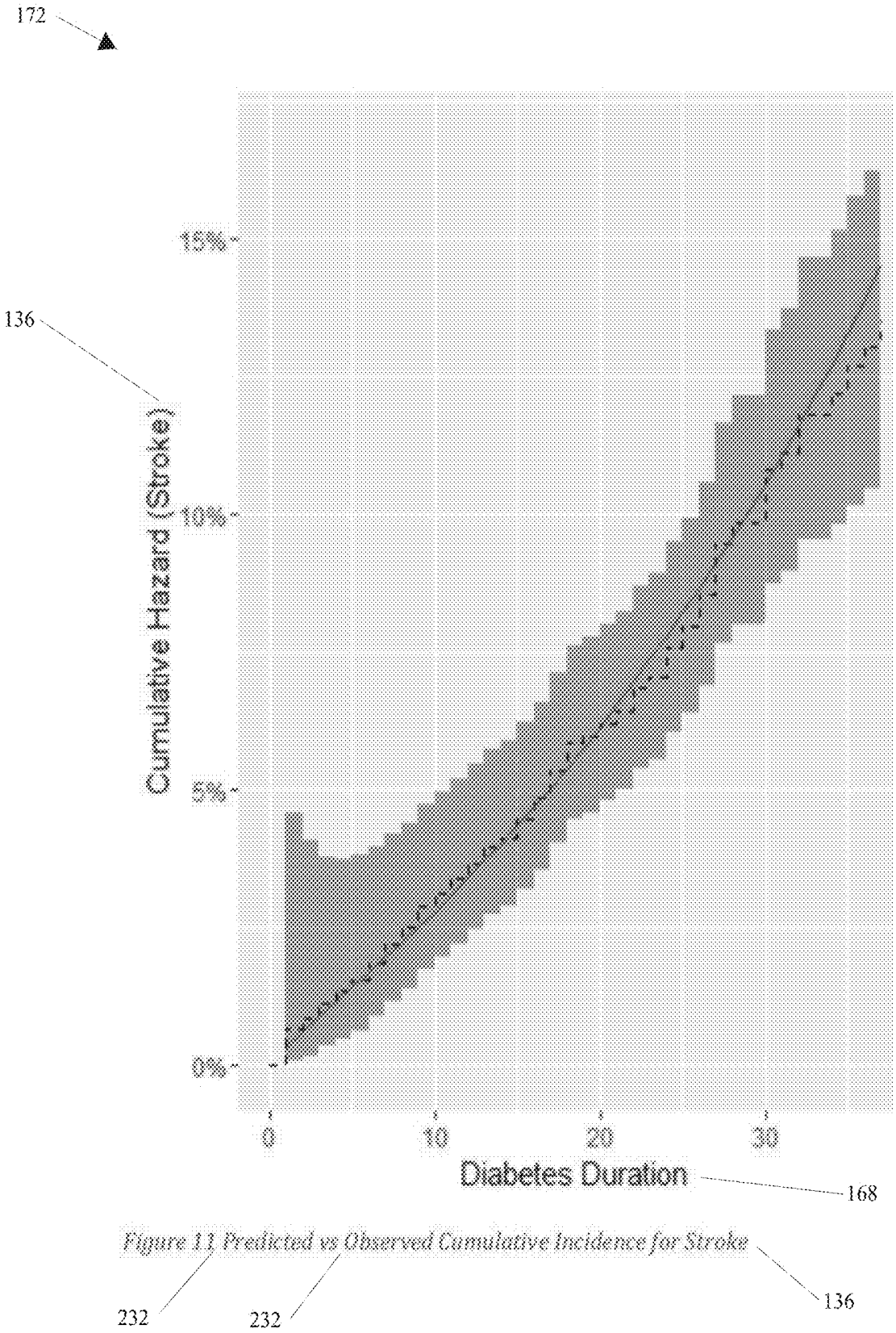

172
136
15%
10%
5%
0%
Cumulative Hazard (Stroke)
0
10
20
30
Diabetes Duration
168
Figure 13 Predicted vs Observed Cumulative Incidence for Stroke
232
232
136

FIG. 15

Table 6. Prediction equation for CHF

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.103	0.052	1.108	1.001	1.227
128	SBP	0.017	0.003	1.017	1.011	1.023
130	BMI	0.058	0.009	1.060	1.041	1.079
156	Sever_Hypoglycemia	0.683	0.231	1.980	1.259	3.114
	Education	-0.547	0.140	0.579	0.440	0.761
	Age_At_Diagonose	0.056	0.007	1.058	1.043	1.072
138	MI History	0.600	0.120	1.822	1.440	2.305
140	CHF_History	1.246	0.131	3.476	2.689	4.494
144	Revasc_History	0.794	0.117	2.212	1.759	2.782
	Log(Scale)	8.029	0.392			
	Log(Shape)	0.728	0.061			

FIG. 16

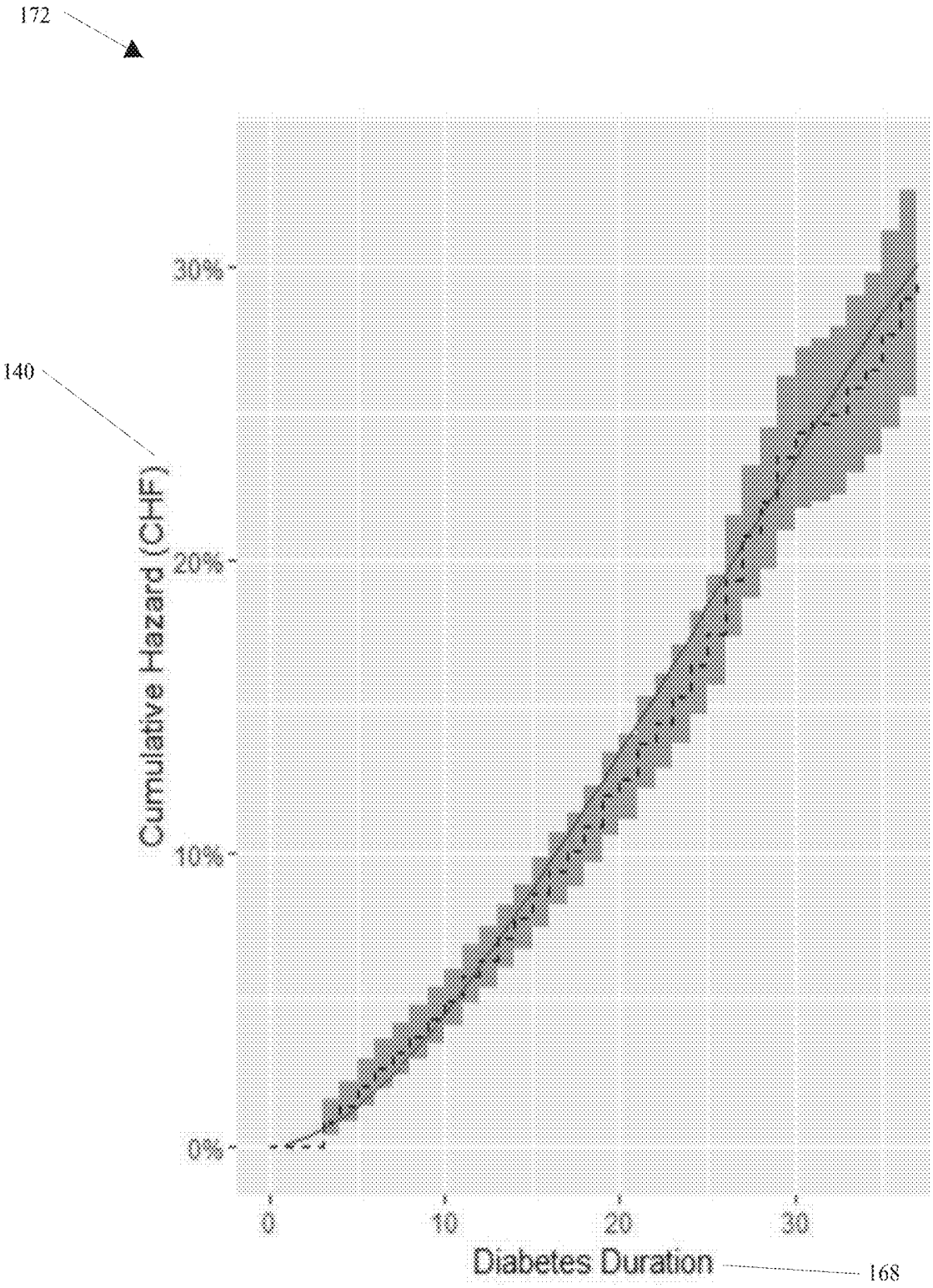

172
140
Cumulative Hazard (CHF)
30%
20%
10%
0%
0
10
20
30
Diabetes Duration
168
Figure 12 Predicted vs Observed Cumulative Incidence for CHF
231
232
140

FIG. 17

172

138

Table 7. Prediction equation for MI

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.165	0.042	1.179	1.086	1.281
132	LDL	0.007	0.001	1.007	1.005	1.009
156	Sever_Hypoglycemia	0.827	0.192	2.286	1.569	3.331
234	Smoking	0.178	0.131	1.195	0.924	1.545
	Age_At_Diagonose	0.031	0.006	1.031	1.019	1.044
	Female	-0.292	0.095	0.747	0.620	0.900
	Race					
	Hispanic	0.237	0.210	1.267	0.840	1.913
	Others	0.246	0.183	1.279	0.893	1.831
	White	0.523	0.129	1.687	1.310	2.172
	Education	-0.384	0.106	0.681	0.553	0.838
138	MI History	0.487	0.105	1.627	1.325	1.999
142	Angina_History	0.217	0.112	1.242	0.997	1.547
144	Revasc_History	0.472	0.100	1.603	1.318	1.950
	Log(Scale)	6.311	0.271			
	Log(Shape)	0.538	0.056			

FIG. 18

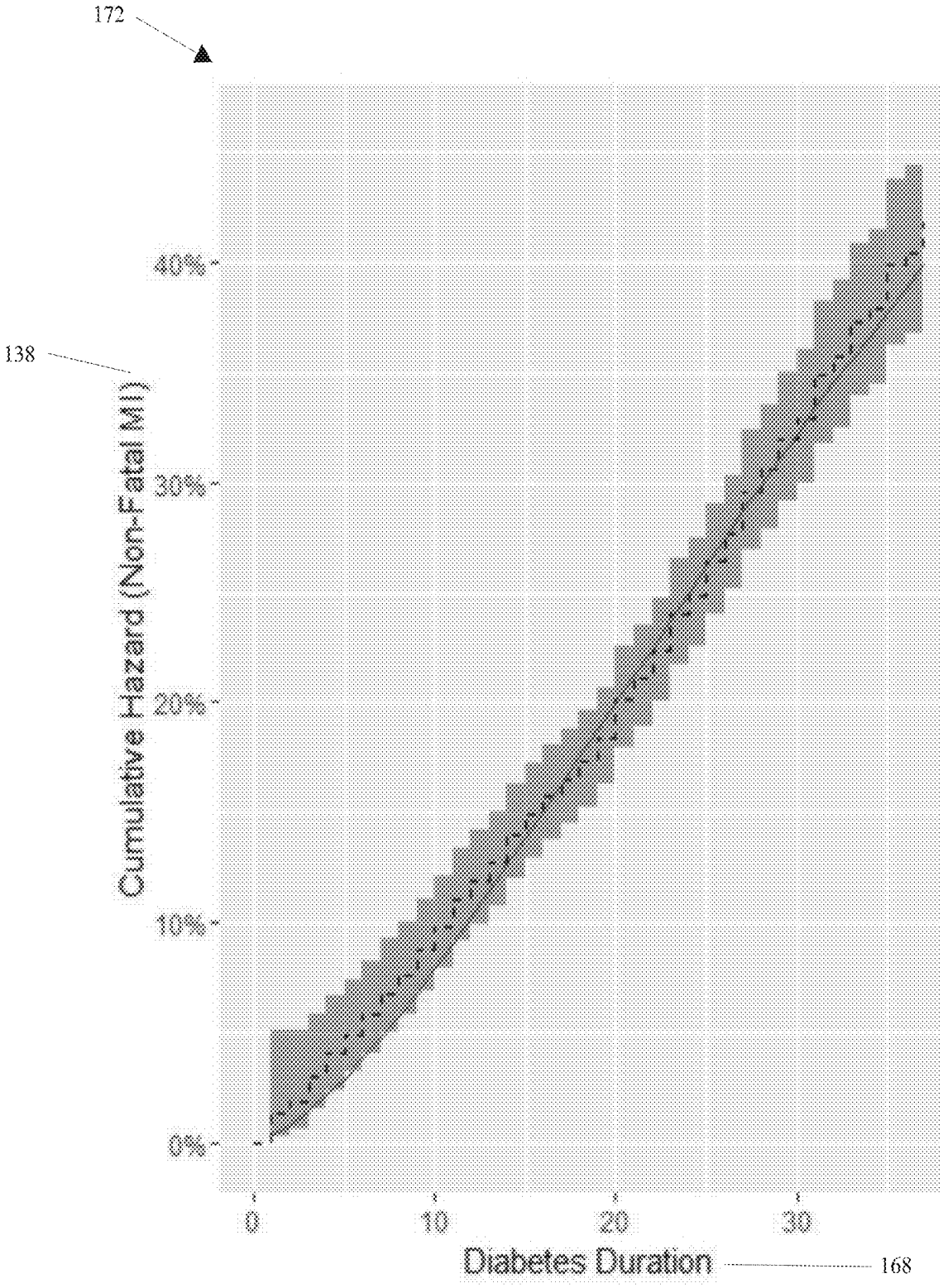


Figure 13 Predicted vs Observed Cumulative Incidence for Non-fatal MI

FIG. 19

172

142

Table 8. Prediction equation for Angina

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.189	0.051	1.208	1.093	1.335
130	BMI	0.027	0.010	1.027	1.007	1.048
132	LDL	0.004	0.002	1.004	1.000	1.008
156	Sever_Hypoglycemia	0.634	0.274	1.885	1.102	3.225
138	MI History	0.379	0.129	1.461	1.134	1.881
142	Angina_History	0.515	0.130	1.674	1.297	2.159
144	Revasc_History	1.191	0.126	3.290	2.570	4.212
	Log(Scale)	7.986	0.596			
	Log(Shape)	0.065	0.078			

FIG. 20

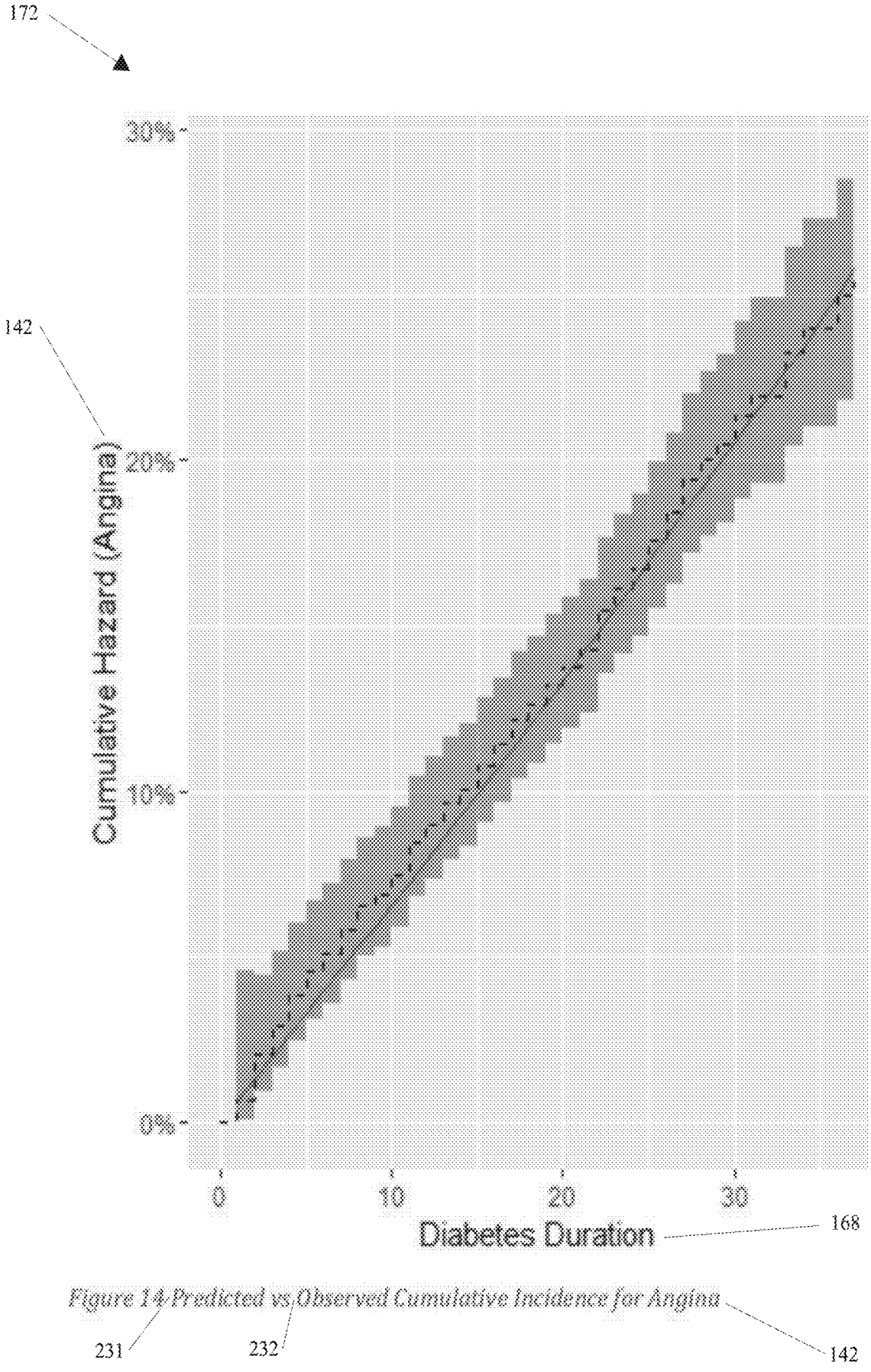


Figure 14-Predicted vs Observed Cumulative Incidence for Angina

FIG. 21

172

144

Table 9. Prediction equation for revascularization surgery

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.068	0.029	1.070	1.011	1.133
128	SBP	0.006	0.002	1.006	1.002	1.010
130	BMI	0.167	0.057	1.182	1.057	1.321
130	BMI^2	-0.002	0.001	0.998	0.996	1.000
	Female	-0.313	0.069	0.731	0.639	0.837
	Race					
	Hispanic	0.104	0.148	1.110	0.830	1.483
	Others	0.166	0.126	1.181	0.922	1.511
	White	0.381	0.090	1.464	1.227	1.746
136	Stroke History	0.320	0.108	1.377	1.114	1.702
142	Angina_History	0.342	0.078	1.408	1.208	1.640
144	Revasc_History	0.845	0.065	2.328	2.050	2.644
	Log(Scale)	7.093	0.783			
	Log(Shape)	0.264	0.037			

FIG. 22

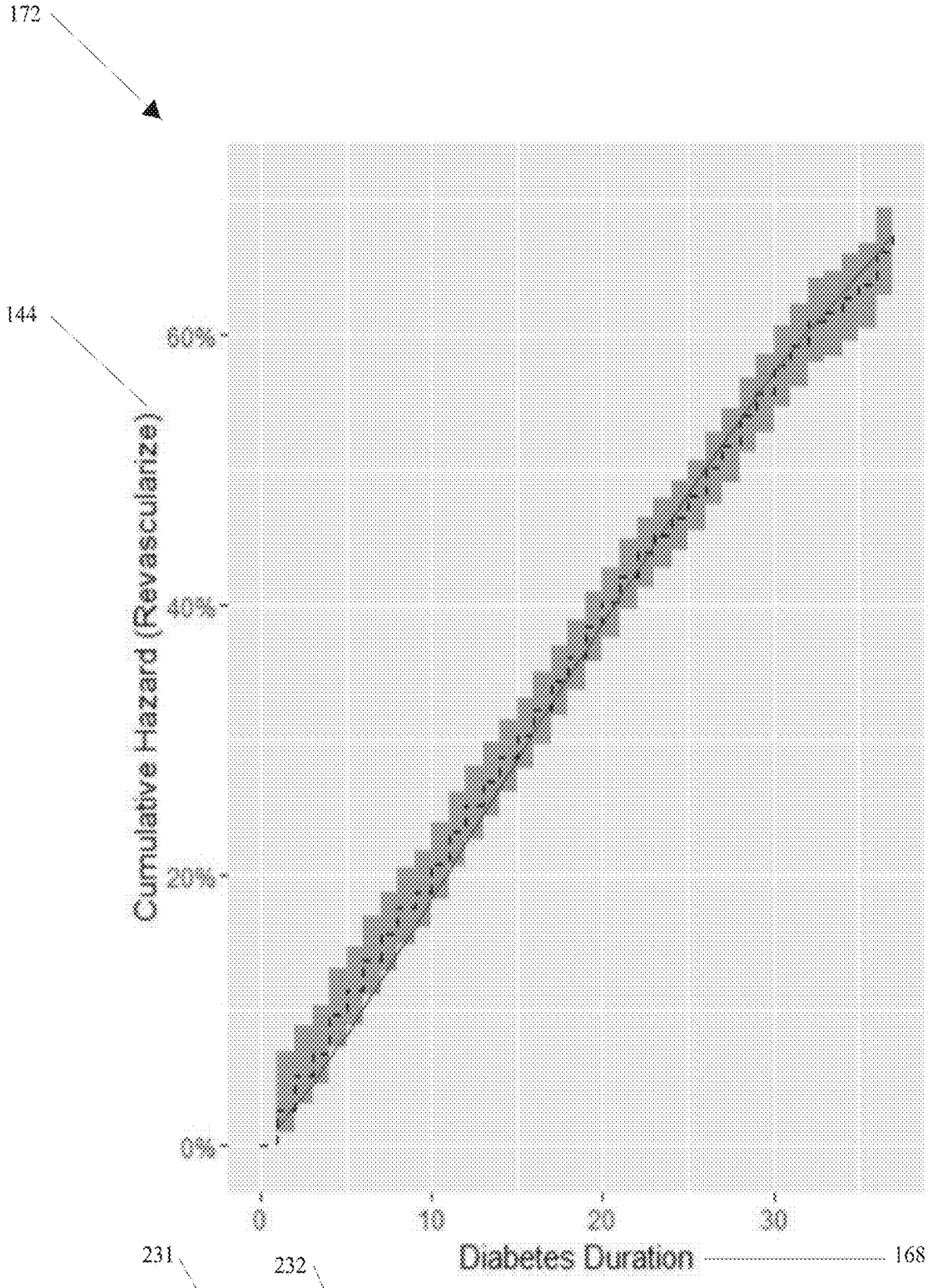


Figure 15 Predicted vs Observed Cumulative Incidence for Revascularization Surgery

FIG. 23

172 148

Table 10. Prediction equation for ESRD

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.121	0.060	1.129	1.003	1.269
128	SBP	0.014	0.004	1.014	1.006	1.022
140	CHF History	0.514	0.215	1.672	1.097	2.548
150	Blindness History	0.689	0.235	1.992	1.257	3.157
	Log(Scale)	6.945	0.601			
	Log(Shape)	0.259	0.080			

FIG. 24

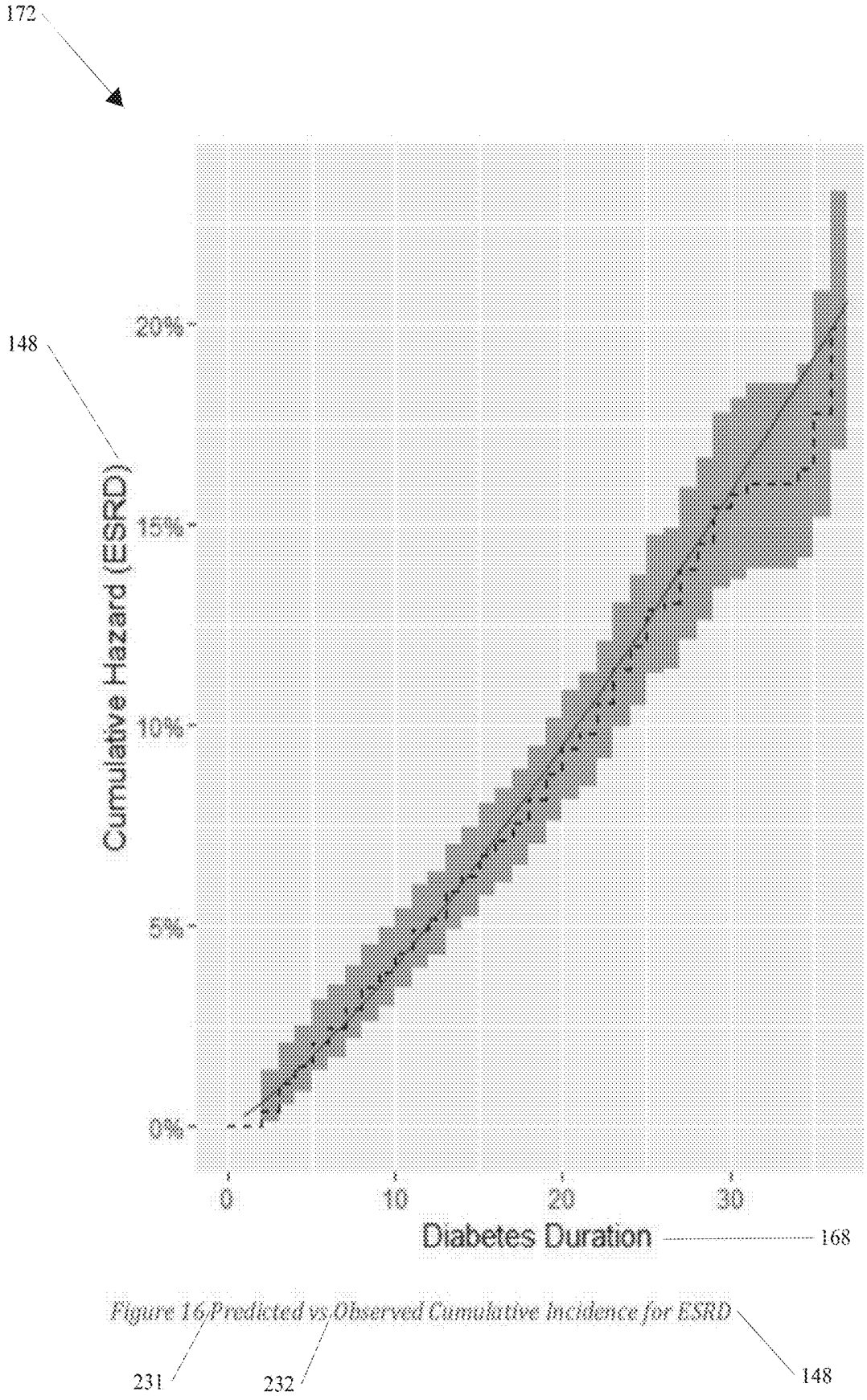


Figure 16 Predicted vs Observed Cumulative Incidence for ESRD

FIG. 25

172 150

Table 11. Prediction equation for Blindness

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.174	0.038	1.190	1.105	1.282
128	SBP	0.015	0.003	1.015	1.009	1.021
132	LDL	0.004	0.001	1.004	1.002	1.006
156	Severe Hypoglycemia	0.417	0.205	1.517	1.015	2.268
	Age at Diagnose	0.021	0.005	1.021	1.011	1.031
	Race					
	Hispanic	0.531	0.144	1.701	1.282	2.255
	Others	0.165	0.141	1.179	0.895	1.555
	White	0.078	0.102	1.081	0.885	1.320
	Education	-0.300	0.095	0.741	0.615	0.892
	Log(Scale)	6.431	0.277			
	Log(Shape)	0.592	0.050			

FIG. 26

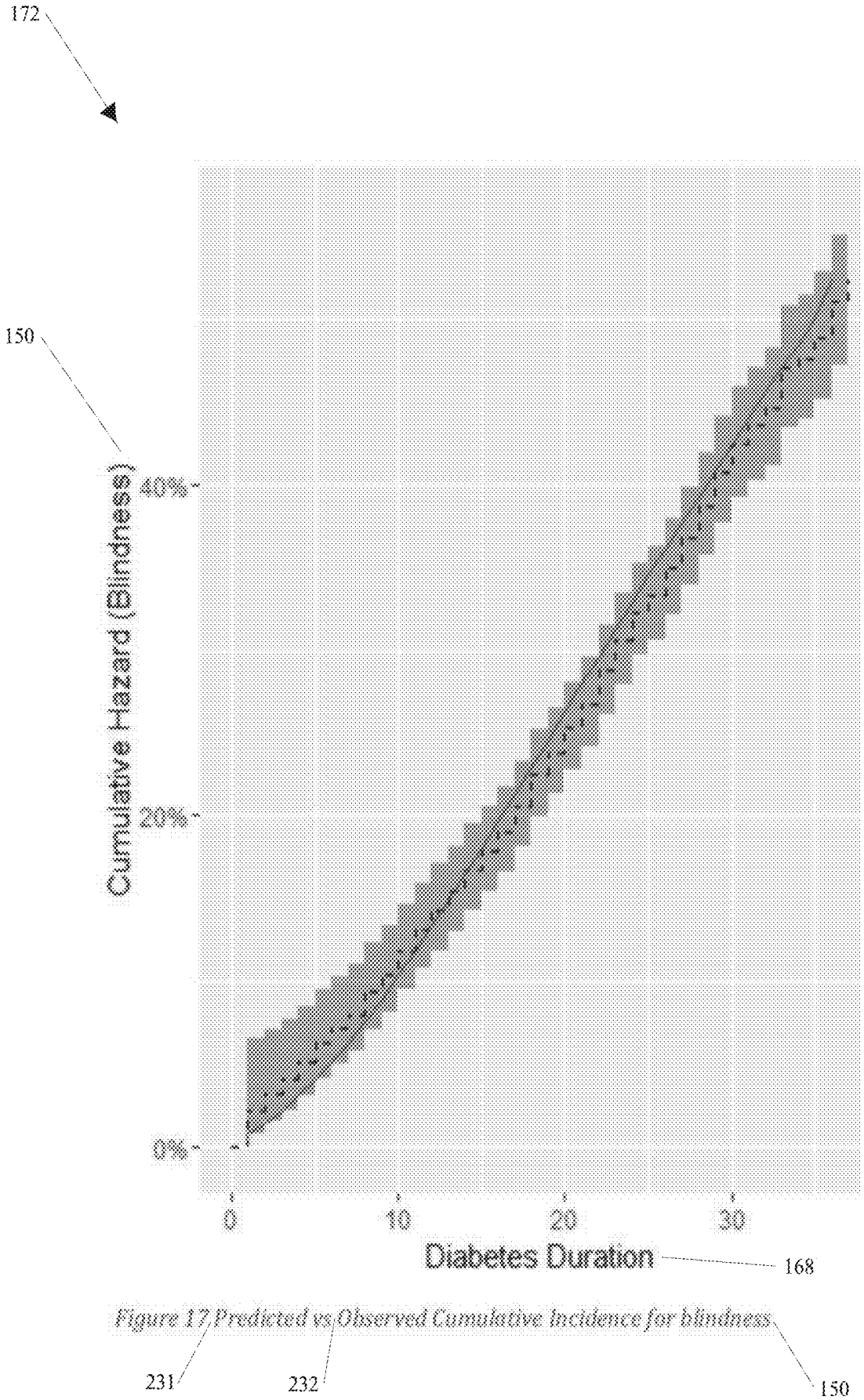

172
150
Cumulative Hazard (Blindness)
40%
20%
0%
0
10
20
30
Diabetes Duration
168
Figure 17 Predicted vs Observed Cumulative Incidence for blindness
231
232
150

FIG. 27

172

152

Table 12. Prediction equation for SPSL

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	0.284	0.030	1.328	1.253	1.409
128	SBP	0.010	0.002	1.010	1.006	1.014
132	LDL	0.002	0.001	1.002	1.000	1.004
	Age at Diagnose	0.024	0.005	1.024	1.014	1.034
	Female	-0.321	0.066	0.725	0.637	0.826
	Race					
	Hispanic	-0.166	0.148	0.847	0.634	1.132
	Others	-0.594	0.140	0.552	0.420	0.726
	White	0.202	0.081	1.224	1.044	1.434
150	Blindness_History	0.312	0.149	1.366	1.020	1.829
	Log(Scale)	6.399	0.251			
	Log(Shape)	0.501	0.042			

FIG. 28

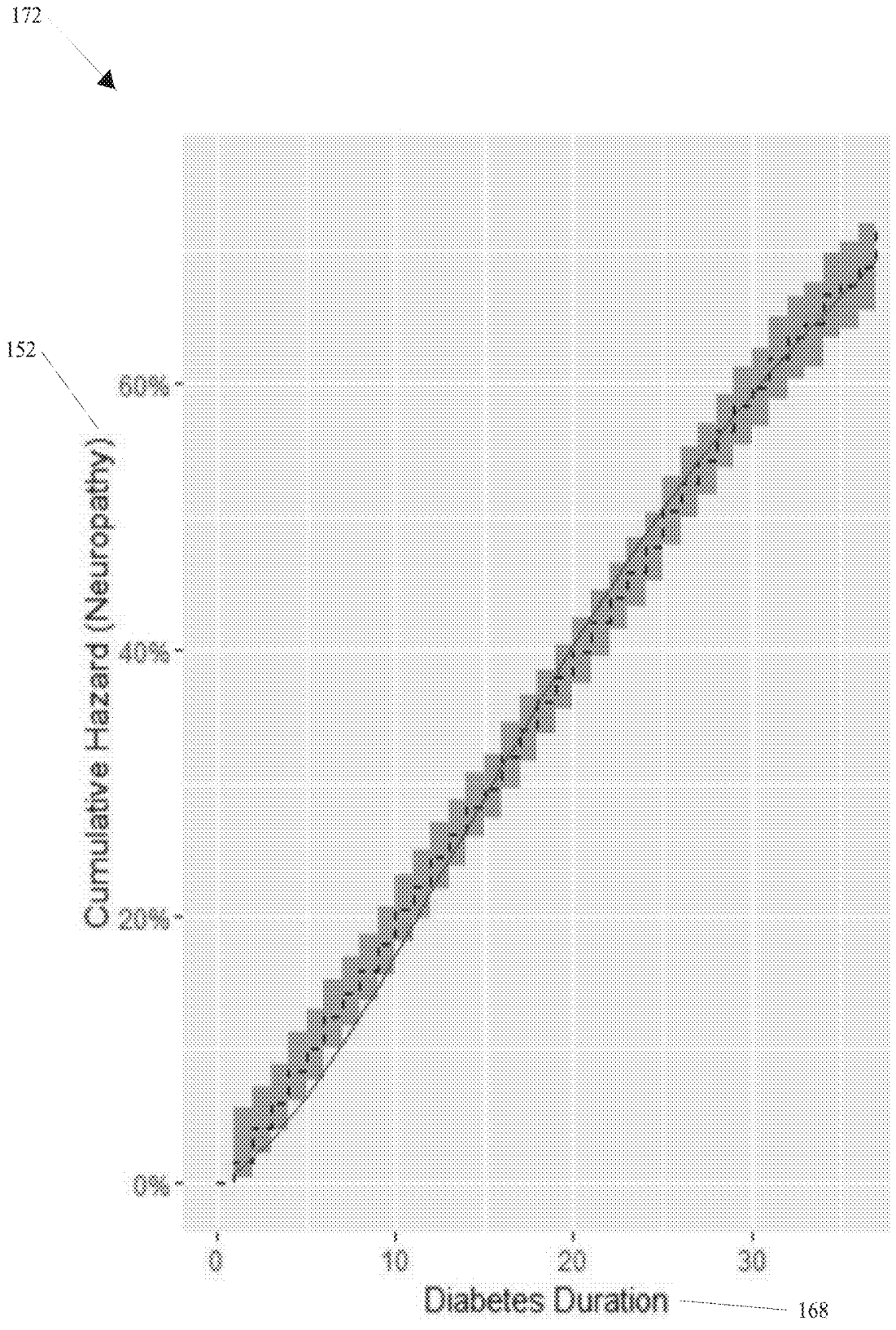


Figure 18 Predicted vs Observed Cumulative Incidence for SPSL

231 232 152

FIG. 29

172

236

Table 13. Prediction equation for All-cause Mortality

	Variables	Coefficient	S.E.	HR	95% CI	
					Lower	Upper
126	HbA1c	-0.669	0.516	0.512	0.186	1.408
126	HbA1c^2	0.047	0.033	1.048	0.982	1.118
130	BMI	0.017	0.009	1.017	0.999	1.035
234	Smoking	0.568	0.154	1.765	1.305	2.387
	Female	-0.551	0.116	0.576	0.459	0.724
	Education	-0.321	0.126	0.725	0.567	0.929
138	MI History	0.202	0.118	1.224	0.971	1.542
136	Stroke History	0.328	0.165	1.388	1.005	1.918
140	CHF History	0.777	0.139	2.175	1.656	2.856
142	Angina History	0.417	0.128	1.517	1.181	1.950
136	Stroke_Event	1.218	0.369	3.380	1.640	6.967
140	CHF Event	1.738	0.185	5.686	3.957	8.171
	Log(Scale)	2.452	0.100			
	Log(Shape)	-6.336	2.112			

FIG. 30

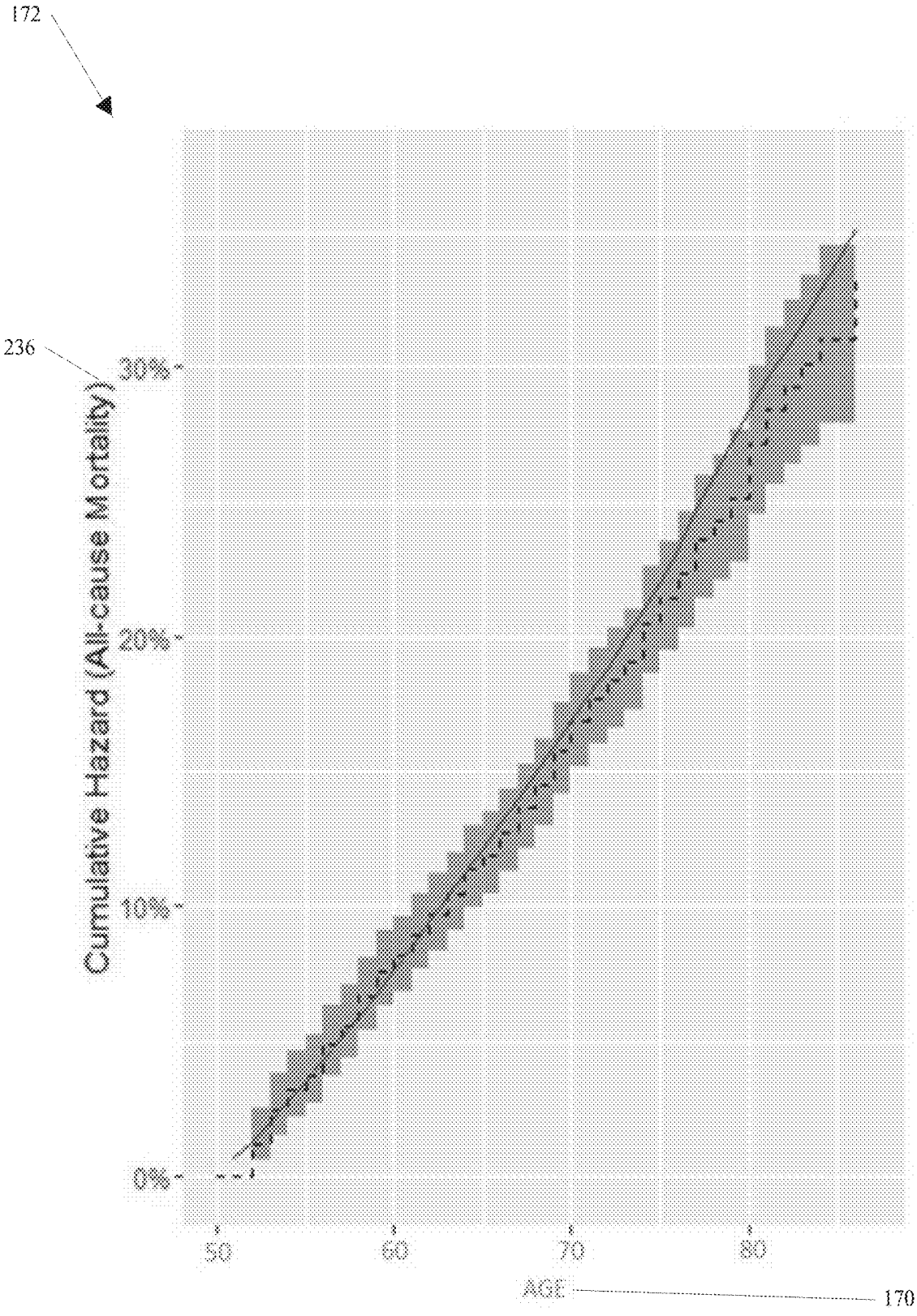


Figure 19 Predicted vs Observed Cumulative Incidence for All-cause Mortality

FIG. 31

172 228 244

Table 14. Prediction equation for CVD death(logistic regression)

	Variables	Coefficient	S.E.	OR	95% CI	
					Lower	Upper
	Intercept	-5.961	1.376	0.003	0.000	0.038
126	HbA1c	0.269	0.100	1.309	1.076	1.592
128	SBP	0.015	0.007	1.015	1.001	1.029
130	BMI	0.032	0.017	1.033	0.999	1.068
234	Smoking	-0.728	0.298	0.483	0.269	0.866
168	Log (Duration)	0.195	0.159	1.215	0.890	1.660
138	MI History	0.799	0.229	2.223	1.419	3.483
136	Stroke History	0.701	0.349	2.016	1.017	3.995
140	CHF History	0.770	0.284	2.160	1.238	3.768
136	Stroke Event	1.951	1.099	7.036	0.816	60.645
140	CHF Event	1.734	0.476	5.663	2.228	14.396

c-statistic=0.7351

FIG. 32

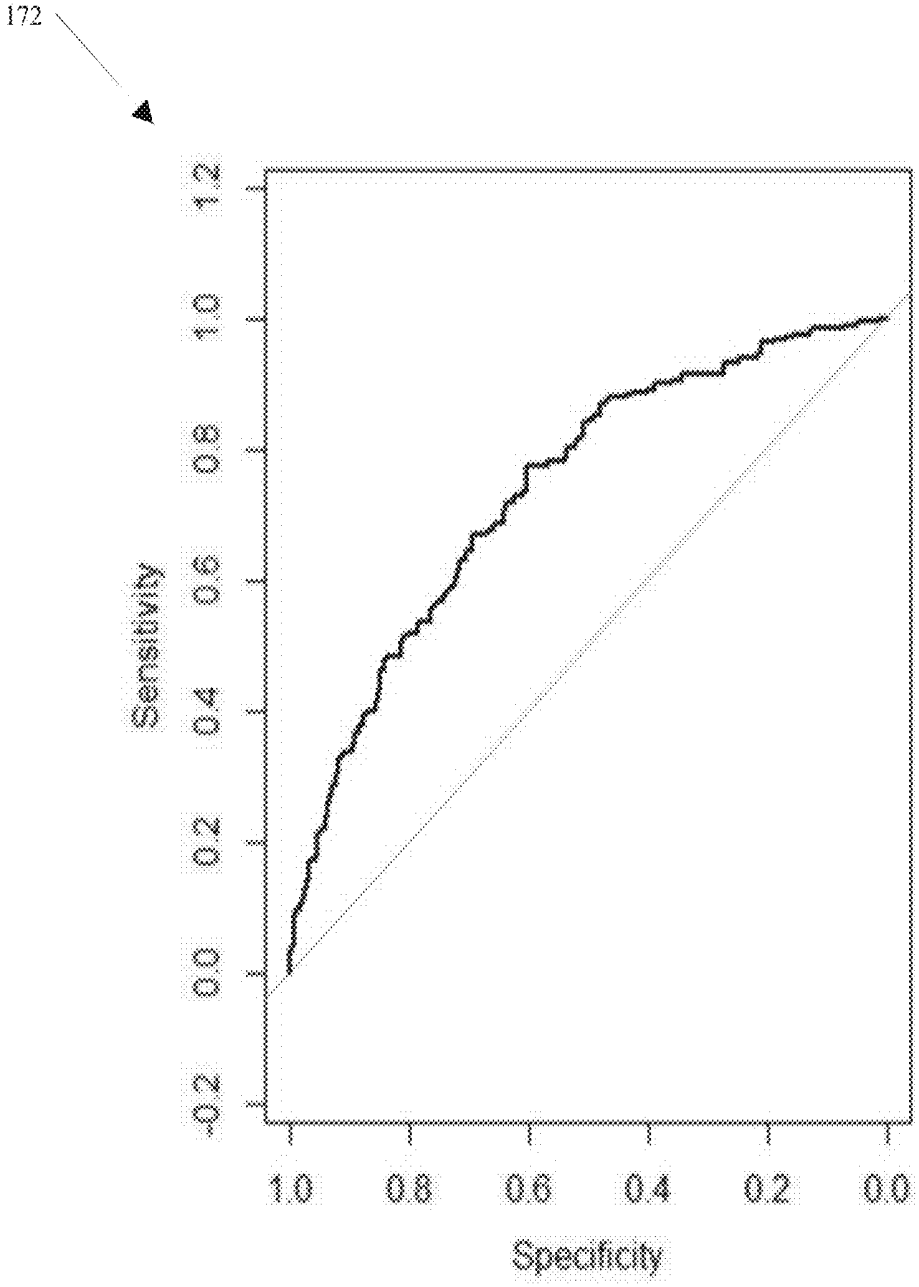


Figure 20 ROC curve for CVD prediction.

FIG. 33

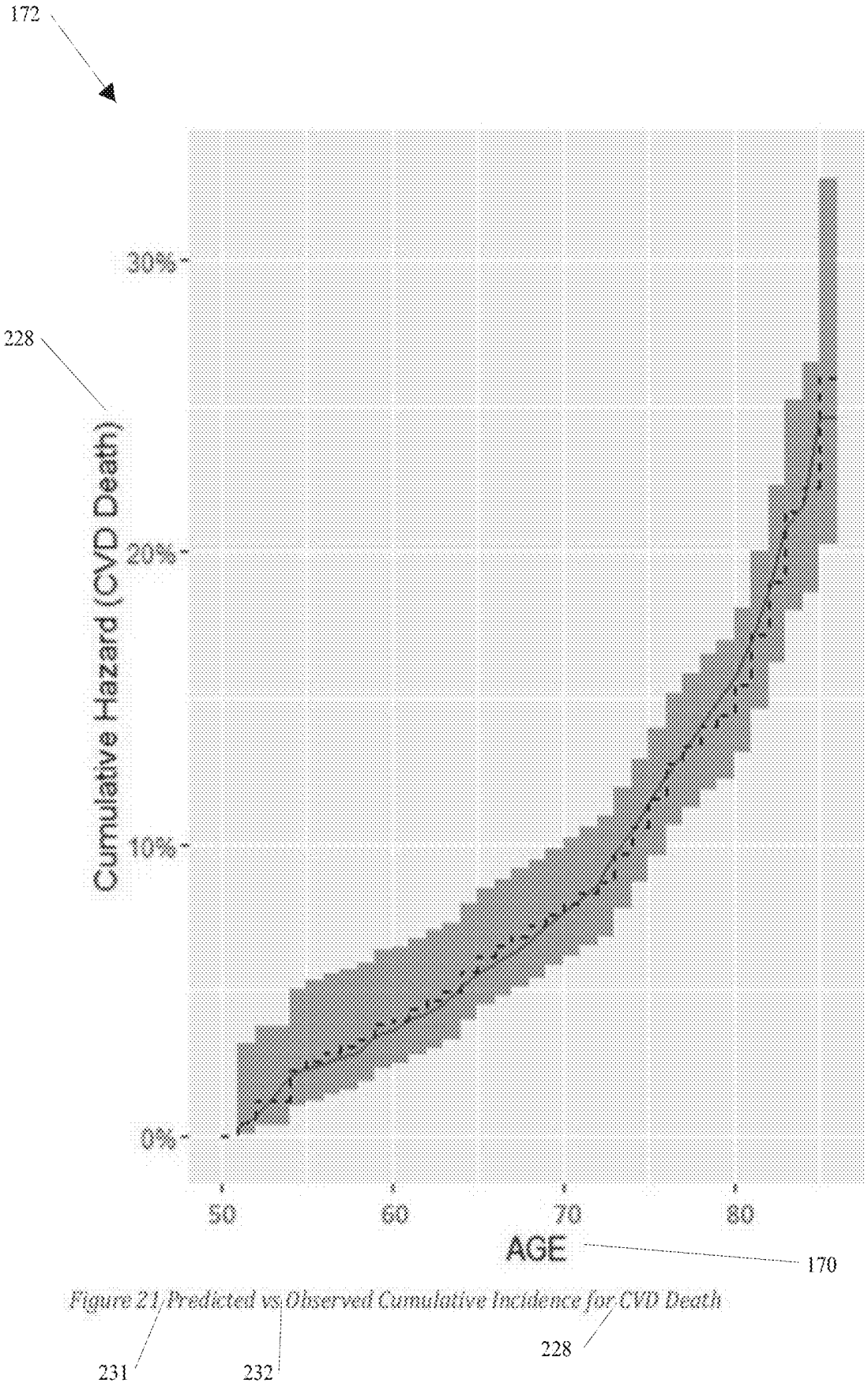


Figure 21 Predicted vs Observed Cumulative Incidence for CVD Death

FIG. 34

172

202

Table 15. Prediction Equations for Time Varying Risk Factors

	HbA1c		SBP		LDL		Weight	
	Coef	S.E.	Coef	S.E.	Coef	S.E.	Coef	S.E.
Intercept	3.330	0.045	69.935	1.047	38.185	0.711	6.126	0.294
170 Second Year	-0.336	0.012	-2.236	0.227	1.162	0.315		
126 L-HbA1c	-0.459	0.006						
128 L-SBP			0.476	0.008				
132 L-LDL					0.590	0.004		
130 L-Weight							0.982	0.001
168 Log(Duration)	0.082	0.008			-1.159	0.218		
Age							-0.064	0.004

FIG. 35

172

156

158

Table 16. Prediction Equations for Hypoglycemia

	Severe Hypoglycemia				Symptomatic Hypoglycemia			
	Coef	S.E.	exp(coef)	P	Coef	S.E.	exp(coef)	P
Intercept	-2.954	1.165	0.052		-5.845	0.254	0.003	
126 HbA1c	-1.009	0.284	0.365	0.001	0.163	0.032	1.177	0.001
HbA1c^2	0.072	0.017	1.075	0.001				
Age	0.039	0.005	1.040	0.001				
168 Duration	0.047	0.004	1.048	0.001	0.045	0.004	1.046	0.001
Female					0.285	0.067	1.330	0.001
Race								
Hispanic	-0.311	0.122	0.733	0.010				
Others	-1.033	0.134	0.356	0.001				
White	-0.663	0.071	0.515	0.001				

FIG. 36

172

234

Table 17. Prediction equation for Smoking

	Variables	Coefficient	S.E.	OR	95% CI	
					Lower	Upper
	Intercept	-1.572				
234	L1-Smoking	3.623	0.068	37.450	32.777	42.789
234	L2-Smoking	2.113	0.068	8.273	7.241	9.453
	Age	-0.032	0.004	0.969	0.961	0.976
130	BMI	-0.016	0.005	0.984	0.975	0.994
	Female	-0.083	0.056	0.920	0.825	1.027
	Race					
	Hispanic	-0.286	0.113	0.751	0.602	0.938
	Others	-0.349	0.097	0.705	0.583	0.853
	White	-0.162	0.067	0.850	0.746	0.970
	education	-0.246	0.064	0.782	0.690	0.886
144	Revasc History	0.324	0.059	1.383	1.232	1.552
144	Revasc Event	-0.806	0.176	0.447	0.316	0.631

FIG. 37

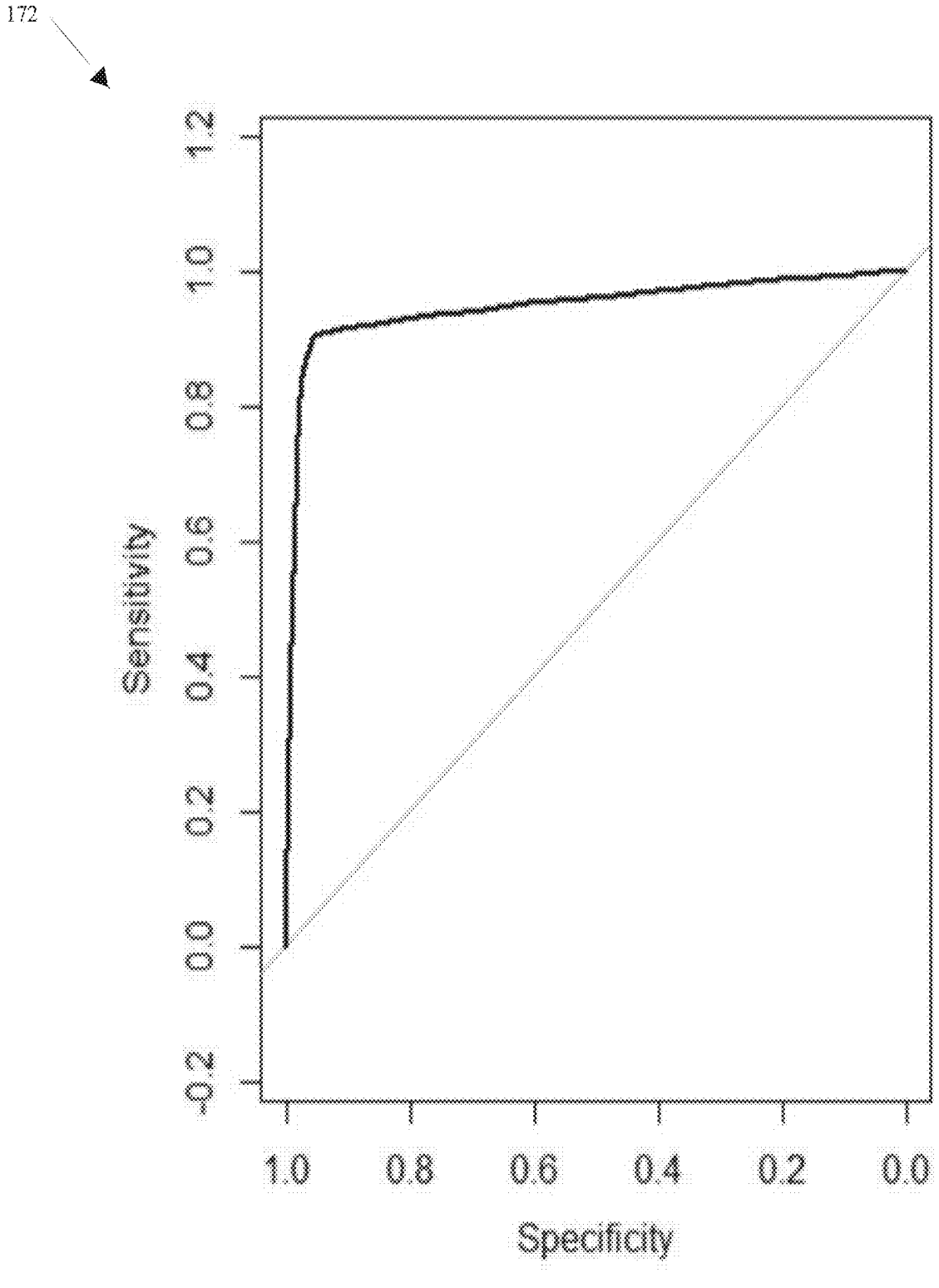


Figure 22 ROC Curve for Smoking Equation

FIG. 38

Table 18. Using UKPDS risk Engine to predict ACCORD cohort

		ACCORD (Standard Glucose)		
		Observed (232)	BRAVO (100)	UKPDS (256)
136 Stroke		1.40%	1.66%	2.30%
	Non-Fatal	1.20%	1.59%	1.80%
	Fatal	0.20%	0.08%	0.50%
138 MI		4.90%	4.66%	6.50%
	Non-Fatal	4.60%	4.14%	2.60%
	Fatal	0.30%	0.52%	3.90%
140 CHF		4.00%	3.39%	2.20%
	Non-Fatal	3.50%	3.13%	2.00%
	Fatal	0.50%	0.26%	0.20%
142 Angina		5.00%	3.00%	N/A
144 Revascularization		14.00%	14.32%	N/A
148 ESRD		3.00%	3.00%	0.50%
150 Blind		8.10%	8.27%	1.35%
152 Neuropathy		14.10%	16.48%	N/A
236 All - cause Mortality		4.00%	3.91%	10.30%
228 CVD Mortality		1.30%	2.00%	4.60%

FIG. 39

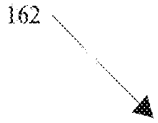


Table 19. Baseline Characteristics of Clinical Trials Used in External Validation

Variables	ASPEN (258)	ADVANCE (260)	CARDS (262)
	Mean	Mean	Mean
Age (yrs)	61.10	66.30	61.50
Proportion Female (0-1)	0.34	0.43	0.32
Duration Diabetes (yrs) (168)	8.00	8.20	7.90
Height (m)	1.70	1.70	1.70
Proportion White (0-1)	0.84	0.00	0.95
Proportion Black (0~1)	0.07	0.00	0.00
Proportion Hispanic (0~1)	0.05	0.00	0.00
Proportion Others (0~1)	0.05	1.00	0.05
Proportion Smoker (0~1)	0.12	0.15	0.20
Education(college Above)	0.26	0.50	0.30
HbA1c % (126)	7.60	8.00	7.80
LDL (132)	113.00	120.08	117.37
SBP (128)	133.00	145.40	144.00
Weight (130)	83.52	78.03	80.00
Complications			
Stroke % (136)	6.15%	9.00%	0.00%
CHF % (140)	4.82%	1.92%	0.00%
MI % (138)	17.18%	12.00%	0.00%
Angina% (142)	11.39%	5.00%	0.00%
Revascularization % (144)	22.40%	22.00%	0.00%
Nuropathy% (152)	0.00%	0.00%	0.00%
Blind % (150)	0.00%	0.00%	0.00%
ESRD % (148)	0.00%	0.00%	0.00%

FIG. 40

174 258

Table 20. Comparing prediction accuracy across different models on ASPEN cohort

		ASPEN 258				
		All-cause Mortality 236	CVD Mortality 228	MI 138	Stroke 136	Angina 142
258	ASPEN (intervention)	5.70%	3.10%	4.00%	3.00%	2.80%
100	BRAVO Risk engine	4.07%	1.92%	4.10%	1.37%	2.50%
	Our Rank	1st	3rd	1st	4th	1st
	IMS Core	8.90%	3.40%	4.50%	2.00%	
256	UKPDS OM	11.10%	4.10%	5.20%	2.50%	2.30%
	CDC-RTI	11.40%	5.00%	8.10%		
	ECHO-T2DM	9.20%	4.30%	6.70%		
	Michigan				3.00%	2.10%
258	ASPEN (Control)	5.70%	3.10%	5.50%	3.10%	3.20%
100	BRAVO Risk engine	4.11%	1.91%	4.90%	1.70%	2.84%
	Our Rank	1st	3rd	2nd	4th	1st
	IMS Core	9.40%	3.90%	5.80%	2.50%	
256	UKPDS OM	11.50%	4.10%	6.10%	2.80%	1.90%
	CDC-RTI	11.90%	5.50%	9.40%		
	ECHO-T2DM	10.10%	5.00%	8.50%		
	Michigan				3.40%	2.70%

FIG. 41

174 262

Table 21. Comparing prediction accuracy across different models on CARDS cohort

		262 CARDS	138	136	228
		MI	Stroke	All CVD	
262 CARDS (Intervention)		3.60%	1.50%	9.40%	
100 Ours		3.40%	1.50%	7.90%	
	Our Rank	1st	1st	1st	
CDC/RTI		4.30%	1.50%	6.90%	
Cardiff		4.50%	2.20%	6.70%	
256 UKPDS Risk Engine		5.20%	2.50%	7.40%	
Archimedes		3.40%	2.70%		
CORE		4.50%	1.70%		
262 CARDS (Control)		5.50%	2.80%	13.40%	
100 Ours		5.40%	2.10%	10.60%	
	Our Rank	1st	4th	1st	
CDC/RTI		6.40%	1.70%	10.20%	
Cardiff		6.70%	2.50%	9.20%	
256 UKPDS Risk Engine		8.00%	2.90%	10.40%	
Archimedes		5.40%	3.20%		
CORE		6.40%	2.00%		

FIG. 42

174

260

Table 22. Comparing prediction accuracy across different models on ADVANCE cohort

		ADVANCE 260						
		236 All-cause Mortality	228 CVD Mortality	138 Nonfatal MI	136 Nonfatal Stroke	134 Major Cardiov-ascular Events	146 Major Microv-ascular Events	140 CHF
260	Intervention	22.10%	4.50%	2.70%	3.80%	10.00%	9.40%	3.90%
100	BRAVO	6.90%	3.00%	4.50%	2.90%	11.00%	11.07%	3.30%
	Rank	3rd	2nd	1st	3rd	2nd	2nd	1st
	IMS Core	14.90%	4.20%	4.60%	2.60%	11.30%	4.40%	3.30%
256	UKPDS OM	6.40%				10.50%		2.90%
	CDC-RTI		11.00%			17.80%	8.20%	
	ECHO-T2DM	19.40%	6.60%	7.20%	3.00%	16.10%		2.70%
	Michigan		5.60%	7.40%	4.70%	16.40%	46.00%	
260	Control	22.40%	5.20%	2.80%	3.80%	10.60%	10.90%	4.10%
100	BRAVO	6.90%	3.30%	5.10%	3.55%	12.00%	12.90%	3.60%
	Rank	3rd	3rd	2nd	1st	2nd	2nd	1st
	IMS Core	15.90%	4.60%	4.90%	2.70%	12.20%	5.40%	3.40%
256	UKPDS OM	6.50%				11.40%		3.20%
	CDC-RTI		11.40%			19.20%	10.30%	
	ECHO-T2DM	21.50%	7.50%	7.90%	3.50%	18.00%		3.00%
	Michigan		5.70%	7.70%	4.70%	16.70%	46.00%	

FIG. 43

174 254

Table 23. Comparing prediction accuracy across different models on ACCORD cohort

		254 ACCORD			
	236	All-cause Mortality	228 CVD Mortality	138 Nonfatal MI	136 Nonfatal Stroke
254	ACCORD (Intervention)	5.00%	1.70%	3.60%	1.30%
100	BRAVO Risk engine	4.10%	1.70%	3.70%	1.30%
	Rank	2nd	1st	1st	1st
	IMS Core	10.10%	1.50%	1.90%	0.90%
256	UKPDS OM	6.70%	4.60%		
	CDC-RTI	11.20%	5.90%		
	ECHO-T2DM	9.40%	3.60%	3.50%	1.30%
	Cardiff	4.80%	1.10%	1.60%	0.80%
254	ACCORD (Control)	4.00%	1.30%	4.60%	1.20%
100	BRAVO Risk engine	3.90%	2.00%	4.14%	1.36%
	Rank	1st	1st	1st	1st
	IMS Core	10.20%	1.90%	2.20%	1.00%
256	UKPDS OM	7.40%	4.70%		
	CDC-RTI	11.30%	6.10%		
	ECHO-T2DM	10.00%	4.10%	3.80%	1.50%
	Cardiff	4.80%	1.30%	1.70%	0.90%

FIG. 44

DIABETES RISK ENGINE AND METHODS THEREOF FOR PREDICTING DIABETES PROGRESSION AND MORTALITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 62/676,273, filed May 24, 2018, the disclosure of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] The present invention generally relates to risk engines for disease management and more particularly relates to diabetes risk engine systems and methods for predicting diabetes progression, mortality, and generating recommendations and actions for healthcare advice for general improvement of patients.

Description of the Related Art

[0003] The growing population of type 2 diabetes mellitus (T2DM) in the United States and abroad has led to dramatically increased costs in managing diabetes, including treating diabetes and its complications. A majority of the diabetes-related costs are the result of micro/macrovascular complication events. The most common diabetes-related macrovascular events include myocardial infarction (MI), congestive heart failure (CHF), and stroke. The most frequent diabetes-related microvascular events include AQ3 retinopathy (e.g., edema, blindness), nephropathy [e.g., end-stage renal disease (ESRD)], and neuropathy [e.g., severe pressure sensation loss (SPSL), amputation].

[0004] To better manage the growing T2DM population in an environment of constrained healthcare resources, there is a need for system-wide improvement and redesign, which in the current 'big data' era, is made possible through embodiments disclosed herein, using outcome-driven and evidence-based diabetes management. As disclosed herein, prediction models can help develop sophisticated and well-designed diabetes management strategies and models. Prediction models, disclosed herein, can better profile the risk of patients so that more healthcare resources can be effectively allocated to those with more health needs.

[0005] Several conventional diabetes models in the United States have been used to describe disease progression and compare the cost effectiveness of different therapeutic strategies, such as, the CORE diabetes model, the University of Michigan model for diabetes, the Swedish Institute of Health Economics model, otherwise known as the Economics and Health Outcomes in T2DM Model, the United Kingdom Prospective Diabetes Study (UKPDS) outcomes model, the Centers for Disease Control-Research Triangle Institute diabetes cost-effectiveness model, the Cardiff Research Consortium model, and several others. These conventional models have been used to support the outcome-driven evidence-based diabetes management in several areas, such as, comparisons between therapeutic plans, evaluating potential benefits of achieving treatment goals, and policy impact on T2DM. However, these diabetes models rely heavily on the UKPDS risk engine and Framingham equation that was developed using data from a UK diabetes cohort collected from the 1970s of European populations. The UKPDS population differs significantly from the current U.S. population in terms of race/ethnicity, definition of diabetes, treatment algorithm, and screening methods to assess complications and comorbidities. Further, the baseline hazard of diabetes-related events may vary over time and may differ between the UKPDS population and the current U.S. population. Using a UK-based risk engine to predict U.S. diabetes management raises significant concerns on the prediction validity.

[0006] While these models may be moderately suitable for the particular purpose employed, they would not be as suitable for the purposes of the present invention as disclosed hereafter.

[0007] Accordingly, there is an urgent need for new and improved risk engines that are developed based on a U.S. population, to better support decision making in clinical practice in the United States.

[0008] There is a need for new and improved diabetes modeling that incorporates new data and that can be tailored to changing national priorities in the prevention and treatment of diabetes.

[0009] Assessing the risks and progression of diseases can be useful in disease prevention and mitigation.

[0010] In light of the discussion above, there is a need for new computer implemented methods and systems for predicting diabetes progression and mortality, which alleviates one or more of the above mentioned deficiencies.

[0011] Therefore, one object of the invention is to provide for a Building, Relating, Assessing, and Validating Outcomes (BRAVO) Diabetes Risk Engine based on the U.S. diabetes population, which provides an alternative risk engine for U.S. researchers and policy makers.

[0012] It is yet another object of the invention to provide a critical predictive modeling tool to evaluate new T2DM drugs.

[0013] It is yet a further object of the invention to provide a diabetes model to include race segmentation relevant to the target population for clinical intervention.

[0014] Another object of the invention is to provide a novel approach to using clinical trials with a limited length of follow-up time.

[0015] Through embodiments disclosed herein, the BRAVO risk engine provides more accurate predictions over a range of long-term outcomes as opposed to other current models. Thus, the BRAVO risk engine provides substantially improved assistance in making clinical and policy decisions.

[0016] As the most commonly used regression class to model the risk of clinical events, the parametric proportional hazard function was applied in the BRAVO risk engine. The main reason for researchers not being able to update the UKPDS risk engine is the data limitation issue. To fit prediction models for a lifetime disease progression, a clinical trial with more than 30 years follow-up time was required. There are no other clinical trial with such a length of follow up as UKPDS trial. However, even if there was one, by the time the 30 years follow-up data would be collected, the data itself would become outdated.

[0017] The BRAVO risk engine uses diabetes duration as a time index to simulate diabetes progression and mortality over a period of 40 years, in accordance with embodiments of the invention. Such embodiments of indexing time by

diabetes duration enables one to estimate the time dependency of diabetes on events and mortality.

[0018] As disclosed in this application, the inventor has discovered novel and unique systems and methods for efficient and comprehensive prediction of diabetes progression and mortality, which exhibit superlative properties.

[0019] Embodiments of the present invention provide for systems and methods, as disclosed herein, defined in the annexed claims which provide for an improved risk engine that can predict a range of long-term diabetes complications and mortality, thus assisting in making clinical and policy decisions for people's health and well-being.

SUMMARY OF THE INVENTION

[0020] The following presents a simplified summary of the present disclosure in a simplified form as a prelude to the more detailed description that is presented herein.

[0021] Therefore, in accordance with embodiments of the invention, there is provided a diabetes risk engine system having at least one processor, at least one memory unit containing computer program code, a diabetes-related events module configured to predict an occurrence of one or more diabetes-related events through an iterative process, a risk factors module to predict a progression of one or more risk factors through the iterative process, a mortality module to predict an occurrence of mortality of a patient through the iterative process, and a display interface configured to display the predicted risk of the one or more diabetes-related events.

[0022] In one embodiment, the risk factor is selected from the group consisting of glycosylated hemoglobin (HbA1c), systolic blood pressure (SBP), weight, and low-density lipoprotein cholesterol (LDL-C).

[0023] In another embodiment, the diabetes-related event is a macrovascular event. Exemplary macrovascular events include stroke, myocardial infarction, congestive heart failure, angina, and revascularization surgery.

[0024] In yet another embodiment, the diabetes-related event is a microvascular event. Exemplary microvascular events include end stage renal failure, blindness, and severe pressure sensation loss.

[0025] In one embodiment, the diabetes-related event is an adverse event. Exemplary adverse events include severe hypoglycemia and symptomatic hypoglycemia.

[0026] The ACCORD dataset used for the BRAVO risk engine features: a record of diabetes duration for each patient and patients' diabetes duration varied from 0 years to 40 years in the dataset. Regardless of the maximum 7 years follow up length for this clinical trial, the invention has detailed records for the incidence of events, as well as the risk factors and history of events at each time point after diabetes onset. This feature enables the BRAVO risk engine to more accurately estimate the hazard rates at each time point after diabetes onset, and a left-truncated survival regression applied to estimate the prediction equations of each diabetes related event.

[0027] Therefore, in accordance with embodiments of the invention, there is provided a method of predicting diabetes progression and mortality. The method includes a first step of receiving a target population dataset having a series of baseline biological characteristics of the target population. The method has a second step of assigning parameter values based upon a user defined distribution of population characteristics. A third step analyzes, using a computer processor, the population dataset for generating a diabetes risk engine wherein diabetes duration is used as a time index. The diabetes risk engine operates one or more inter-correlated risk equations which can be used as a predictor to determine the risk of a diabetes-related event or mortality of the patient. A fourth step of the method adjusts the risk engine based upon new data collected based upon a new set of annual values collected during the generating of the population dataset. A fifth step of the method receives a first patient medical information, which includes clinical, biomedical, and demographic factor information. A sixth step of the method predicts a risk of an occurrence of one or more diabetes-related events with the diabetes risk engine based upon said parameter values by comparing the first patient medical information to the population dataset. A seventh step of the method provides at least one clinical or behavioral modification recommendation based upon the predicted risk of the occurrence of one or more diabetes-related events or mortality. An eighth step of the method tracks a progression and survival status of a user taking action toward achieving goals associated with improving health based upon at least one clinical or behavioral modification recommendation.

[0028] In one embodiment, the method further includes a step of predicting a progression of risk factors of the first patient.

[0029] In another embodiment, the inter-correlated risk equations account for risk escalation as diabetes progresses and during interactions between complications.

[0030] In yet another embodiment, the first patient medical information includes risk factors such as medication adherence, lifestyle modification, and therapy escalation.

[0031] In one embodiment, the diabetes-related event is a macrovascular event. Exemplary macrovascular events include stroke, a myocardial infarction, congestive heart failure, angina, and revascularization surgery.

[0032] In another embodiment, the diabetes-related event is a microvascular event. Exemplary macrovascular events include end stage renal failure, blindness, and severe pressure sensation loss.

[0033] In yet another embodiment, the diabetes-related event is an adverse event. Exemplary adverse events include hypoglycemia and symptomatic hypoglycemia.

[0034] In accordance with embodiments of the invention, there is provided a method of predicting an occurrence of one or more diabetes-related events having the first step of receiving a target population dataset comprising a series of baseline characteristics of the target population. A second step of the method assigns parameter values based upon a user defined distribution of population characteristics. A third step of the method includes analyzing, using a computer processor, the population dataset for generating a diabetes risk engine wherein diabetes duration is used as a time index. In the third step, the diabetes risk engine operates one or more inter-correlated risk equations configured to determine the risk of a diabetes-related event or mortality of the patient. A fourth step of the method adjusts the risk engine based upon new data collected based upon a new set of annual values collected during the generating of the population dataset. A fifth step of the method receives a first patient medical information such as clinical, biomedical, and demographic factor information from a first patient user. A sixth step of the method predicts a risk of an occurrence of one or more diabetes-related events with the

diabetes risk engine based upon the parameter values by comparing the first patient medical information to the population dataset of the diabetes risk engine. A seventh step of the method provides at least one clinical or behavioral modification recommendation based on the risk of the occurrence of one or more diabetes-related events. An eighth step tracks the survival status of a user taking action toward achieving goals associated with improving health based upon the at least one clinical or behavioral modification recommendation.

[0035] These and other features, aspects, and advantages of the present invention will become better understood with reference to the following description and appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] Illustrative embodiments of the present invention are described herein with reference to the accompanying drawings, in which like numerals throughout the figures identify substantially similar components, in which:

[0037] FIG. **1** is a schematic of an exemplary embodiment of a diabetes risk engine system and environment, in accordance with embodiments of the invention;

[0038] FIG. **2** is the functional form of risk equations and model selection processes, in accordance with embodiments of the invention;

[0039] FIG. **3** is a flowchart for microsimulation, including a flow control engine and a risk engine, in accordance with embodiments of the invention;

[0040] FIG. **4** is a table displaying baseline characteristics of the ACCORD cohort, in accordance with embodiments of the invention;

[0041] FIG. **5** is a table displaying variables included in the risk engine, in accordance with embodiments of the invention;

[0042] FIG. **6** is a table displaying prediction equations for time varying risk factors, in accordance with embodiments of the invention;

[0043] FIG. **7** is a table displaying differences between RECODE risk equations and BRAVO risk equations, in accordance with embodiments of the invention;

[0044] FIG. **8** is a table displaying parameter estimates of risk equations in the BRAVO risk engine, in accordance with embodiments of the invention;

[0045] FIG. **9** is an exemplary flowchart illustrating an exemplary method of implementing the BRAVO risk engine, in accordance with embodiments of the invention;

[0046] FIG. **10** is an exemplary flowchart illustrating an exemplary method of implementing the BRAVO risk engine, in accordance with embodiments of the invention;

[0047] FIG. **11** is a graphic display of exemplary external validation results plotting predicted incident rates against observed incidence rates of CHF (congestive heart failure), CVD (cardiovascular disease), and MI (myocardial infarction), in accordance with embodiments of the invention;

[0048] FIG. **12** is a table displaying definitions of variables included in the risk engine, in accordance with embodiments of the invention;

[0049] FIG. **13** is a table displaying exemplary demographic characteristics of the ACCORD cohort, in accordance with embodiments of the invention;

[0050] FIG. **14** is a table displaying an exemplary prediction equation for stroke events, in accordance with embodiments of the invention;

[0051] FIG. **15** is a graphic display of the predicted versus observed cumulative incidence for stroke events according to diabetes duration, in accordance with embodiments of the invention;

[0052] FIG. **16** is a table displaying an exemplary prediction equation for CHF, in accordance with embodiments of the invention;

[0053] FIG. **17** is a graphic display of the predicted versus observed cumulative incidence for CHF according to diabetes duration, in accordance with embodiments of the invention;

[0054] FIG. **18** is a table displaying an exemplary prediction equation for MI, in accordance with embodiments of the invention;

[0055] FIG. **19** is a graphic display of the predicted versus observed cumulative incidence for non-fatal MI according to diabetes duration, in accordance with embodiments of the invention;

[0056] FIG. **20** is a table displaying an exemplary prediction equation for angina, in accordance with embodiments of the invention;

[0057] FIG. **21** is a graphic display of the predicted versus observed cumulative incidence for angina according to diabetes duration, in accordance with embodiments of the invention;

[0058] FIG. **22** is a table displaying an exemplary prediction equation for revascularization surgery, in accordance with embodiments of the invention;

[0059] FIG. **23** is a graphic display of the predicted versus observed cumulative incidence for revascularization surgery according to diabetes duration, in accordance with embodiments of the invention;

[0060] FIG. **24** is a table displaying an exemplary prediction equation for ESRD, in accordance with embodiments of the invention;

[0061] FIG. **25** is a graphic display of the predicted versus observed cumulative incidence for ESRD according to diabetes duration, in accordance with embodiments of the invention;

[0062] FIG. **26** is a table displaying an exemplary prediction equation for blindness, in accordance with embodiments of the invention;

[0063] FIG. **27** is a graphic display of the predicted versus observed cumulative incidence for blindness according to diabetes duration, in accordance with embodiments of the invention;

[0064] FIG. **28** is a table displaying an exemplary prediction equation for SPSL, in accordance with embodiments of the invention;

[0065] FIG. **29** is a graphic display of the predicted versus observed cumulative incidence for SPSL according to diabetes duration, in accordance with embodiments of the invention;

[0066] FIG. **30** is a table displaying an exemplary prediction equation for all-cause mortality, in accordance with embodiments of the invention;

[0067] FIG. **31** is a graphic display of the predicted versus observed cumulative incidence for all-cause mortality according to age, in accordance with embodiments of the invention;

[0068] FIG. **32** is table displaying an exemplary prediction equation for CVD death (logistic regression), in accordance with embodiments of the invention;

[0069] FIG. **33** is a graphic display of the ROC curve for CVD prediction, in accordance with embodiments of the invention;

[0070] FIG. **34** is a graphic display of the predicted versus observed cumulative incidence for CVD death according to age, in accordance with embodiments of the invention;

[0071] FIG. **35** is a table displaying exemplary prediction equations for time varying risk factors, in accordance with embodiments of the invention;

[0072] FIG. **36** is a table displaying exemplary prediction equations for hypoglycemia, in accordance with embodiments of the invention;

[0073] FIG. **37** is a table displaying an exemplary prediction equation for smoking, in accordance with embodiments of the invention;

[0074] FIG. **38** is a graphic display of the ROC curve for smoking equation, in accordance with embodiments of the invention;

[0075] FIG. **39** is a table displaying the exemplary use of the UKPDS risk engine to predict the ACCORD cohort, in accordance with embodiments of the invention;

[0076] FIG. **40** is a table displaying exemplary baseline characteristics of the clinical trials used in external validation, in accordance with embodiments of the invention;

[0077] FIG. **41** is a table displaying the exemplary comparison of prediction accuracy across different models on the ASPEN cohort, in accordance with embodiments of the invention;

[0078] FIG. **42** is a table displaying the exemplary comparison of prediction accuracy across different models on the CARDS cohort, in accordance with embodiments of the invention;

[0079] FIG. **43** is a table displaying the exemplary comparison of prediction accuracy across different models on the ADVANCE cohort, in accordance with embodiments of the invention; and

[0080] FIG. **44** is a table displaying the exemplary comparison of prediction accuracy across different models on the ACCORD cohort, in accordance with embodiments of the invention.

DETAILED DESCRIPTION

[0081] For a further understanding of the nature and function of the embodiments, reference should be made to the following detailed description. Detailed descriptions of the embodiments are provided herein, as well as the best mode of carrying out and employing the present invention. It will be readily appreciated that the embodiments of the invention are well adapted to carry out and obtain the ends and features mentioned, as well as those inherent herein. It is to be understood, however, that the present invention may be embodied in various forms. Therefore, persons of ordinary skill in the art will realize that the following disclosure is illustrative only and not in any way limiting, as the specific details disclosed herein provide a basis for the claims and a representative basis for teaching to employ the present invention in virtually any appropriately detailed system, structure or manner. It should be understood that the devices, materials, methods, procedures, and techniques described herein are presently representative of various embodiments. Other embodiments of the disclosure will readily suggest themselves to such skilled persons having the benefit of this disclosure.

[0082] Therefore, in accordance with embodiments of the invention, there is provided a diabetes risk engine system **100** and an exemplary environment **218**, which may include multiple devices. Referring initially to FIGS. **1** and **3**, the Building, Relating, Assessing, and Validating Outcomes (BRAVO) risk engine **100** and the exemplary environment **218** have at least one processor **102**, at least one memory unit **104** containing computer program code **106**, at least one client user device **220**, at least one application server or other device **222** for running the various engines described herein, and at least one additional server or database **224**. The processor **102** is configured to execute software instructions **106** stored on a tangible, non-transitory computer readable storage medium **104** (e.g., hard drive, solid state drive, RAM, flash, ROM, etc.). The software instructions **106** preferably configure the computing device **220** to provide the roles, responsibilities, or other functionality as discussed herein with respect to the disclosed apparatus and methods. In such preferred embodiment, the various servers **222**, systems, databases **224**, or interfaces **220** exchange data using standardized protocols or algorithms **106**, possibly based on HTTP, HTTPS, AES, public-private key exchanges, web service APIs, known financial transaction protocols, or other electronic information exchanging methods. Data exchanges preferably are conducted over a network **226** (e.g., packet-switched network, the Internet, LAN, WAN, VPN, or other type of packet switched network). Processors **102** can be embodied by any computational or data processing device **220**, such as a central processing unit (CPU), application specific integrated circuit (ASIC), or comparable device. The processors **102** can be implemented as a single controller, or as a plurality of controllers or processors. For example, the processors **102** can be implemented using a single core chip or one or more multi-core chips, among other possible configurations.

[0083] The exemplary memories **104** can independently be any suitable storage device, such as a non-transitory computer-readable medium. A hard disk drive (HDD), random access memory (RAM), flash memory, or other suitable memory can be used. The memories **104** can be combined on a single integrated circuit as the processor **102**, or may be separate from the one or more processors **102**. Furthermore, the computer program instructions **106** stored in the memory **104**, and which may be processed by the processors **102**, can be any suitable form of computer program code **106**; for example, a compiled or interpreted computer program written in any suitable programming language. The memory **104** and the computer program instructions **106** can be configured with the processor **102** for the particular device to cause a hardware apparatus, such as the user device **220**, the application server **222**, and additional servers or databases **224** to perform any of the processes described below. Therefore in certain embodiments, a non-transitory computer-readable medium **104** can be encoded with computer instructions **106** that when executed in hardware performs a process such as one of the processes described herein. Alternatively, certain embodiments of the invention can be performed entirely in hardware. The BRAVO risk engine **100** has been developed to predict **174** a series of diabetes complications **186** and mortality **178**. The BRAVO risk engine **100** has found a glycosylated hemoglobin level **126** slightly above 7.0% to be associated with the lowest risk for all-cause mortality **236**. With good internal and external validation, the BRAVO risk engine **100** can be applied as a

diabetes prediction model **100** and assists in decision making for clinical practice **186** and health policy **188**.

[0084] Referring to FIGS. **4**, **11**, and **40**, when evaluating the prediction **174** accuracy of the BRAVO risk engine **100**, especially to explore if it is capable of providing more accurate predictions **174** compared to the existing models, a prediction model was applied on ASPEN trials **258**, ADVANCE trials **260** and CARDS trials **262**. Because those three trials had been used as challenges in the Fourth and Fifth Mount Hood challenge meeting, in implementing the BRAVO risk engine **100**, the prediction **174** results of each current model on those three trials were extracted and compared to simulation results of the BRAVO risk engine **100**. The prediction accuracy of each model is outlined in FIG. **43**.

[0085] The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) **258** was a 4-year, double-blind, parallel group trial of 10 mg of atorvastatin versus placebo inpatients with type 2 diabetes. The target LDL **132** level of the treatment group and control group was 83 mg/dl and 113 mg/dl, respectively. The provided outcomes included 4 years all-cause mortality **236** rate, CVD **228** mortality rate, nonfatal/fatal MI **138** incidence rate, nonfatal/fatal stroke **136** incidence rate, and angina **142** incidence rate.

[0086] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) **260** is a 5-year, double-blind trial, with a total of 11,140 T2DM patients **122** randomly assigned to either standard glucose control or intensive glucose control. The HbA1c **126** target for treatment group and control group was 6.5% and 7.5% respectively. The provided outcomes included 5-year all-cause mortality **236** rate, CVD **228** mortality rate, nonfatal MI **138** incidence rate, nonfatal stroke **136** incidence rate, major macrovascular events **134** incidence rate, major microvascular events **146** incidence rate, and CHF **140** incidence rate.

[0087] The Collaborative Atorvastatin Diabetes Study (CARDS) **262** is a 4 years, multicenter randomized placebo-controlled trial. The target LDL **132** level of treatment group and control group was 80 mg/dl and 120 mg/dl, respectively. The provided outcomes included 4-year fatal/nonfatal MI **138** incidence rate, fatal/nonfatal stroke **136** incidence rate, and all CVD **228** incidence rate. The prediction accuracy of CARDS **262** has been compared to the BRAVO risk engine's **100** prediction accuracy, as illustrated in FIG. **42**.

[0088] The baseline characteristics **162** and treatment target **200** of each trial was input into the BRAVO risk engine **100**, and end points for each trial was simulated and recorded. The predicted incidence rate **192** for each end point are compared to the observed incidence rate **232** in each trial. This embodiment also calculates the absolute difference between the predicted **192** and observed incidence rate **232**, and compared if the absolute difference of the BRAVO risk engine **100** prediction **174** was smaller than the absolute difference provided by other models.

[0089] In such preferred embodiments, illustrated in FIGS. **1-3**, the BRAVO risk engine **100** contains three separate modules (a diabetes-related events events module **108**, a risk factors module **114**, and a mortality module **118**), each of which preferably contains a series of regression equations **172** to predict the occurrence of events **110**, progression in risk factors **116**, and mortality **178**, as illustrated in FIG. **2**. Risk factors progress **116** very differently under different circumstances, and largely depend on factors such as medication adherence **212**, lifestyle modification **214**, and therapy escalation **216**. A few potential comorbidities such as ulceration and amputation were not explicitly included in the BRAVO risk engine **100**. However, these comorbidities were not included as endpoints in the ACCORD trial **254**, and thus cannot be incorporated into the BRAVO risk engine **100**. Having said that, alternative embodiments may include these comorbidities. The diabetes-related events module **108** is configured to predict **174** an occurrence of one or more diabetes-related events **110** through an iterative process **112**. The risk factors module **114** is configured to predict **174** a progression of one or more risk factors **116**, which are based on one or more parameter values **164** and a set of predefined risk factors **202**, through the iterative process **112**. The mortality module **118** is configured to predict **174** an occurrence of mortality **120** of a patient **122** through the iterative process **112**, and a display interface **124** is configured to display the predicted risk of the one or more diabetes-related events **176**. In certain systems **100**, only the user device **220** and application server **222** may be present, and in other systems **100** the user device **220**, application server **222**, and a plurality of other servers **224** may be present. Other configurations are also possible. The additional server or database **224** may be, for example, a database **224** securely storing one or more population datasets **160** comprising a series of baseline characteristics **162**, medical records, facts, and recommendations **196**. The at least one user device **220** can be, for example, a smartphone, tablet, portable computer, laptop computer, or other computing device. The user device **220** is preferably provided with a graphical user interface **124** and inputs, such as a touch-sensitive screen, display, keyboard, mouse, or the like. Other features are also permitted on the user device **220**. The user device **220** can be a terminal device. Preferably, the user interface **124** is constructed based on Visual Basic Application (VBA) in Excel **2013** and the risk engine **100** is coded with C++ via Microsoft Visual Studio 15.0 Enterprise Edition.

[0090] Referring to FIGS. **4**, **13**, **39** and **44**, ACCORD **254** is one of the largest studies ever conducted in adults with type 2 diabetes who were at especially high risk of cardiovascular events **134**, such as heart attacks **138**, stroke **136**, or death from cardiovascular disease **228**. The multicenter clinical trial tested three potential strategies to lower the risk **192** of major cardiovascular events **134**: intensive control of blood sugar, intensive control of blood pressure, and treatment of multiple blood lipids. The lipids targeted for intensive treatment were high density lipoprotein (HDL) cholesterol and triglycerides, in addition to standard therapy of lowering low density lipoprotein (LDL) cholesterol **132**.

[0091] ACCORD **254** researchers from 77 medical centers in the United States and Canada studied **10,251** participants between the ages of 40 and 79 who had type 2 diabetes for an average of 10 years. When they joined the study, all participants were at especially high risk of cardiovascular events **134** because they had pre-existing cardiovascular disease **228**, evidence of subclinical cardiovascular disease **228**, or at least two cardiovascular disease **228** risk factors **202** in addition to diabetes.

[0092] All participants were enrolled in the ACCORD blood sugar treatment clinical trial **254** and maintained good control of blood sugar levels during the study. In addition,

participants were enrolled in either the blood pressure trial or the lipid trial and were treated and followed for an average of about five years.

[0093] All the diabetes related events **110** were recorded during the study. Patients **122** in the intensive-therapy group attended monthly visits for the first 4 months and then every 2 months thereafter, with at least one interim phone call, with the aim of rapidly and safely reducing glycated hemoglobin **126** levels to below 6.0%. Additional visits were scheduled as needed to achieve glycemic **156**, **158** goals, as described previously. Patients **122** in the standard-therapy group had glycemic-management **196** visits every 4 months.

[0094] The ACCORD trial **254** began in January 2001. The glycemia trial was terminated due to higher mortality **178** in the intensive compared with the standard glycemia treatment strategies. Study-delivered treatment for all ACCORD **254** participants was stopped on Jun. 30, 2009. All participants are continuing to be followed in a non-treatment observational study.

[0095] Detailed baseline characteristics **162** of the ACCORD cohort **254** are provided in FIG. **13**.

[0096] The Definition of all risk factors **202** initially included at the beginning of the variable selection process is provided in FIG. **12**. Acknowledging the potential fluctuation at each measurement of biomedical factors **188** (i.e., HbA1c **126**, SBP **128**, LDL **132** and BMI **130**), a moving-average technique is applied by calculating the average value of the previous 2 years to extrapolate the value for the current year. This approach improves the stability of the measurement on time-varying **170** factors **202** and has been previously applied to the UKPDS risk engine **256**. An embodiment of the invention uses the value from last period to predict **174** the probability of current events **176**, to account for potential bias caused by lag of measurement, as well as the reverse causal effect.

[0097] In the Events Module **108**, eight exemplary risk equations **172** were fitted to predict Stroke **136**, nonfatal MI **138**, CHF **140**, Angina **142**, Revascularization Surgery **144**, ESRD **148**, Blindness **150**, and neuropathy (measured by severe pressure sensation loss (SPSL) **152**). The UKPDS risk engine **256** was used as the benchmark, combining current knowledge on other potential risk factors **202** as well as other potential functional forms **172** to improve the model fitting process. The clinical **186** definition for each event **110** were reported in the ACCORD trial **254** protocol.

[0098] A Weibull survival regression **240** was fitted to predict **174** the hazard of stroke **136**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **14-15**. HbA1c **126**, SBP **128**, LDL **132**, Age at diagnoses, MI **138** history and Stroke **136** history were included in the risk equation **172**.

[0099] A Weibull survival regression **240** was fitted to predict **174** the hazard of CHF **140**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **22-23**. HbA1c **126**, SBP **128**, BMI **130**, age at diagnose, severe hypoglycemia **156**, education, MI **138** history, CHF **140** history and history of revascularization surgery **144** were included in the risk equation **172**.

[0100] A Weibull survival regression **240** was fitted to predict **174** the hazard of angina **142**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **20-21**. HbA1c **126**, SBP **128**, female, race, stroke **136** history, angina **142** history and history of revascularization surgery **144** were included in the risk equation **172**, as well as both first order BMI **130** and second order BMI **130**.

[0101] A Weibull survival regression **240** was fitted to predict **174** the hazard of blindness **150**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **26-27**.

[0102] A Weibull survival regression **240** was fitted to predict **174** the hazard of neuropathy or SPSL **152**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **28-29**. HbA1c **126**, SBP **128**, LDL **132**, age at diagnose, female, race, and retinopathy **150** history were included in the risk equation **172**.

[0103] The risk factors module **114** of this embodiment tracked the progression **116** of HbA1c **126**, SBP **128**, LDL **132** and body weights **130** by fitting prediction equations **172** for each risk factor **202**. In addition, as smoking **234** was identified as a risk factor **202** for several cardiovascular events **134**, **146**, a prediction equation **172** was fitted using previous and current smoking **234** status to predict the future smoking **234** status. At last, as one of the most important features of the BRAVO risk engine **100**, a series of prediction models for predicting **174** both severe hypoglycemia **156** and symptomatic hypoglycemia **158** were fitted.

[0104] Parameter **164** estimates for OLS regressions **248** to predict **174** risk factors **202** are provided in FIG. **35**. In general, the method is used to predict **174** the value of current year based on value from previous year. L-HbA1c **126** denotes the HbA1c **126** level at last year. For HbA1c **126**, as evidence suggests an increasing trend over time **170**, the method added the duration of diabetes **168** as a risk factor **202** to introduce the upward tendency over time **170**. On the other hand, the body weights **130** for T2DMs tend to increase over time **170**, but start to decline after around their 80s. The method included age as a covariates with negative coefficient to represent this declining trend.

[0105] The BRAVO risk engine **100** uses two poisson regression models **246** to predict **174** the frequency of having severe hypoglycemia **156** and symptomatic hypoglycemia **158** in each cycle. The parameter **164** estimates are provided in FIG. **36**.

[0106] Since smoking **234** was identified as an important risk factor **202** to predict **174** all-cause mortality **236** and CVD **228** death, a logistic regression **244** was fitted to predict the likelihood of being a current smoker. Details regarding parameter **164** estimates are provided in FIGS. **37-38**.

[0107] The mortality engine **118** of this embodiment used a proportional hazard model applied to predict **174** the all-cause mortality **236** rates during the lifetime of diabetes patients **122**, to serve as the ceiling of the mortality risk **236**. After that, a logistic regression **244** predicting **174** the probability of death **120** due to CVD **228** events was fitted among all patients **122** who encountered all-cause mortality **236**. Weibull **240** distribution and Gompterz **242** distribution were both tested and compared to pick the baseline function that fitted the data best.

[0108] The parameters **164** for a fitted risk equation **172** is better described using a distribution of values, rather than a single value. In the BRAVO model **100**, a boot-strapped method was applied by repeatedly resampling the population and re-running the risk equations **172** to generate the distributions of parameters **164** for each risk equation **172**. Patient heterogeneity was handled using a patient-level

microsimulation process, in which each patient **122** has different characteristics and simulation was carried out one person at a time.

[0109] Comparing to the Markov model approach, the BRAVO risk engine **100** may be based on a series of discrete inter-correlated risk equations **172**. The discrete equations **172** approach accounts for the risk escalation **204** as diabetes progress **206** and interactions between complications **208**. It also allows for adjusting a large number of demographic **190** and biological characteristics **188** and thus provides better estimation.

[0110] The BRAVO risk engine **100** tracks risk factors **202** over time **170**. For example, as diabetes progresses **206**, the function of β cells declines. This led to a constantly increased HbA1c **126** level across time **170**. In addition, due to the feature of diabetes as well as a common side effect of diabetes treatment, the weight of T2DMs increased over-time. However, as people age, especially over 80 years old, their body weight **130** reduced over time **170**. This lead to a reversed "U" shape of body weights **130** for diabetes patients over the course of diabetes **206**. The risk engine **100** contains a series of equations **172** designed to represent the potential trend of change for each risk factor **202**, as illustrated in FIG. **6**.

[0111] The processors **102** and memories **104**, or a subset thereof, can be configured to provide a means of corresponding to the methods (**300** and **400**) disclosed herein and various flowcharts and blocks of the Figures. Although not shown, the devices **220** may also include additional accessories and peripherals, such as security accessories, printers, and keyboards.

[0112] In one embodiment, as illustrated in FIGS. **3-8**, the risk factor **202** is selected from the group consisting of glycosylated hemoglobin (HbA1c) **126**, systolic blood pressure (SBP) **128**, weight **130**, and low-density lipoprotein cholesterol (LDL-C) **132**. In such embodiment, each risk factor **202** [glycosylated hemoglobin (HbA1c) **126**, systolic blood pressure (SBP) **128**, weight **130**, and low-density lipoprotein (LDL) **130**] in the current cycle was predicted jointly by its value from the last cycle and other risk factors **202**.

[0113] In another embodiment, as illustrated in FIGS. **3-8**, the diabetes-related event **110** is a macrovascular event **134**. Exemplary macrovascular events **134** include stroke **136**, myocardial infarction **138**, congestive heart failure **140**, angina **142**, and revascularization surgery **144**.

[0114] In yet another embodiment, the diabetes-related event **110** is a microvascular event **146**. Exemplary microvascular events **146** include end stage renal failure **148**, blindness **150**, and severe pressure sensation loss **152**, as illustrated in FIGS. **3-8**.

[0115] In one embodiment, as illustrated in FIGS. **3-8**, the diabetes-related event **110** is an adverse event **154**. Exemplary adverse events **154** include severe hypoglycemia **156** and symptomatic hypoglycemia **158**.

[0116] In an exemplary embodiment of the events module **108**, a series of risk equations **172** may be fitted to predict **174** diabetes-related macrovascular events **134** (stroke **136**, MI **138**, CHF **140**, angina **142**, and revascularization surgery **144**), microvascular events **146** (ESRD **148**, blindness **150**, and SPSL **152**), and adverse events **154** (severe hypoglycemia **156** and symptomatic hypoglycemia **158**), for example, as illustrated in FIGS. **2-8**.

[0117] Details regarding the functional form of each risk equation **172** and model selection process, in accordance with embodiments disclosed herein, are provided in FIG. **2**. Based on the type of each clinical outcome (i.e., time to event, binary, continuous and count), multiple functional forms were tested correspondingly. Referring to FIGS. **2** and **8**, for time to event outcomes (i.e., macrovascular **134** and microvascular events **146** and all-cause mortality **236**), Exponential, Weibull **240**, Log-logistic **244**, Log-normal, Gompertz **242** and Gamma distribution were tested. For binary outcomes (i.e. smoking **234** and CVD **228** death), logistic **244**, probit and linear probability models **250** were tested, as shown in FIGS. **2**, **6**, and **8**. For count outcomes (i.e., symptomatic **158** and severe hypoglycemia **156**), Poisson **246** and negative binomial regressions were tested, as shown in FIG. **6**. For continuous outcomes, as illustrated in FIG. **8**, OLS **248** and Log-normal regression were tested. The ones with best prediction **174** accuracy were selected. The risk **176** of myocardial infarction (MI) **138**, congestive heart failure (CHF) **140**, stroke **136**, angina **142**, revascularization **144**, blind **150**, end stage renal disease (ESRD) **148** and severe pressure sensation loss (SPSL) **152** were modelled using Weibull survival model **240**, as provided in FIG. **8**. The risk of all-cause mortality **236** were modelled using Gompertz survival model **242**. The risk of smoking **234** and cardiovascular (CVD) **228** death were modelled using logistic regression **244**, illustrated in FIGS. **6** and **8**. The value **164** of HbA1c **126**, SBP **128**, BMI **130** and LDL **132** were modelled using ordinary least squares (OLS) **248**, as illustrated in FIG. **6**. And the frequency of symptomatic hypoglycemia **158** and severe hypoglycemia **156** were modelled using poisson regression **246**, as shown in FIG. **6**. Functions of these models are shown in FIG. **2**.

[0118] A Weibull survival regression **240** was fitted to predict **174** the hazard of ESRD **148**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **24-25**. HbA1c **126**, SBP **128**, CHF **140** history and history of blindness **150** were included in the risk equation **172**.

[0119] During the simulation process, if a person died in one cycle, the cause of that death would be decided based on equation (2) **172**. A logistic regression **244** was fitted to predict **174** the likelihood for that death caused by CVD **228**. Details regarding the parameter **164** estimates of the equation (2) **172** are provided in FIGS. **32-34**.

[0120] Referring to FIG. **2**, a Weibull survival model **240** was implemented in the risk equations **172**. In the Weillbull survival model **240** "h" denotes the hazard rates of encountering the events **176** at time "t" (diabetes duration **168**), or to be more specific, between time "t−1" and "t". Shape and Scale are the two parameters **164** that co-specified the shape and size of the Weibull **240** distribution. "βX" is the linear form **250** of the regression model, in which "X" is a vector of included predictors **174** and "β" is a vector containing coefficients of each predictor **174**. The Weibull survival model **240** was applied to predict **174** the incidence **192** of MI **138**, CHF **140**, Stroke **136**, Angina **142**, Revascularization **144**, Blindness **150**, ESRD **148** and neuropathy **152**. The proportional hazard assumption was tested for each equation **172** through Schoenfeld residual plots for each of the predictors **174**.

[0121] Referring to FIG. **2**, a Gompertz survival model **242** was implemented in the risk equations **172**. In the Gompertz survival model **242** "h" denotes the hazard rates

of encountering the events **176** at time "t" **170**, or to be more specific, between time "t−1" and "t". Shape and Scale are the two parameters **164** that co-defined the shape and size of the Weibull **240** distribution. "βX" is the linear form **250** of the regression model, in which "X" is a vector of included predictors **174** and "β" is a vector containing coefficients of each predictor **174**. The Gompertz survival model **242** was applied to predict **174** the all-cause mortality **236** rates.

[0122] Referring to FIG. **2**, a Logistic regression model **244** was implemented in the risk equations **172**. In the Logistic regression model **244** "Pr" denotes the probability **176** of encountering the events **134**, **146**, **154** at the current year. "βX" is the linear form **250** of the regression model, in which "X" is a vector of included predictors **174** and "β" is a vector containing coefficients of each predictor **174**. Logistic regression model **244** was applied to predict **174** the smoking **234** status and CVD **228** death.

[0123] Referring to FIG. **2**, a Poisson regression model **246** was implemented in the risk equations **172**. In the Poisson regression model **246** "Count" denotes the expected frequency of the events **154** in that cycle. "βX" is the linear form **250** of the regression model, in which "X" is a vector of included predictors **174** and "β" is a vector containing coefficients of each predictor **174**. Poisson regression **246** was applied to predict **174** the frequency of severe hypoglycemia **156** and symptomatic hypoglycemia **158**.

[0124] Other datasets with relevant outcome measures may be used to either further refine prediction equations **172** or add supplementary risk equations **172** to the original BRAVO risk engine **100**. Furthermore, referring to FIGS. **2** and **8**, all the risk equations **172** were estimated separately and a microsimulation algorithm was used to combine them into one risk engine **100**. Considering the mutually exclusive nature of some complications **210**, this approach might still have competing risk bias. Moreover, the type of antidiabetic drugs were not included in the risk equations **172** because the underlying assumption of the BRAVO risk engine **100** is that all types of treatments, including lifestyle modification **214**, impact the risk of events **176** only through key risk factors **202** (e.g., HbA1c **126**, BMI **130**). In one embodiment, the RECODe risk equation **252** may be used to directly explore the impact of different medications. Finally, ESRD **148** was found to be associated with a lower mortality rate **178** in the study, owing to a low sample size. Thus, as illustrated in FIGS. **24-25**, ESRD **148** was excluded from the all-cause mortality **236** equation. However, ESRD **148** may be included upon receipt of the long-term follow-up data **180**, **182** from the ACCORD trial **254**.

[0125] In an exemplary embodiment of the mortality module **118**, as illustrated in FIGS. **2-8**, an equation **172** was fitted to predict **174** patient **122** death **178**, and a second equation **172** was developed to explore the cause of death (i.e., cardiovascular disease (CVD) **228** or other death causes **230**).

[0126] Referring to FIGS. **30-32**, the mortality module **118** contains two equations **172**: (1) an equation **172** predicting **174** the likelihood of all-cause mortality **236**, and (2) an equation **172** predicting **174** the likelihood of CVD **228** death. The patients **122** would go through the all-cause mortality **236** equation **172** to decide whether he/she survived from this simulated cycle. If a patient **122** died during this cycle based on equation (1) **172**, then the engine would calculate the likelihood of this death caused by CVD **228** using the equation (2) **172**.

[0127] Embodiments of the invention include the Weibull survival regression **240** and Gompertz survival regression **242**, which are fitted to predict **174** all-cause mortality **236**. The Gompertz survival regression **242** provides a better fit according to the BRAVO risk engine **100** internal validation process. Compared to previous risk equations **172**, this equation **172** was fitted using age as time index **170** instead of diabetes duration **168**.

[0128] Details regarding the parameter **164** estimates of the equation (1) **172** are provided in FIG. **41**. BMI **130**, smoking **234**, female, education, MI **138** history, CHF **140** history, angina **142** history, stroke **136** event, and CHF **140** event were included in the risk equation **172**, as well as both first order and second order of HbA1c **126**.

[0129] Referring to FIG. **12**, the structure of the BRAVO risk engine simulation model **100** is illustrated. To reflect the chronic nature of diabetes, the model **100** follows T2DM patients from any specified time point to death or a user specified time horizon. "K" cohorts was generated from the user defined distribution of the population characteristics **166**, and "I" patients **122** for each cohorts was then simulated. For each patient **122** in the same cohort, demographic characteristics **190** and risk factors **202** were assigned based on the assigned cohorts' parameter values **164**. And then, based on that information, the first year macrovascular **134**, microvascular **146**, adverse events **154** and mortality for this patient **178** were predicted **174** through the BRAVO risk engine **100** risk equations **172**. All of the events **134**, **146**, **154** were predicted **174** at a random order to account for events **134**, **146**, **154** interdependency. After that, the comorbidities will be updated for this patient **122** and their survival status **198** will be checked. If this patient **122** is identified to be dead during this year, then the simulation for this patient **122** was finished and the model **100** moved on to the next patient **122** in the same cohort. If the patient **122** is not dead, risk factors **202** (i.e. HbA1c **126**, SBP **128**, weights **130**, Lipids **132**) were updated based on the equations **172** implemented in the BRAVO risk engine **100** and the simulation **100** moved on to the next cycle, and all the diabetes-related events **176** were predicted **174** based on newly updated risk factors **202**. This iteration was kept going until either the patient **122** is dead **178** or the simulation reached its time horizon **170**. And after all the patients **122** in this cohort have been simulated, the model moved on to the next cohort until all the cohorts are simulated. The incidence for each diabetes related **110** comorbidity and mortality rates **120** were recorded on a yearly basis.

[0130] The BRAVO risk engine **100** with good internal and external validity, see FIG. **40**, was developed to offer an alternative to the established UKPDS risk engine **256**, an alternative that was based on the US population, to support decision making in US clinical practices. Health outcome predictions **174** from the BRAVO risk engine **100** were consistent with the previous findings of the ACCORD trial **254** on non-fatal MI **138**, angina **142**, and revascularization surgery **144**, as illustrated in FIGS. **18-23**. Although not statistically significant, a previous study has found that intensive glycemic control was associated with lower HRs of ESRD **148**, blindness **150**, and SPSL **152**. The BRAVO risk engine **100** included HbA1c **126** as an important risk factor **202** for predicting **174** these microvascular events **146**, as illustrated in FIGS. **24-29**. More interestingly, even when including the extensive covariate list from the BRAVO risk engine **100**, these associations between HbA1c **126** and

microvascular events **146** were still statistically significant in the BRAVO risk equations **100**.

[0131] A Weibull survival regression **240** was fitted to predict **174** the hazard of non-fatal MI **138**. Details regarding the parameter **164** estimates of the regression are provided in FIGS. **18-19**. HbA1c **126**, LDL **132**, smoking **234**, age at diagnose, female, severe hypoglycemia **156**, race, education, MI **138** history, Angina **142** history, and history of revascularization surgery **144** were included in the risk equation **172**.

[0132] The impact of hypoglycemia **156**, **158** on diabetes outcomes and mortality **178** has been studied extensively in recent years. The occurrence of hypoglycemia **156**, **158** was found to be associated with major macrovascular **134** and microvascular events **146**, death **236**, and other nonvascular outcomes. A previous study also found that in addition to the direct impact of hypoglycemia **156**, **158** on vascular risk, the fear for hypoglycemia **156**, **158** was also associated with an additional quality-adjusted life-year decrement. The risk engine **100** is the first to fully incorporate hypoglycemia's **156**, **158** impact on disease course, as illustrated in FIG. **23**.

[0133] Referring to FIG. **30**, the engine **100** provides a critical predictive tool to evaluate new T2DM drugs, which usually have lower hypoglycemic **156**, **158** incidents than the older class of antidiabetic drugs, such as sulfonylureas. One of the major limitations of T2DM models based on the UKPDS risk engine **256** is that they did not model hypoglycemia **156**, **158** as a risk factor **202** for diabetes complications **210**. To capture the impact of hypoglycemia **156**, **158**, the BRAVO risk engine **100** included severe hypoglycemia **156** as a risk factor **202** to predict **174** CHF **140**, MI **138**, angina **142**, and blindness **150**, as shown in FIG. **8**. Encountering hypoglycemia **156**, **158** was also found to be associated with higher CVD-related **228** mortality rates **178**, as shown in FIGS. **30-34**. This feature of the BRAVO risk engine **100** can directly capture the benefits of hypoglycemia **156**, **158** prevention on cardiovascular **134**, **146** outcomes and mortality **178** for future diabetes models, which is a substantial innovation, compared with previously developed diabetes-related risk engines **100**.

[0134] The BRAVO risk engine **100** included severe hypoglycemia **156** in multiple risk equations **172**. Encountering one more episode of severe hypoglycemia **156** in the current year was associated with increased risks for CHF **140** [hazard ratio (HR)=198%], MI **138** (HR=228.6%), angina **142** (HR=188.5%), and blindness **150** (HR=151.7%). Although not statistically significant, quadratic polynomials of HbA1c **126** levels were also found to be an important predictor **174** for predicting all-cause mortality **236** as indicated by Bier scores and c-statistics. An HbA1c **126** level of 7.12% was calculated to be associated with the lowest mortality risks **178**. The equations **172** to model time-varying risk factors **202**, including HbA1c **126**, SBP **128**, LDL **132**, body weights **130**, smoking status **234**, and occurrence of severe hypoglycemia **156** and symptomatic hypoglycemia **158**, are presented in FIG. **6**.

[0135] The existence of racial disparities in outcomes among a wide range of diabetic complications made it essential for a diabetes model to include race segmentation relevant to the target population for clinical intervention. Referring to FIG. **5**, the BRAVO risk engine **100** categorizes race into Caucasian, African American, Hispanic, and Asian individuals in accordance with their representation in the US population. The BRAVO risk engine **100** predicted disparity patterns close to the finding from the Karter et al. study. Among all four race groups, being white was associated with the highest risk for MI **138** and nephropathy **238**, while being African American was found to be a protecting factor with the lowest risk for MI **138**, blindness **150**, and the need for revascularization surgery **144**.

[0136] Therefore, in accordance with embodiments of the invention, there is provided a method **300** of predicting diabetes progression **206** and mortality **178**. Referring to FIG. **9**, the method **300** includes a first step of receiving **302** a target population dataset **160** having a series of baseline biological characteristics **162** of the target population **160**. The method **300** has a second step of assigning **304** parameter values **164** based upon a user defined distribution of population characteristics **166**. A third step of analyzing **306**, using a computer processor **102**, the population dataset **160** for generating a diabetes risk engine **100**, wherein diabetes duration **168** is used as a time index **170**. The diabetes risk engine **100** operates one or more inter-correlated risk equations **172** which can be used as a predictor **174** to determine a risk of a diabetes-related event **176** or mortality of a patient **178**. A fourth step of adjusting **308** the risk engine **100** based upon new data collected **180** and based upon a new set of annual values collected **182** during the generating of the population dataset **160**. The method **300** has a fifth step of receiving **310** a first patient medical information **184** including clinical **186**, biomedical **188**, and demographic **190** factor information. The method **300** includes a sixth step of predicting **312** a risk **192** of an occurrence of one or more diabetes-related events **110** with the diabetes risk engine **100** based upon the parameter values **164** by comparing the first patient medical information **184** to the population dataset **160**. A seventh step of providing **314** at least one clinical or behavioral modification recommendation **196** based on the predicted risk **192** of the occurrence of the one or more diabetes-related events **110** or mortality **178**. The eighth step tracks **316** a progression and survival status **198** of a user **200** taking action toward achieving goals associated with improving health based upon the at least one clinical or behavioral modification recommendation **196**.

[0137] In one embodiment, the method **300** further includes a step of predicting **318** a progression of risk factors **202** of the first patient **184**, as shown in FIG. **9**.

[0138] In another embodiment, as shown in FIGS. **2** and **9**, the inter-correlated risk equations **172** account for risk escalation **204** based upon diabetes progress **206** and interactions **208** between complications **210**.

[0139] In yet another embodiment, the first patient medical information **184** includes risk factors **202** such as medication adherence **212**, lifestyle modification **214**, and therapy escalation **216**, as shown in FIG. **9**.

[0140] In one embodiment, as shown in FIG. **9**, the diabetes-related event **110** is a macrovascular event **134**. Exemplary macrovascular events **134** include stroke **136**, myocardial infarction **138**, congestive heart failure **140**, angina **142**, and revascularization surgery **144**.

[0141] In another embodiment, the diabetes-related event **110** is a microvascular event **146**. Exemplary microvascular events **146** include end stage renal failure **148**, blindness **150**, and severe pressure sensation loss **152**, as shown in FIG. **9**.

[0142] In yet another embodiment, as shown in FIG. **9**, the diabetes-related event **110** is an adverse event **154**. Exem-

plary adverse events **154** include severe hypoglycemia **156** and symptomatic hypoglycemia **158**.

[0143] Referring to FIG. **4**, a literature review was conducted to identify the initial list of baseline biological characteristics **162** and a backward selection process was conducted to remove those with no improvement for model fitting, in accordance with embodiments of the invention. Baseline biological characteristics **162** can be categorized into groups such as biomedical factors **188**, demographic characteristics **190**, and complications **186**, for example. The definitions of these baseline biological characteristics **162** are provided in FIG. **4**. The main modeling strategy utilized a left-censored, time-dependent, parametric proportional hazard model, in which diabetes duration **168** was used as the time index **170**, instead of real time in the clinical trial. To smooth measurement fluctuation for biomarkers, a moving average technique was applied: as the models were developed based on annual cycles, all the parameter values **164** should be aggregated annually. Parameter values **164** for each year were aggregated by averaging all the measurements conducted within the previous 2 years. Parameter values **164** from the current year were used to predict **174** the probability of encountering an outcome event **134**, **146** in the next year to account for potential bias caused by reverse causality. A person having the ordinary skill in the art will appreciate that these parameters **164** may be varied depending on application specifics. The history of events was also included in the initial list of baseline biological characteristics **162**. Having had an event **134**, **146**, **154** at baseline or during the study periods before the current year would both be identified as a history of that event for the current year. A mixed-method algorithm including a cross-validation-based, backward model selection process, literature review, and consultation from endocrinologists was used to support the model fitting process. For binary outcomes, the c-statistic has been applied to measure the discrimination power of the model.

[0144] As illustrated in FIG. **4**, race was identified as a significant risk factor **202** for predicting **174** MI **138**, revascularization surgery **144**, blindness **150**, and nephropathy **238**. Compared with African Americans, Caucasian, Hispanic, and other race/ethnicities were associated with 68.7% (95% CI 31.0-117.2), 26.7% (95% CI—16.0 to 91.3), and 27.9% (95% CI—10.7 to 83.1) higher risks for MI **138**, respectively. In addition, Caucasian, Hispanic, and other race/ethnicities were associated with a 46.4% (95% CI 22.7-74.6), 11.0% (−17.0 to 48.3), and 18.1% (95% CI—7.8 to 51.1) higher likelihood of receiving revascularization surgery **144**, compared with African Americans. Caucasian, Hispanic, and other race/ethnicities were correlated with a risk escalation **204** of 8.1% (95% CI—11.5 to 32.0), 70.1% (95% CI 28.2-125.5), and 17.9% (95% CI—10.5 to 55.5), respectively, compared with African Americans for blindness **150**. Last, Hispanic individuals and others were associated with risk reductions of SPSL **152** for 15.3% (95% CI—13.2 to 36.6) and 44.8% (95% CI 27.4-58.0), respectively, while Caucasians were associated with a 22.4% (95% CI 4.4-43.4) higher risk for SPSL **152** compared with African Americans.

[0145] The BRAVO risk engine **100** analyzed both the discrimination power of the model and prediction **174** accuracy. Thus, both the c-statistic and Brier score were calculated to support the model selection process. For continuous outcomes [HbA1c **126**, SBP **128**, LDL **132**, and body mass index (BMI) **130**], the mean square prediction error was used to select the models. A ten-fold cross-validation framework was applied to adjust the c-statistic, Brier score, and mean square prediction error for possible over-fitting in low-dimension regressions. All risk factors **202** that improved model performance were included into the final model. For those risk factors **202** that did not have a significant impact on model performance, inclusion and exclusion were judged by clinical endocrinology knowledge and evidence found from the current literature. Risk factors **202** that were not statistically significant in the BRAVO **100** model selection processes, but that were supported as risk factors **202** by existing clinical evidence **186**, were included in the risk equations **172**.

[0146] Referring to FIGS. **11-18**, the internal validation process was conducted by plotting the predicted cumulative hazard against the Kaplan-Meier cumulative hazard for all outcome measures. The log-log 95% confidence interval (CI) for cumulative incidence rate across a diabetes duration **168** of 0-40 years in the ACCORD trial **254** was calculated using the left-truncated method, and the predicted curve was examined if it fell within the 95% CI of the Kaplan-Meier curve.

[0147] As the gold standard of internal validation, plotting the predicted cumulative hazard against Kaplan-Meiers cumulative hazard was applied to all the events prediction equations **172**. For each timepoint from newly onset diabetes to 40 years after diagnoses were calculated using the log-log 95% confidence interval, and the predicted curve was examined if it falls within the 95% confidence interval of the Kaplan-Meiers Curve.

[0148] The predicted cumulative hazard was plotted over time, as shown in FIGS. **14-31**. Plotted on the same chart is the Kaplan-Meier cumulative hazard for each age year. This process works as a supplement for the machine learning algorithm and is especially helpful on selecting the correct functional form (i.e. Weibull **240** or Gompertz survival models **242**), shown in FIG. **2**.

[0149] One of the important findings in the ACCORD trial **254** was a higher mortality rate **120** in the intensive glycemic control group (HbA1c \ 6%) compared with the standard glycemic control group (HbA1c 7.0-7.9%). The association between HbA1c **126** and mortality rate **178** was found to be 'U' shaped in the standard control group, with an optimal HbA1c **126** level between 7.0% and 7.5%. As illustrated in FIG. **6**, the BRAVO risk engine **100** included a second-degree polynomial in the HbA1c **126** level that fits the data better than a linear relationship between the HbA1c **126** level and all-cause mortality **236**. The BRAVO risk engine **100** estimated the optimal glycemic control level for the ACCORD **254** population was 7.12%, and any deviation from this point was associated with an increased risk of mortality **120**.

[0150] In accordance with embodiments of the invention, there is provided a method **400** of predicting an occurrence of one or more diabetes related events **110**. Referring to FIG. **10**, the method **400** has a first step of receiving **402** a target population dataset **160** comprising a series of baseline characteristics **162** of the target population **160**. A second step of assigning **404** parameter values **164** based upon a user defined distribution of population characteristics **166**. The method **400** includes a third step of analyzing **406**, using a computer processor **102**, the population dataset **160** for generating a diabetes risk engine **100** wherein diabetes

duration **168** is used as a time index **170**. In the third step **406**, the diabetes risk engine **100** operates one or more inter-correlated risk equations **172** configured to determine the risk of a diabetes-related event **176** or mortality of a patient **178**. A fourth step of adjusting **408** the risk engine **100** based upon new data collected **180** based upon a new set of annual values collected **182** during the generating of the population dataset **160**. The method **400** includes a fifth step of receiving **410** a first patient medical information **184** such as clinical **186**, biomedical **188**, and demographic **190** factor information from a first patient user **194**. A sixth step predicts **412** a risk **192** of an occurrence of one or more diabetes-related events **110** with the diabetes risk engine **100** based upon the parameter values **164** by comparing the first patient medical information **184** to the population dataset **160** of the diabetes risk engine **100**. A seventh step provides **414** at least one clinical or behavioral modification recommendation **196** based on the risk **192** of the occurrence of said one or more diabetes-related events **194**. An eighth step tracks **416** the survival status **198** of a user **200** taking action toward achieving goals associated with improving health based upon the at least one clinical or behavioral modification recommendation **196**.

[0151] Referring to FIGS. **4-8**, a total of 28 exemplary endpoints were predicted **174** using the BRAVO risk engine **100** through a discrete-time event microsimulation process under the corresponding time horizon of each trial. The baseline characteristics **162** of each trial have been reported and applied directly as the characteristic of simulation samples. Normal distribution was assumed for all input variables, as shown in FIG. **5**, and the standard error of each variable was extracted from the corresponding literature. The values of key risk factors **202**, including HbA1c **126**, LDL **132**, SBP **128**, and BMI **130** in each validation trial were assumed to reach the corresponding treatment target **196** at the first year and remained constant in the following years. Then, 10,000 simulation runs were used to reach convergence in outcomes. An ordinary least-square model **248**, as shown in FIG. **2**, was used to fit the BRAVO-predicted incidence rates **174** to observed incidence rates **232**, and slope, intercept, and R2 were used to show prediction **174** accuracy. As shown in FIG. **3**, the microsimulation was conducted using a joint program **106** written through Visual Basic and C++ language. In addition, one-way sensitivity analyses were conducted to explore the impact of six risk factors **202** on the life expectancy in the ACCORD trial **254** population, shown in FIG. **4**. The values of continuous risk factors **202** (HbA1c **126**, SBP **128**, LDL **132**, and BMI **130**) were set from one standard deviation below the mean to one standard deviation above, while categorical risk factors **202** (smoking **234** and severe hypoglycemia **156**) ranged from 50% to 200% of the population average.

[0152] The structure of the simulation model is provided in FIG. **3**. To reflect the chronic nature of diabetes, the model followed T2DM patients from any specified time point to death or a user specified time horizon. K cohorts were generated from the user defined distribution of the population characteristics, and i patients for each of the cohorts were then be simulated. For each patient **194** in the same cohort, demographic characteristics **190** and risk factors **202** were assigned based on the assigned cohorts' parameter values **164**. Then, based on that information, the first year macrovascular **134**, microvascular **146**, adverse events **154** (e.g. hypoglycemia **156**, **158**) and mortality **178** for this patient **194** were predicted **174** through the risk equations **172**. All of the events **134**, **146**, **154** were predicted **174** at a random order to account for event inter-dependency. After that, the comorbidities were updated for this patient **194** and his/her survival status **198** was checked. If this patient **194** was identified to be dead during this year, then the simulation for this patient **194** ended and the model moved on to the next patient **194** in the same cohort. If the patient **122** is not dead, risk factors **202** (i.e. HbA1c **126**, SBP **128**, weight **130**, lipids **132**) are updated based on the BRAVO risk engine **100** equations **172** and the simulation moved on to the next cycle and the same prediction process was conducted again. This iteration **112** was kept going until either the patient **194** was dead or the simulation reached its time horizon. And after all the patients **194** in this cohort had been simulated, the model moves on to the next cohort until all the cohorts were simulated. After simulation is completed, all of the outcomes were summarized, including incidence rates of each event type **134**, **146**, **154**, mortality rates **178**, life expectancy and etc.

[0153] The variable selection process was conducted through a mixed algorithm. Variables were included into the final model based on the following criteria:

[0154] C-statistic has been widely applied when selecting appropriate variables for regression models intended to predict **174** the risk of events **134**, **146**, **154**, as it is a good measurement for the discrimination power of the model. However, in the BRAVO risk engine **100**, the engine **100** includes discrimination power of the model, but also the prediction **174** accuracy. Thus, both c-statistic and Bier Score were calculated to support the model selection process. For logistic regression **244**, the calculation process of c-statistic and Bier Score are straight forward. However, it became difficult in the survival regression framework, as it has multiple time periods. Two approaches were applied in this embodiment: 1) calculations for the five-year cumulative incidence as the predicted probability **174**, and calculations of c-statistic and Bier Score based on five-year observed data **232** and, 2) calculations for time **170** dependent c-statistic and Bier Score, using formula suggested by Gerds et al and Potapov et al. For continuous variables as the outcome (e.g., HbA1c **126**, SBP **128**, LDL **132**, BMI **130**), the mean square error (MSE) was calculated.

[0155] A recently published RECODe risk engine **252** has also used the ACCORD trial **254** data to develop a set of risk equations for modeling the risk of diabetes complications. Referring to FIG. **7**, besides the methodological differences in the modeling strategy, outcomes inclusion, and variable definition, the BRAVO risk engine **100** and RECODe risk engine **252** have very different purposes of risk predictions **174**. The RECODe risk engine **252** is intended for use in clinical settings to assist the initial treatment decision because the models only use baseline characteristics **162** to predict **174** the incidence rates of diabetes outcomes in a specified period (5 or 10 years). The BRAVO risk engine **100** aims to use an agent-based microsimulation modeling algorithm and to ultimately develop a diabetes model which is a predictor **174** for life-time disease progression **198**, **202**. Because the BRAVO risk engine **100** uses all time-dependent biomarkers **188**, disease history **186**, and other risk factors **202**, the BRAVO risk engine **100** will be more appropriate than the RECODe risk engine to support a cost-effectiveness analysis such as prioritizing therapeutic

strategies **196** or treatment targets of HbA1c **126**, LDL **132**, and blood pressure **128**. A table has been developed to briefly summarize the key differences between the RECODe risk engine **252** and the BRAVO risk engine **100**, as shown in FIG. **7**.

[0156] Referring to FIGS. **11**, **16**, and **17**, an analysis of the CHF **140** equation shows that having a history of MI **138** increased the risk of CHF **140** by 82.2%. In addition, repeat events were also taken into consideration. Having a history of CHF **140** was associated with a 247.6% increase in the risk **202** of a second CHF event **140**.

[0157] The modeling approach of the present embodiment has also demonstrated a novel approach to using clinical trials with a limited length of follow-up time. While the ACCORD trial **254** only ran for 7 years, the ACCORD cohort **254** covered a wide range of diabetes durations, characteristics of ACCORD **254** are shown in FIGS. **4** and **13**. Therefore, as illustrated in FIGS. **14-29** the BRAVO risk engine **100** used diabetes duration **168** as a time index **170** to simulate diabetes progression **198** and mortality **178** over 40 years. Further, indexing time **170** by diabetes duration **168** allowed us to estimate the time dependency of diabetes on events **134**, **146**, **154** and mortality **178**.

[0158] Equations **172**, illustrated in FIG. **2**, from the BRAVO risk engine **100** have been validated internally and externally, as shown in FIG. **11**. The external validation results, shown in FIG. **11**, plot the observed incidence rates **232** against the predicted incidence rates **231**. A simulation disease model based on the BRAVO risk engine **100** can be applied to predict **174** a range of long-term diabetes-related outcomes **176** to assist clinical **186** and policy decision making.

[0159] One having ordinary skill in the art will readily understand that the invention as discussed above may be practiced with steps in a different order, and/or with hardware elements in configurations that are different than those which are disclosed. Therefore, although the invention has been described based upon these preferred embodiments, it would be apparent to those of skill in the art that certain modifications, variations, and alternative constructions would be apparent, while remaining within the spirit and scope of the invention. In order to determine the metes and bounds of the invention, therefore, reference should also be made to the appended claims.

[0160] All U.S. patents and publications identified herein are incorporated in their entirety by reference thereto.

The claimed invention is:

1. A method of predicting diabetes progression and mortality comprising:

receiving a target population dataset comprising a series of baseline biological characteristics of the target population;

assigning parameter values based upon a user defined distribution of population characteristics;

analyzing, using a computer processor, the population dataset for generating a diabetes risk engine wherein diabetes duration is used as a time index, said diabetes risk engine operating one or more inter-correlated risk equations can be used as a predictor to determine a risk of a diabetes-related event or mortality of a patient;

adjusting the risk engine based upon new data collected based upon a new set of annual values collected during the generating of the population dataset;

receiving a first patient medical information comprising clinical, biomedical, and demographic factor information;

predicting a risk of an occurrence of one or more diabetes-related events with said diabetes risk engine based upon said parameter values, by comparing the first patient medical information to the population dataset;

providing at least one clinical or behavioral modification recommendation based on the predicted risk of the occurrence of said one or more diabetes-related events or mortality; and

tracking a progression and survival status of a user taking action toward achieving goals associated with improving health based upon the at least one clinical or behavioral modification recommendation.

2. The method of claim **1**, further comprising a step of predicting a progression of risk factors of said first patient.

3. The method of claim **1**, wherein the inter-correlated risk equations account for risk escalation as diabetes progress and during interactions between complications.

4. The method of claim **1**, wherein said first patient medical information comprises risk factors comprising medication adherence, lifestyle modification, and therapy escalation.

5. The method of claim **1**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is a stroke.

6. The method of claim **1**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is myocardial infarction.

7. The method of claim **1**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is congestive heart failure.

8. The method of claim **1**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is angina.

9. The method of claim **1**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is revascularization surgery.

10. The method of claim **1**, wherein said diabetes-related event is a microvascular event, wherein said microvascular event is end stage renal failure.

11. The method of claim **1**, wherein said diabetes-related event is a microvascular event, wherein said microvascular event is blindness.

12. The method of claim **1**, wherein said diabetes-related event is a microvascular event, wherein said microvascular event is severe pressure sensation loss.

13. The method of claim **1**, wherein said diabetes-related event is an adverse event, wherein said adverse event is severe hypoglycemia.

14. The method of claim **1**, wherein said diabetes-related event is an adverse event, wherein said adverse event is symptomatic hypoglycemia.

15. A method of predicting an occurrence of one or more diabetes related events comprising:

receiving a target population dataset comprising a series of baseline characteristics of the target population;

assigning parameter values based upon a user defined distribution of population characteristics;

analyzing, using a computer processor, the population dataset for generating a diabetes risk engine wherein diabetes duration is used as a time index, said diabetes risk engine operating one or more inter-correlated risk

equations configured to determine the risk of a diabetes-related event or mortality of the patient;

adjusting the risk engine based upon new data collected based upon a new set of annual values collected during the generating of the population dataset;

receiving a first patient medical information comprising clinical, biomedical, and demographic factor information from a first patient user;

predicting a risk of an occurrence of one or more diabetes-related events with said diabetes risk engine based upon said parameter values, by comparing the first patient medical information to the population dataset of said diabetes risk engine;

providing at least one clinical or behavioral modification recommendation based on the risk of the occurrence of said one or more diabetes-related events; and

tracking the survival status of a user taking action toward achieving goals associated with improving health based upon the at least one clinical or behavioral modification recommendation.

16. A diabetes risk engine system comprising:

at least one processor;

at least one memory unit containing computer program code;

a diabetes-related events module configured to predict an occurrence of one or more diabetes-related events through an iterative process;

a risk factors module to predict a progression of one or more risk factors through the iterative process;

a mortality module to predict an occurrence of mortality of a patient through the iterative process; and

a display interface configured to display the predicted risk of the one or more diabetes-related events.

17. The diabetes risk engine system of claim **16**, wherein the risk factor is selected from the group consisting of glycosylated hemoglobin (HbA1c), systolic blood pressure (SBP), weight, and low-density lipoprotein cholesterol (LDL-C).

18. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is a stroke.

19. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is myocardial infarction.

20. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is congestive heart failure.

21. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is angina.

22. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a macrovascular event, wherein said macrovascular event is revascularization surgery.

23. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a microvascular event, wherein said microvascular event is end stage renal failure.

24. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a microvascular event, wherein said microvascular event is blindness.

25. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is a microvascular event, wherein said microvascular event is severe pressure sensation loss.

26. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is an adverse event, wherein said adverse event is severe hypoglycemia.

27. The diabetes risk engine system of claim **16**, wherein said diabetes-related event is an adverse event, wherein said adverse event is symptomatic hypoglycemia.

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专利名称(译)	糖尿病风险引擎及其预测糖尿病进展和死亡率的方法		
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摘要(译)

本公开内容提供了针对美国人群的糖尿病风险引擎系统和方法，该系统和方法用于预测2型糖尿病患者的糖尿病进展和死亡率，包括建立，关联，评估和验证结果（BRAVO）风险引擎。 BRAVO风险引擎包括：糖尿病相关事件模块，用于预测一个或多个事件的发生；风险因子模块，用于预测风险因素的进展；死亡率模块，用于预测死亡率的发生；以及显示界面，用于显示糖尿病相关事件或死亡率的预测风险。使用“控制糖尿病中心血管风险的措施”（ACCORD）试验中的数据估算了预测糖尿病相关的微血管和大血管事件，低血糖，死亡率和糖尿病危险因素进展的风险方程。与UKPDS风险引擎相比，BRAVO风险引擎最好包括包括严重低血糖和常见的美国种族/民族类别在内的风险因素。