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ORIGINAL ARTICLE

A risk score including body mass index, glycated haemoglobin and triglycerides predicts future glycaemic control in people with type 2 diabetes

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Aim: To identify, predict and validate distinct glycaemic trajectories among patients with newly diagnosed type 2 diabetes treated in primary care, as a first step towards more effective patient-centred care.

Methods: We conducted a retrospective study in two cohorts, using routinely collected individual patient data from primary care practices obtained from two large Dutch diabetes patient registries. Participants included adult patients newly diagnosed with type 2 diabetes between January 2006 and December 2014 (development cohort, n = 10 528; validation cohort, n = 3777). Latent growth mixture modelling identified distinct glycaemic 5-year trajectories. Machine learning models were built to predict the trajectories using easily obtainable patient characteristics in daily clinical practice.

Results: Three different glycaemic trajectories were identified: (1) stable, adequate glycaemic control (76.5% of patients); (2) improved glycaemic control (21.3% of patients); and (3) deteriorated glycaemic control (2.2% of patients). Similar trajectories could be discerned in the validation cohort. Body mass index and glycated haemoglobin and triglyceride levels were the most important predictors of trajectory membership. The predictive model, trained on the development cohort, had a receiver-operating characteristic area under the curve of 0.96 in the validation cohort, indicating excellent accuracy.

Conclusions: The developed model can effectively explain heterogeneity in future glycaemic response of patients with type 2 diabetes. It can therefore be used in clinical practice as a quick and easy tool to provide tailored diabetes care.

KEYWORDS

cohort study, database research, diabetes, glycaemic control, primary care, type 2

1 | INTRODUCTION

Archibold Garrod is considered the founding father of precision medicine. In 1931, he was the first to recognize interpersonal variation in disease development and impact. Garrod noted that "individual cases of any particular disease are not exactly alike; they resemble rather the drawings made from the same model by individual members of a drawing class."[1] Nowadays, precision medicine is becoming more

popular because of an increase in electronic clinical data and a decline in genome sequencing costs.[2,3] In 2012, former UK Prime Minister David Cameron initiated the 100 000 Genomes Project and in 2015 former US president Barack Obama launched the Precision Medicine Initiative.[4,5] The aim of both initiatives was to predict the process of disease and to create personalized patient care by gaining more knowledge on genetic variation in disease.

Significant advances have been made thus far, such as the discovery of certain genetic variations that are linked to the effectiveness of a drug or specific genes that predict cancer risk.[6,7] Nevertheless, the implementation of precision medicine based solely on genomics has proven to be difficult for certain diseases, such as type 2 diabetes. Recently, new efforts have been undertaken to unravel the genetic background of type 2 diabetes by studying not only common gene variants, but also infrequent and rare variants.[8] To date, only 10% of its heritability has been unveiled, which has been referred to as a "geneticist's nightmare" by some experts.[9] Consequently, precision medicine based on a genotyping approach is still far away for type 2 diabetes. Shifting to a phenotyping approach of precision medicine seems a more promising alternative, in particular in the short-term, to improve patients' health outcomes.[10,11] The US National Institutes of Health defines precision medicine as an emerging approach for disease treatment and prevention that takes into account not only individual variability in genes, but also a patient's environment and lifestyle.[12] Currently, such a phenotyping approach to precision medicine is only sparsely adopted in evidence-based guidelines for diabetes treatment. Barring some exceptions for older people, these guidelines are usually highly standardized.[13,14]

As a first step towards more patient-centred care, the aim of the present study was 3-fold. It aimed: (1) to identify subgroups of people with newly diagnosed type 2 diabetes with distinct glycaemic trajectories; (2) to predict trajectory membership using patient characteristics that are commonly assessed in diabetes primary care; and (3) to validate these findings in a different cohort of patients with type 2 diabetes.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design and patients

In this retrospective cohort study, patients were selected using the electronic health records (EHRs) of two large Dutch diabetes care networks (DCNs) that routinely collect individual patient data and have been frequently used for research.[15–19] General practitioners and practice nurses from the participating practices recorded these data in the EHRs from the start of diabetes diagnosis. They use the information in the EHRs for the treatment and follow-up of their patients and as proof that they provided the care as agreed upon with health insurers for declaration purposes; therefore, it can be considered accurate. Patients from both DCNs received managed diabetes primary care based on the Netherlands Diabetes Federation Care Standard,[13] which describes the norm for generic multidisciplinary diabetes care.

The first DCN, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC),[20] was used for the development cohort and contained the anonymous longitudinal health records of 93 981 adult patients (age ≥ 18 years) with type 2 diabetes from 731 primary care practices in the city of Rotterdam, and in northern, north-western and eastern parts of the Netherlands. The data in the present study were collected during the yearly visits between January 1, 2006 and December 31, 2013. Those patients with a new diagnosis of type 2 diabetes during the study period and with at least one glycated haemoglobin (HbA1c) value, measured ±3 months from diagnosis (baseline), were selected for further analysis.

The second DCN, the regional care group ZIO,[18] was used as the validation cohort. The ZIO database contains the anonymous longitudinal health records of 11 833 adult patients (age ≥ 18 years) with type 2 diabetes from 95 primary care practices in Maastricht, in the south of the Netherlands. Data were collected and registered in the EHRs between January 1, 2009 and December 31, 2014. The inclusion criteria were the same as for the development cohort.

Both cohorts were open and dynamic, and patients were followed from diagnosis until the end of the study period or until censoring because no more HbA1c measurements were available (because of death, no show or change of practice). Patients' date of entry into the study (baseline) was fixed at their registered date of diagnosis of type 2 diabetes.

No ethical approval was needed for the study; as the data used were already available and patients were not physically involved in the research, the study was not subject to the Dutch Medical Research (Human Subjects) Act.

2.2 | Outcome

The outcome of interest was glycaemic control trajectories, based on HbA1c values during a maximum of 4 years (development cohort) or 5 years (validation cohort). Baseline HbA1c values were included if measured ±3 months from diagnosis. Follow-up HbA1c values were included if measured 1 year from the previous HbA1c measurement with a deviation of ±3 months.

2.3 | Predictors

The baseline patients' characteristics were used as potential predictors for an individual's glycaemic trajectory membership. Characteristics included baseline age, sex, and race, which was categorized into a binary variable of white or non-white because participants were mainly white. Non-white included Moroccan, Turkish, black-African, Indian, Indonesian and non-Indian in the development cohort, and black, Indian and other Asian in the validation cohort. HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile (LDL cholesterol, HDL cholesterol, total cholesterol and triglycerides), and body mass index (BMI) were also included as baseline characteristics if measured ±3 months from diagnosis. Urinary albumin-to-creatinine ratio (ACR), presence of heart failure (only reported in the development cohort), smoking (yes/no) and alcohol consumption (≤3 glasses/d or >3 glasses/d) were included as baseline characteristics if

measured ±12 months from diagnosis. Patient-reported history of cardiovascular disease (CVD) in family members aged <60 years (yes/no) was included in the analysis if obtained at any point before diagnosis or a maximum 12 months after diagnosis.

Outliers, most likely attributable to errors in recording, were removed based on cut-off points determined by diabetologists (Martijn Brouwers and Nicolaas Schaper).

2.4 | Statistical methods

To identify systematically the latent trajectories of glycaemic control, latent growth mixture modelling (LGMM) was used. This method allows the clustering of patients into an optimal number of growth trajectories.[21] Full information maximum likelihood was used as a missing data estimation approach.[22] A protocol, as recommended previously,[23,24] was followed to identify the best LGMM model. A series of latent class growth analysis and latent growth mixture models were estimated. Latent class growth analysis assumes no within class variance, whereas LGMM freely estimates the within-class variance.[23] The best model was determined by comparing the model fits of a progressive number of trajectories. Fit indices included the Akaike Information Criterion,[25] Bayesian Information Criterion[26] and the Lo-Mendel-Rubin-likelihood ratio test.[27] Lower values of Akaike Information Criterion and Bayesian Information Criterion, and/or a significant result on the the Lo-Mendel-Rubin-likelihood ratio test indicate a better model fit in terms of the number of trajectories. To determine model classification performance, entropy was used. Higher entropy values indicate less ambiguity in trajectory allocation.[28] The usefulness and clinical interpretation of each trajectory model was also taken into account. Analyses were performed using Mplus version 7.1.[29] and are reported according to the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist.[24] Baseline characteristics were assessed for the development and validation cohorts. Significant differences between cohorts were determined using two-sample t-tests and chi-squared tests. ANOVA and χ^2 tests were used to identify significant differences between glycaemic control trajectories within each cohort. To gain insight into the influence of glucose-lowering drugs and insulin on the patterns of the trajectories, the percentage of patients with oral glucose-lowering drugs and/or insulin prescriptions was compared at baseline and at each follow-up year between the trajectories of the development cohort using chi-squared tests.

For the development and validation of the prediction model, only patients with no missing baseline values were included. A 5-fold cross-validation was performed in the development cohort. Because there is no consensus on the best-performing classifier, several machine learning classification methods were used.[30] The correlations between SBP and DBP, lipid profile characteristics and CVD characteristics were calculated using the Spearman (for non-normally distributed variables) and Pearson (for normally distributed variables) correlation coefficients. If there was a significant correlation coefficient ≤−0.4 or ≥0.4 between two potential predictors, only one potential predictor was included in the analysis to avoid over-adjustment. To examine the generalizability of the developed prediction model, an external validation was computed in the validation cohort. Receiver-operating characteristic (ROC) curves were generated to

show the discrimination of the models. To examine the agreement between predicted and observed trajectory membership, calibration slopes were produced. Diagnostic values (sensitivities and specificities) and prognostic values (positive predictive values [PPVs] and negative predictive values [NPVs]) were also calculated.

For further details regarding the analyses see File S1.

3 | RESULTS

3.1 | Development and validation cohorts

The initial development cohort included 20 414 patients who were diagnosed with type 2 diabetes between January 1, 2006 and December 31, 2013. Of these, 10 528 patients had a baseline HbA1c measurement and were included in the analysis. The group of patients without a baseline HbA1c measurement had significantly higher LDL cholesterol levels (3.0 vs 2.9 mmol/L, 95% confidence interval [CI] 0.05–0.14; P < .001) and included a lower percentage of women (46.9% vs 48.4%, 95% CI 0.2–3.0; P = .031). Other characteristics did not differ. The mean (SD) age of the included patients in the development cohort was 62.9 (12.7) years and 51.6% were men (Table 1).

The initial validation cohort included 4164 patients who were diagnosed with type 2 diabetes between January 1, 2009 and December 31, 2014. Of these, 3337 adult patients had a baseline HbA1c measurement and were therefore selected for inclusion in the analysis. The group of patients without a baseline HbA1c measurement was significantly older (64.9 vs 63.7 years, 95% CI 0.3–2.1, P = .009) and had a lower percentage of CVD in the family (19% vs 24.2%, 95% CI 1.4–8.0; P = .008). Other characteristics did not differ. The mean (SD) age of the included patients in the validation cohort was 63.7 (12.2) years and 52.3% were men (Table 1).

In both the development and validation cohort, date of diagnosis (and inclusion into the study) differed considerably between patients: some patients were, for example, diagnosed in 2009 and others in 2013, resulting in a variable follow-up. Because of this variable follow-up, 78.7% of the patients in the development cohort did not have an HbA1c measurement after 4 years of follow-up and 72.9% did not have an HbA1c measurement after 5 years of follow-up in the validation cohort (Table S1). It was therefore decided to restrict follow-up in the development cohort to 4 years and in the validation cohort to 5 years. The median (interquartile range) number of HbA1c measurements during the research period was 2 (2) in the development cohort and 3 (3) in the validation cohort.

3.2 | Latent growth mixture modelling

The model with the strongest fit in the development cohort was the 3-trajectory LGMM (Table S2). The largest (76.5%) and most stable trajectory showed a pattern of good glycaemic control (HbA1c ≤7% [53 mmol/mol]) over time (Figure 1). This trajectory was named "stable, adequate glycaemic control." The middle trajectory, including 21.3% of the population, was named "improved glycaemic control," because patients in this trajectory adequately responded to glycaemic treatment and subsequently remained stable at a HbA1c level just

TABLE 1 Baseline patient characteristics of the development cohort and the validation cohort

	Development cohort	Validation cohort	P
N	10 528	3337	
Mean (SD) age, years	62.9 (12.7)	63.7 (12.2)	.001
Not recorded, *n*	0	0	
Men, *n* (%)	5433 (51.6)	1744 (52.3)	<.001
Not recorded	0	0	
Ethnic group[a], *n* (%)			.797
White	6669 (95.3)	2913 (95.5)	
Non-white	330 (4.7)	137 (4.5)	
Not recorded	3529	287	
Smoking status[a], *n* (%)			<.001
Non-smoker	7748 (80.1)	2065 (74.8)	
Current smoker	1928 (19.9)	695 (25.2)	
Not recorded	852	577	
Mean (SD) BMI, kg/m^2	30.4 (5.5)	30.6 (6.1)	.073
Not recorded, *n*	4443	595	
Alcohol consumption[a], *n* (%)			.308
<3 glasses/d	6029 (76.3)	3147 (94.6)	
≥3 glasses/d	1876 (23.7)	178 (5.4)	
Not recorded	2623	12	
Mean (SD) HbA1c, mmol/mol	53.0 (15.3)	56.9 (18.8)	<.0001
Not recorded, *n*	0	0	
Mean (SD) HbA1c, %	7.0 (1.4)	7.4 (1.7)	<.0001
Not recorded, *n*	0	0	
Mean (SD) SBP, mm Hg	138.5 (17.6)	138.4 (18.8)	.321
Not recorded, *n*	3762	483	
Mean (SD) DBP, mm Hg	80.8 (10.0)	80.8 (10.4)	.801
Not recorded, *n*	4014	489	
Mean (SD) LDL cholesterol, mmol/mol	2.9 (1.0)	3.2 (1.1)	.954
Not recorded, *n*	1910	663	
Mean (SD) HDL cholesterol, mmol/mol	1.23 (0.4)	1.16 (0.35)	<.001
Not recorded, *n*	1536	638	
Mean (SD) total cholesterol, mmol/mol	5.0 (1.1)	5.3 (1.3)	<.001
Not recorded, *n*	1500	628	
Mean (SD) triglycerides, mmol/L	2.0 (1.2)	2.2 (1.4)	<.001
Not recorded, *n*	1809	659	
Mean (SD) ACR, mg/mmol	2.7 (9.9)	2.3 (9.8)	.002
Not recorded, *n*	2717	812	
Mean (SD) eGFR, ml/min/1.73m^2	80.1 (21.6)	77.7 (24.0)	.005
Not recorded	9620	454	
Heart failure[a], *n* (%)		-	-
Yes	437 (6.6)		
No	6153 (93.4)		
Not recorded	3938		
CVD in family[a], *n* (%)			0.018
Yes	2718 (37.9)	810 (24.3)	
No	4457 (62.1)	2521 (75.7)	
Not recorded	3353	6	

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SBP, systolic blood pressure. Percentages have been rounded and might not total 100.
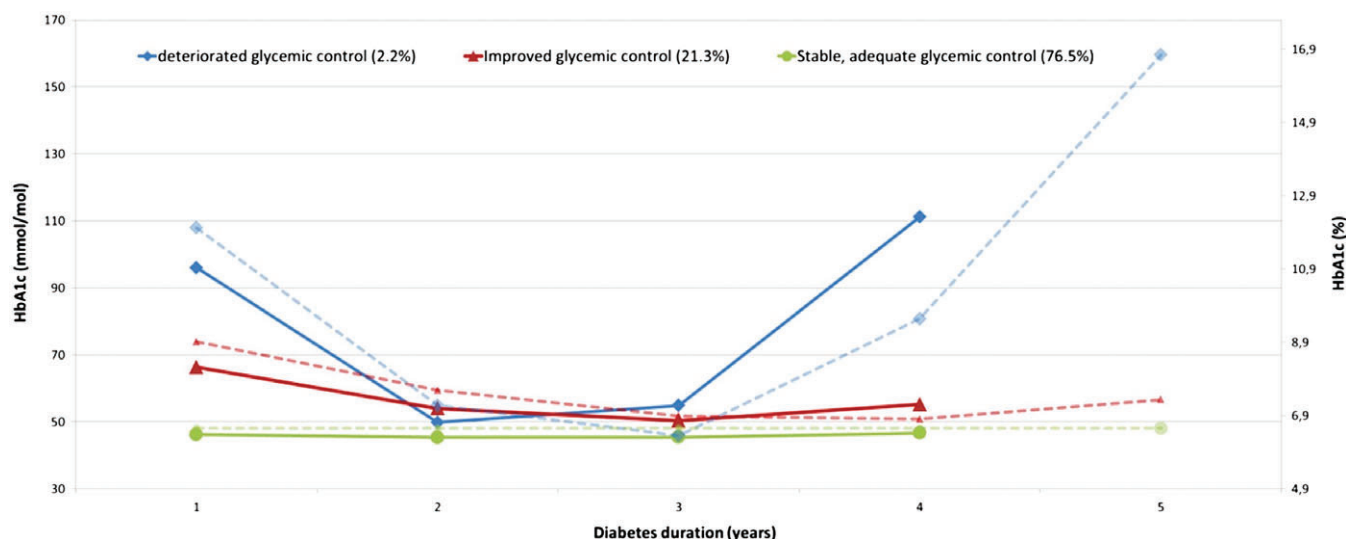[a] Percentages are out of total with recorded values.

FIGURE 1 Latent class growth trajectories of the best-fitting models of the development and validation cohorts identified by latent growth mixture modelling. Solid lines = development cohort; dashed lines = validation cohort

above 7% (53 mmol/mol). The smallest trajectory (2.2%) showed very high HbA1c at diagnosis of diabetes, but adequately responded to treatment; however, 2 years after diagnosis, HbA1c started to increase again to levels >7% (53 mmol/mol). This trajectory was named "deteriorated glycaemic control." The mean intercepts and slopes for each class are presented in Table S3. All intercepts and slope growth parameters were statistically significant. The observed individual trajectories and estimated mean trajectory of the three-trajectory model are shown in Figure S1.

In the validation cohort, a three-trajectory model was also identified based on model fit (Table S4) and population trajectory distribution (Figure 1). This model was similar in shape and population distribution to the three-trajectory model of the development cohort. All intercepts and slope growth parameters were statistically significant (Table S3).

Figures S1–S5 show all fitted trajectory models in the development and validation cohorts with linear and quadratic slopes, in accordance with the GRoLTS guidelines.[24]

There were significant differences between trajectories at all time points in the percentages of patients with oral glucose-lowering drugs and insulin prescriptions (P < .0001). Figures S6 and S7 show that more oral glucose-lowering drugs and insulin were prescribed to patients in the deteriorated and improved glycaemic control trajectories compared with the stable, adequate glycaemic control trajectory. Prescription of oral glucose-lowering drugs increased over time in all trajectories.

3.3 | Classification into glycaemic control trajectories

In both cohorts, patients in the deteriorated glycaemic control trajectory were more frequently male, current smokers and younger. Their baseline HbA1c, triglycerides and total cholesterol levels were higher compared with the other trajectories (Table 2).

After excluding significant correlations between patient characteristics (Table S5), 13 baseline characteristics were retained in the analyses as potential predictors: age; gender; race; HbA1c; SBP; LDL

cholesterol; triglycerides; ACR; BMI; smoking; alcohol; CVD; and CVD in family members. The 5-fold cross-validation in the development cohort showed that the K-nearest neighbour machine learning classifier had the highest accuracy (92.3%; Table S6). Using this classifier, the 13-patient feature prediction model had good-to-excellent diagnostic and prognostic properties, with sensitivities between 78.4% and 98.3%, specificities between 81.2% and 99.4%, PPVs between 78.0% and 94.7% and NPVs between 93.7% and 99.5% (Table S7). Baseline BMI, HbA1c and triglycerides were the most salient characteristics for predicting trajectory membership according to their weight (Table 3). The 13-patient feature prediction model had a ROC-AUC of 0.95 (Figure 2). The external validity of the model with the three most salient patient characteristics (3-patient feature prediction model) was determined in the validation cohort. The linear discriminant classifier had the highest accuracy (92.0%; Table S8). Sensitivities were between 67.9% and 99.1%, specificities between 85.3% and 98.6%, PPVs between 45.8 and 96.1% and NPVs between 91.9% and 99.4% (Table S9). The ROC-AUC was 0.96 (Figure 2). The calibration plot in the validation cohort showed a good fit for all three trajectories (Figure S8). The developed tool can be found on the webpage www.patientprofiles.nl and provides the opportunity to fill in different BMI, HbA1c and triglyceride values and to view the related trajectory.

4 | DISCUSSION

In the present retrospective cohort study in patients with newly diagnosed type 2 diabetes treated in primary care, three distinct glycaemic trajectories were identified during the first 5 years after diagnosis: (1) stable, adequate glycaemic control; (2) improved glycaemic control; and (3) deteriorated glycaemic control. Our most important finding was that trajectory membership can be predicted with good-to-excellent accuracy using no more than three patient characteristics (baseline BMI, HbA1c and triglycerides). The generalizability of the model, obtained by training the model on the development cohort and testing it on the validation cohort, was also excellent.

TABLE 2 Baseline characteristics of the development cohort and the validation cohort according to the different trajectories of HbA1c

	Latent trajectories development cohort			P	Latent trajectories validation cohort			P
	Stable, adequate glycaemic control	Improved glycaemic control	Deteriorated glycaemic control		Stable, adequate glycaemic control	Improved glycaemic control	Deteriorated glycaemic control	
N (%)	8049 (76.5)	2246 (21.3)	233 (2.2)		2516 (75.4)	702 (21.0)	119 (3.6)	
Mean (SD) age, years	63.8 (12.3)	60.3 (13.6)	59.3 (12.6)	<.001	64.9 (11.6)	60.3 (13.5)	59.7 (12.2)	<.001
Men, n (%)	4026 (50.0)	1261 (56.1)	146 (62.7)	<.001	1249 (49.6)	417 (59.4)	78 (65.5)	<.001
Ethnic group[a], n (%)				.013				.797
White	5116 (95.7)	1415 (94.0)	138 (93.2)		2185 (95.4)	623 (96)	105 (95.5)	
Non-white	230 (4.3)	90 (6.0)	10 (6.8)		106 (4.6)	26 (4.0)	5 (4.5)	
Smoking status[a], n (%)				<.001				<.001
Non-smoker	6008 (80.9)	1595 (77.8)	145 (71.8)		1585 (76.9)	415 (69.5)	65 (64.4)	
Current smoker	1416 (19.1)	455 (22.2)	57 (28.2)		477 (23.1)	182 (30.5)	36 (35.6)	
Mean (SD) BMI, kg/m^2	30.3 (5.3)	30.8 (6.1)	29.2 (4.8)	.103	30.4 (6.1)	31.0 (5.7)	31.1 (6.3)	.073
Alcohol consumption[a], n (%)				.553				.308
<3 glasses/d	4595 (76.0)	1301 (76.9)	133 (78.7)		2375 (94.8)	664 (94.7)	108 (91.5)	
≥3 glasses/d	1450 (24.0)	390 (23.1)	36 (21.3)		131 (5.2)	37 (5.3)	10 (8.5)	
Mean (SD) HbA1c, mmol/mol	46.5 (5.7)	70.3 (14.1)	107.2 (15.2)	<.001	48.4 (5.8)	78.0 (16.9)	112.5 (16.7)	<.001
Mean (SD) HbA1c, %	6.4 (0.5)	8.6 (1.3)	11.9 (1.4)	<.001	6.6 (0.5)	9.3 (1.5)	12.5 (1.5)	<.001
Mean (SD) SBP, mm Hg	138.5 (17.3)	138.8 (18.5)	137.2 (17.7)	.460	138.2 (18.7)	139.8 (19.2)	135.3 (17.4)	.321
Mean (SD) DBP, mm Hg	80.5 (9.8)	81.7 (10.6)	82.3 (10.3)	.003	80.3 (10.5)	82.6 (10.3)	81.7 (9.8)	.238
Mean (SD) LDL cholesterol, mmol/mol	2.9 (1.0)	3.0 (1.0)	3.3 (1.0)	<.001	3.2 (1.1)	3.3 (1.1)	3.5 (1.2)	.954
Mean (SD) HDL cholesterol, mmol/mol	1.3 (0.4)	1.1 (0.3)	1.2 (0.3)	<.001	1.2 (0.4)	1.0 (0.3)	1.1 (0.3)	<.001
Mean (SD) total cholesterol, mmol/mol	4.9 (1.1)	5.1 (1.3)	5.4 (1.2)	<.001	5.3 (1.2)	5.4 (1.3)	5.9 (1.7)	.003
Mean (SD) triglycerides, mmol/L	1.9 (1.1)	2.2 (1.4)	2.4 (1.8)	<.001	2.1 (1.2)	2.6 (1.6)	3.6 (2.9)	<.001
Mean (SD) ACR, mg/mmol	2.4 (9.2)	3.8 (12.2)	3.4 (8.4)	<.001	2.2 (10.3)	2.3 (7.1)	3.7 (12.5)	.002
Heart failure[a], n (%)				.901	-	-	-	-
Yes	337 (6.7)	92 (6.5)	8 (5.9)					
No	4697 (93.3)	1328 (93.5)	128 (94.1)					
CVD in family[a], n (%)				.534				.018
Yes	2072 (37.8)	591 (38.6)	55 (34.2)		603 (24.0)	189 (27.0)	18 (15.3)	
No	3409 (62.2)	942 (61.4)	106 (65.8)		1909 (76.0)	512 (73.0)	100 (84.7)	

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; SBP, systolic blood pressure. Percentages have been rounded and might not total 100.
[a] Percentages are out of total with recorded values.

To our knowledge, only two previous studies have examined latent glycaemic trajectories in patients with type 2 diabetes.[31,32] Both studies identified four glycaemic trajectories, which had notable similarities to the trajectory patterns we observed in the present study. The similarities between the previous and present studies were most notable for the "stable, adequate glycaemic control" trajectory. In both previous studies, this trajectory was identified and included 83% of their patients, slightly higher than the 72% we found. These results indicate that current practice enables a majority of patients to reach and maintain recommended glycaemic control levels. The present study shows that this group of patients can be identified at diagnosis by applying a model that has a high PPV and NPV.

These findings have important implications for more precision medicine in type 2 diabetes. The main goal of precision medicine is to develop models that can predict disease development or disease outcomes in order to tailor treatment.[3] Our model uses three relatively simple clinical characteristics, BMI, HbA1c and triglycerides, to divide patients into three groups, each with different future glycaemic trajectories. Predicting patients' future glycaemic control enables care professionals to provide tailored diabetes management. For patients classified in the stable, adequate glycaemic control group, for example, less intensive monitoring might suffice, whereas patients classified in the deteriorated glycaemic control group could benefit more from frequent monitoring. Previous research suggests that less frequent monitoring of patients with stable, adequate glycaemic control – that is, biannual instead of quarterly check-ups by a general practitioner – is possible without negative effects on health, allowing considerable cost reductions.[33] More generally, our model enables tailoring of a range of diabetes care components to patients' care needs, including pharmacotherapy, lifestyle advice and self-management support.

TABLE 3 Patient feature ranking of the 5-fold cross-validation as observed in the development cohort

Ranking	Patient baseline characteristics	Patient feature weight
1	BMI	0.3571
2	HbA1c	0.1571
3	Triglycerides	0.1148
4	LDL	0.0754
5	Age	0.0749
6	SBP	0.0737
7	ACR	0.0618
8	Sex	0.0142
9	Alcohol consumption	0.0142
10	Smoking	0.0142
11	CVD in family	0.0142
12	Heart failure	0.0142
13	Race	0.0142

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.
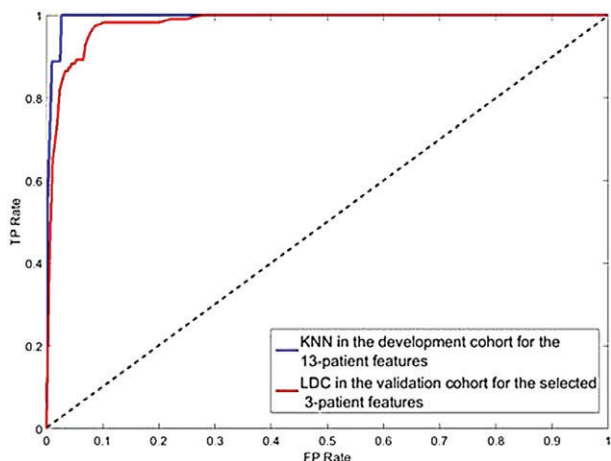
FIGURE 2 Receiver-operating characteristic curve of the 13-patient feature prediction model and the 3-patient feature prediction model. TP, true-positive; FP, false-positive; KNN, K-nearest neighbour; LDC, linear discriminant classifier

In the present study we applied a unique approach by combining LGMM with machine learning techniques. There were three follow-up HbA1c measurements in the development cohort and four in the validation cohort, allowing the identification of heterogeneity in future glycaemic response. Prescription of glucose-lowering drugs and insulin may have influenced the patterns of the trajectories. HbA1c levels in the stable, adequate and improved glycaemic control trajectories remained stable or improved, possibly because of an increase in oral and insulin prescriptions over time. In the deteriorated glycaemic control trajectory, however, HbA1c increased, despite an increase in glucose-lowering drugs and insulin prescriptions. Disease progression or difficulties adhering to drug treatment and healthy lifestyle could be explanations for this.[34,35]

The external validation is an important strength of the present study, considering that many research findings are based solely on the basis of a single study.[36] A limitation was that both cohorts consisted of a predominantly white population. When compared with white populations, other races tend to have higher HbA1c values,[37] and their inclusion might have resulted in glycaemic control trajectories that differed in size and shape. One of the previous studies that examined latent glycaemic control trajectories[31] included a mixed-race population, with ~50% non-white participants; however, as stated before, the identified trajectories in that study were similar to the trajectories in the present study.

So far, predictive models and tools based on machine learning techniques have not been widely used in clinical decision support systems.[38] One of the reasons for this could be that data obtained from EHRs are considered a byproduct of healthcare delivery, rather than a resource to improve its performance.[39] In addition, most machine learning models are complex and difficult to interpret because they depend heavily on aspects related to feature distribution, data availability and data representation.[40] In the present study we built and validated a simple and interpretable algorithm with excellent accuracy. Despite the high PPV and NPV in the stable, adequate glycaemic control trajectory, the PPV in the deteriorated glycaemic control trajectory was only 45.8% in the validation cohort. This implies that more than half the patients classified in this trajectory do not belong there (false-positives), which is a point for further refinement. The counterpart is that the NPV is high, implying that membership of this trajectory can be ruled out with high certainty.

In conclusion, only three patient characteristics (BMI, HbA1c and triglycerides) are needed to accurately predict glycaemic response of patients with newly diagnosed type 2 diabetes. The model can be used in practice as a quick, easy and accurate tool to determine patients' care needs and provide tailored diabetes treatment.

Conflict of interest

All authors declare: no support from any organization for the submitted work: no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

DH, AE, MB, DR and NS conceived and designed the study. DH and SH did the data extraction. DH, SK, and MP did the analyses. DH wrote the first draft of the study. All authors contributed to the interpretation of results and drafting of the manuscript. All authors read and approved the final manuscript. DH is the guarantor.

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REFERENCES

1. Garrod AE. *The Inborn Factors if Disease: An Essay*. Oxford, UK: Oxford University Press; 1931.
2. Dance A. Medical histories. *Nature*. 2016;537(7619):S52–S53.
3. Joyner MJ, Paneth N. Seven questions for personalized medicine. *JAMA*. 2015;314(10):999–1000.
4. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372(9):793–795.
5. Torjesen I. Genomes of 100,000 people will be sequenced to create an open access research resource. *BMJ*. 2013;347:f6690.
6. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363(18):1693–1703.
7. Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA*. 2015;313(13):1347–1361.
8. Fuchsberger C, Flannick J, Teslovich TM, et al. The genetic architecture of type 2 diabetes. *Nature*. 2016;536(7614):41–47.
9. Rich SS. Diabetes: still a geneticist's nightmare. *Nature*. 2016;536(7614):37–38.
10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364–1379.
11. Riddle MC, Karl DM. Individualizing targets and tactics for high-risk patients with type 2 diabetes: practical lessons from ACCORD and other cardiovascular trials. *Diabetes Care*. 2012;35(10):2100–2107.
12. Lister Hill National Center for Biomedical Communications, U.S. National Library of Medicine, National Institutes of Health, Department of Health & Human Services. Help me understand genetics: precision medicine. 2017; https://ghr.nlm.nih.gov/primer. Accessed November 16, 2017
13. Netherlands Diabetes Federation. *NDF care standard. transparency and quality of diabets care for people with diabetes type 2 [NDF Zorgstandaard. Transparantie en kwaliteit van diabeteszorg voor mensen met type 2 diabetes]*. Netherlands Diabetes Federation: Amersfoort, Netherlands; 2015.
14. Virkamaki A, Saltevo J. Finnish current care guideline for diabetes: interactive approach to improve individualised treatment. *Diabetologia*. 2011;54(5):1264–1265.
15. Hendriks SH, van Dijk PR, van Hateren KJ, et al. High-sensitive troponin T is associated with all-cause and cardiovascular mortality in stable outpatients with type 2 diabetes (ZODIAC-37). *Am Heart J*. 2016;174:43–50.
16. Landman GW, van Dijk PR, Drion I, et al. Midregional fragment of proadrenomedullin, new-onset albuminuria, and cardiovascular and all-cause mortality in patients with type 2 diabetes (ZODIAC-30). *Diabetes Care*. 2014;37(3):839–845.
17. Roelofsen Y, van Vugt M, Hendriks SH, et al. Demographical, clinical, and psychological characteristics of users and nonusers of an online platform for T2DM patients (e-VitaDM-3/ZODIAC-44). *J Diabetes Res*. 2016;2016:6343927.
18. Steuten LM, Vrijhoef HJ, Landewe-Cleuren S, Schaper N, Van Merode GG, Spreeuwenberg C. A disease management programme for patients with diabetes mellitus is associated with improved quality of care within existing budgets. *Diabet Med*. 2007;24(10):1112–1120.
19. Elissen AM, Duimel-Peeters IG, Spreeuwenberg C, Spreeuwenberg M, Vrijhoef HJ. Toward tailored disease management for type 2 diabetes. *Am J Manag Care*. 2012;18(10):619–630.
20. Ubink-Veltmaat LJ, Bilo HJ, Groenier KH, Rischen RO, Meyboom-de Jong B. Shared care with task delegation to nurses for type 2 diabetes: prospective observational study. *Neth J Med*. 2005;63(3):103–110.
21. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Ann Rev Clin Psychol*. 2010;6:109–138.
22. Muthén B. On structural equation modeling with data that are not missing completely at random. *Psychometrika*. 1987;52:431–462.
23. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personal Psychol Compass*. 2008;2:302–317.
24. van de Schoot R, Sijbrandij M, Winter SD, Depaoli S, Vermunt JK. The GRoLTS-checklist: guidelines for reporting on latent trajectory studies. *Struct Equ Modeling*. 2016;24(3):451–467.
25. Akaike H. Information theory as an extension of the maxium likelihood principle. In: Petrov BN, Csaki F, eds. *Second International Symposium on Information Theory*. Budapest, Hungary: Akademiai Kiado; 1973:267.
26. Schwarz G. Estimating the dimension of a model. *The Annals of Statistics*. 1978;6:461–464.
27. Lo Y, Mendell N, Rubin D. Testing the number of components in a normal mixture. *Biometrika*. 2001;88:767–778.
28. Depaoli S. Mixture class recovery in GMM under varying degrees of class separation: frequentist versus Bayesian estimation. *Psychol Methods*. 2013;18(2):186–219.
29. Muthén LK, Muthén BO. *Mplus User's Guide*. 7th ed. Muthén & Muthén: Los Angeles, CA; 2012.
30. Brazdil PB, Soares C. A comparison of ranking methods for classification algorithm selection. *Machine Learning: ECML, 2000*. Berlin and Heidelberg, Germany: Springer; 2003:63–75.
31. Laiteerapong N, Karter AJ, Moffet HH, et al. Ten-year hemoglobin A1c trajectories and outcomes in type 2 diabetes mellitus: the Diabetes & Aging Study. *J Diabetes Complications*. 2017;31(1):94–100.
32. Walraven I, Mast MR, Hoekstra T, et al. Distinct HbA1c trajectories in a type 2 diabetes cohort. *Acta Diabetol*. 2015;52(2):267–275.
33. Wermeling PR, Gorter KJ, Stellato RK, de Wit GA, Beulens JW, Rutten GE. Effectiveness and cost-effectiveness of 3-monthly versus 6-monthly monitoring of well-controlled type 2 diabetes patients: a pragmatic randomised controlled patient-preference equivalence trial in primary care (EFFIMODI study). *Diabetes Obes Metab*. 2014;16(9):841–849.
34. Jin J, Sklar GE, Min Sen OV, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269–286.
35. Look ARG, Wing RR, Bolin P, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369(2):145–154.
36. Ioannidis JP. Why most published research findings are false. *PLoS Med*. 2005;2(8):e124.
37. Campbell JA, Walker RJ, Smalls BL, Egede LE. Glucose control in diabetes: the impact of racial differences on monitoring and outcomes. *Endocrine*. 2012;42(3):471–482.
38. Miotto R, Li L, Kidd BA, Dudley JT. Deep patient: an unsupervised representation to predict the future of patients from the electronic health records. *Sci Rep*. 2016;6:26094.
39. Murdoch TB, Detsky AS. The inevitable application of big data to health care. *JAMA*. 2013;309(13):1351–1352.
40. Luo G. Automatically explaining machine learning prediction results: a demonstration on type 2 diabetes risk prediction. *Health Inf Sci Syst*. 2016;4:2.

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