

# The Potential Value of Identifying Type 2 Diabetes Subgroups for Guiding Intensive Treatment: A Comparison of Novel Data-Driven Clustering to Risk-driven Subgroups

Short Running Title:

The Value of Subgroups for Guiding Treatment

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Twitter Summary:

Classifying type 2 diabetes by predefined risk factor levels may be more cost-effective than data-driven clustering. Cholesterol and weight control significantly benefited a contemporary cohort.

Keywords

Type 2 Diabetes; Economic Analysis; Cost Effectiveness; Cost Analysis; Disease Modeling; Diagnosis/Stratification; Reclassification; Clusters; Guidelines; Healthcare Models; Healthcare Costs

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## Abstract

### OBJECTIVE

To estimate the impact on lifetime health and economic outcomes of different methods of stratifying individuals with type 2 diabetes, followed by guideline-based treatment intensification, targeting BMI and LDL in addition to HbA1c.

### RESEARCH DESIGN AND METHODS

We divided 2,935 newly diagnosed individuals from the Hoorn Diabetes Care System (DCS) cohort into five RHAPSODY data-driven clustering subgroups (based on age, BMI, HbA1c, C-peptide and HDL) and four risk-driven subgroups using fixed cut-offs for HbA1c and risk of cardiovascular disease based on guidelines. The UKPDS Outcomes Model 2 estimated discounted expected lifetime complication costs and quality-adjusted life-years (QALYs) for each subgroup and across all individuals. Gains from treatment intensification were compared to “care-as-usual” as observed in DCS. A sensitivity analysis was conducted based on Ahlqvist’s subgroups.

### RESULTS

Under care-as-usual, prognosis in the RHAPSODY data-driven subgroups ranged from 7.9 to 12.6 QALYs. Prognosis in the risk-driven subgroups ranged from 6.8 to 12.0 QALYs. Compared to homogenous type 2 diabetes, treatment for individuals in high-risk subgroups could cost 22.0% and 25.3% more and still be cost-effective for data-driven and risk-driven subgroups respectively. Targeting BMI and LDL in addition to HbA1c might deliver up to ten-fold increases in QALYs gained.

### CONCLUSIONS

Risk-driven subgroups better discriminated regarding prognosis. Both stratification methods supported stratified treatment intensification, with the risk-driven subgroups being somewhat better in identifying individuals with the most potential to benefit from intensive treatment. Irrespective of stratification approach, better cholesterol and weight control showed substantial potential for health gains.

Article highlights:

- Data-driven diabetes subgroups have received ample attention. However, their added value to inform treatment strategies in diabetes remains unclear.
- Do data-driven subgroups better stratify individuals compared to simpler risk-driven subgroups? Could subgroups inform cost-effective treatment intensification?
- Risk-driven subgroups discriminated between health outcomes better than data-driven subgroups. Compared to homogenous type 2 diabetes, treatment for individuals in high-risk subgroups could cost 22.0% and 25.3% more and still be cost-effective for data-driven and risk-driven subgroups respectively.
- Both stratifications inform treatment prioritization, with risk-driven subgroups performing better. Improvements in cholesterol and BMI offer substantial health gains.

## Introduction

To capture the heterogeneity and refine the current stratification of type 2 diabetes, a novel data-driven clustering analysis by Ahlqvist et al. (1) identified five subgroups, including Severe Autoimmune Diabetes, Severe Insulin Deficiency Diabetes (SIDD), Severe Insulin Resistance Diabetes (SIRD), Mild Obesity-related Diabetes (MOD), and Mild Age-related Diabetes (MARD) based on clinical parameters. These data-driven clustering methods have been replicated in many cohorts (2-6). However, questions remain concerning their clinical utility and cost-effectiveness. Soft clustering (7) or stratification based on predicted risk as estimated from continuous clinical features (2; 8; 9) might also identify type 2 diabetes phenotypes or predict outcomes for individuals, and it has been shown that using clinical measures in a regression model may outperform clustering for prediction of nephropathy risk and response to treatment (2). Nonetheless, data-driven clustering analysis might identify underlying phenotypic and pathologic subgroups and thus benefit medical decisions (6; 10; 11).

Alternatively, individuals could be classified based on clinically relevant risk thresholds as applied in diabetes and cardiovascular guidelines. European guidelines on cardiovascular disease prevention (12-14) recommend the use of the Systematic Coronary Risk Evaluation (SCORE) system (15) to inform the intensity of care. U.S. and European guidelines for type 2 diabetes focus on HbA1c values or goals to inform medical care (16; 17).

In addition to uncertainty concerning the clinical utility of stratification approaches, it is unclear whether these approaches could potentially support a cost-effective use of healthcare resources. Allocating individuals into subgroups may help clinicians to make decisions about whether to treat the individuals intensively, because individuals in some subgroups may benefit more from intensive treatment than the average or those in other subgroups (2).

However, the potential benefit of this strategy to help decision-making has not yet been explicitly evaluated. Hence, we used data from 2,935 contemporary individuals with type 2 diabetes from the Hoorn Diabetes Care System (DCS) to simulate the potential effect of their stratification (via data-driven clustering or using prespecified cut-offs for risk factor levels) and treatment intensification, relative to usual care, on predicted costs and (quality-adjusted) life expectancy. We further explored the potential gains from targeting cholesterol and weight, in addition to HbA1c, in each subgroup and across all individuals.

To help decision making, we expressed our results as the maximum annual price in the U.S. and U.K. settings that can be spent in the healthcare sector for identification and treatment of a certain subgroup while remaining cost-effective. This will be a straightforward indicator to inform clinicians and decision makers whether it is beneficial to intensify treatment and whether this is a cost-effective strategy.

## Research Design and Methods

### *Study Population*

The DCS is a comprehensive dynamic prospective cohort of the natural course of type 2 diabetes from 103 general practitioners (GPs) in the West-Friesland region of the Netherlands (18). Laboratory measurements have been described in details in previous studies (18; 19).

The study population consisted of 2,935 newly diagnosed individuals with type 2 diabetes over the period 1998–2019 in the DCS cohort (Supplementary Appendix 1). Our inclusion criteria were age at diagnosis  $\geq 35$  years, clinical parameters available within 2 years after diagnosis, GAD-negative, complete data in clustering variables and presence of genome-wide association study data (19). This was approved by the Ethical Review Committee of the VU University Medical Center (VUmc), Amsterdam. Informed consent was obtained from all participants.

### *Data-driven Subgroups and Risk-driven Subgroups*

A recent study (RHAPSODY) (19) applied the data-driven clustering approach by Ahlqvist et al. (1) to diabetes participants in three routine care cohorts, including the DCS. The RHAPSODY subgroups used clinical parameters available in routine care, replaced homoeostatic model assessment (HOMA) estimates in Ahlqvist's subgroups by C-peptide, and added HDL as an extra cluster indicator. This cluster replication in external data demonstrated a good concordance between cohorts and with the original clustering by Ahlqvist et al., while additionally refining the MARD into two subgroups (1; 19; 20).

Hence, as in Table 1, individuals in DCS were assigned to one of five RHAPSODY subgroups (19), including RHAPSODY SIDD (RHAP-SIDD), RHAPSODY SIRD (RHAP-

SIRD), RHAPSODY MOD (RHAP-MOD), RHAPSODY Mild Diabetes (RHAP-MD), and RHAPSODY Mild Diabetes with high HDL (RHAP-MDH) based on sex-specific k-means clustering by five scaled clustering indicators including age, BMI, HbA1c, C-peptide and HDL. The full details of the clustering methods and results have been published previously (1; 19).

We also stratified individuals in DCS according to a combination of HbA1c values and SCORE levels using pre-specified thresholds (Table 1). The values were selected to reflect American Diabetes Association (ADA) (17) and European recommendations (16) on glucose goals (HbA1c <7% or 53 mmol/mol) and European recommendations on cardiovascular risk management (a SCORE of 5% discriminates between high or higher- and moderate lower-cardiovascular risk categories) (14).

#### *Care-as-usual and Intensive Diabetes Management Strategies*

The observed trajectories of risk factors such as HbA1c and lipid levels captured care-as-usual in the contemporary DCS population. Intensive diabetes management interventions were simulated as guideline-based treat-to-target strategies, because subgroup-specific treatment effects are unknown. We assumed that pre-specified glycemic targets based on the ADA (17) and European Guidelines (16) would be achieved (Supplementary Table 2.1). We followed European Guidelines (14) for LDL and weight treatment targets. We analyzed a five-year intensive intervention. Once intensive management interventions were discontinued, we assumed that risk factors would revert immediately to values observed under care-as-usual (base case).

#### *Simulation*

We used the United Kingdom Prospective Diabetes Study Outcomes Model version 2

(UKPDS-OM2) to simulate lifetime health outcomes and costs of the DCS cohort (21). UKPDS-OM2 predicts an individual's absolute probability of experiencing any of eight diabetes complications (myocardial infarction, stroke, heart failure, ischemic heart diseases, amputation, renal failure, blindness in one eye, foot ulcers, and death) (21). These predictions depend on the individual's age, ethnicity, sex, and time-varying clinical risk factors (including diabetes duration, SBP, HbA1c, lipid levels, smoking status, and history of previous complications) (21). Model outputs include annual event probabilities, life expectancy, quality-adjusted life years (QALYs), and lifetime costs.

The UKPDS-OM2 has been validated both internally and externally (21-23), and it has shown good performance in predicting macrovascular events in DCS (23). As our study focuses on the model's ability to capture differences between subgroups, we validated the relative risks of incidence for subgroups by testing whether simulated relative risks fell within the 95% confidence interval (CI) of observed relative risks.

The model input variables are listed in Supplementary Appendix 2. We simulated an individual's lifetime outcomes for both care-as-usual and intensive diabetes management strategies. A maximal 70-year simulation period was chosen to reflect lifetime (study population minimum age 35).

After data cleaning (Supplementary Appendix 3; 0.95% missing data), baseline characteristics of each data-driven and risk-driven subgroup, as included in the simulation, were reported by frequency (percentage) for categorical variables or mean (standard deviation) for continuous variables. Chi-square tests were applied to check for significant differences between subgroups within each stratification approach.

We used observed data until the end of the follow-up in the DCS cohort. For HbA1c, LDL, BMI, and eGFR values after the end of follow-up, we extrapolated their progression using

linear dynamic models fitted to DCS observations (Supplementary Appendix 4). As HDL and SBP remained relatively constant throughout the observation period (Supplementary Figures 2.1 and 2.2), we extrapolated these by “last observation carried forward”.

A healthcare perspective was applied and costs and utilities associated with diabetes management and diabetes-related complications were obtained for the U.S. and U.K. settings (Supplementary Table 2.3). Costs were expressed in 2019 values, inflated to that year using price inflation indices. Costs and QALYs were discounted at 3.0% in the U.S. setting (24) and 3.5% in the U.K. setting (25).

#### *Simulated Outcomes and Standardization*

Lifetime costs and QALYs for each subgroup under care-as-usual were simulated (mean and 95% CI). To remove the effect of unmodifiable confounding risk factors (i.e., age and sex), we standardized the estimates to average age for males and females separately in DCS (i.e., males aged 62 and females aged 63) by regressing the individual-level UKPDS-OM2 simulated outcomes on their age and sex.

#### *Maximum Annual Cost-effective Price of Stratification and Intensive Management Interventions*

Intensive management interventions were deemed cost-effective if the incremental cost-effectiveness ratio was below the threshold of \$100,000 and £20,000 per QALY in the U.S. and U.K, respectively (25; 26). We estimated the maximum annual price for each strategy that would not exceed cost-effectiveness thresholds (formulas in Supplementary Appendix 5) by subgroup and overall. A higher maximum annual price indicates the subgroup can spend more on diabetes management costs while remaining cost-effective. The range (maximum–minimum) in maximum prices and in incremental QALYs among subgroups was used to

indicate to what degree subgroups could distinguish between groups of individuals for whom intensive treatment was potentially very or less cost-effective.

### *Uncertainty*

The analysis accounted for two types of uncertainty: Monte-Carlo simulation error and parameter uncertainty. Monte-Carlo error was reduced by averaging 50,000 simulations per individual. Parameter uncertainty was propagated by performing 400 random draws of different sets of model parameters derived from the UKPDS trial population (21). Maximum cost-effective prices of stratification and intensive treatments and further model outcomes were estimated for each of the 400 draws, and the 2.5% and 97.5% percentiles were used to present the level of uncertainty.

### *Sensitivity Analyses*

To analyze the difference caused by different data-driven clustering approaches, individuals in DCS were also assigned to one of four subgroups following Ahlqvist et al.(1), including SIDD, SIRD, MOD, and MARD based on sex-specific k-means clustering by five scaled clustering indicators including age at diagnosis, BMI, HbA1c, and HOMA estimates (27) of  $\beta$ -cell function and insulin resistance by C-peptide and fasting glucose.

Because reaching treatment targets might be difficult, especially involving weight loss, we also assumed a conservative 5%-improvement scenario, in which the values of care-as-usual risk factors will be improved by 5%, based on the recommendation of achieving and maintaining  $\geq 5\%$  weight loss by the ADA Guideline (28).

We varied the duration of the intensive management interventions, from 5 years to 10, 15, and 20 years. Moreover, we considered risk factors returning to a care-as-usual trajectory gradually, rather than immediately, by introducing a scenario analysis, in which the linear

dynamic models for risk factor progression would inform the subsequent risk factor trajectories until they reached the observed care-as-usual values (Scenario 1). Graphical representations of the scenario assumptions are presented in Supplementary Figure 2.3.

#### *Data and Resource Availability*

The data are not publicly available, but can be requested from VUmc. We accessed the data via a formal data request as a part of the RHAPSODY project.

## Results

### *Baseline Characteristics*

We found significant differences in baseline characteristics in both data-driven subgroups and risk-driven subgroups (Table 2 and Supplementary Appendix 6). Of note, higher mean age was observed in the RHAP-SIRD, RHAP-MDH, and subgroups with high SCORE values, compared to the remaining subgroups.

### *Lifetime Costs and Outcomes of Subgroups under Care-as-usual*

Supplementary Figures 7.1 and 7.2 show that simulated relative risks fit within the 95% CI of observed relative risks among subgroups, indicating UKPDS-OM2 was able to reflect differences between subgroups in risks. Fig.1 and Supplementary Appendix 8 show the simulated lifetime costs and QALYs and their standardization to an average individual (62-year-old male or 63-year-old female) for all data-driven and risk-driven subgroups and across all type 2 diabetes individuals in DCS under care-as-usual (i.e. without intensive management intervention).

On average, an individual with type 2 diabetes in DCS was predicted to accrue 10.57 QALYs and \$165,000 in complication costs in their remaining lifetime. Both stratification methods showed significant differences in QALYs and complication costs among subgroups. For data-driven subgroups, as expected, subgroups with older individuals had the worst simulated outcomes. The RHAP-SIRD subgroup had the lowest QALYs and complication costs (7.90; \$125,000), and was predicted to have highest diabetes-related macrovascular complication rates, explaining its lowest QALYs (Supplementary Figure 8.2). For risk-driven subgroups, the high HbA1c and SCORE levels-subgroup had the lowest QALYs and complication costs (6.83; \$114,000), with the highest simulated diabetes-related complication rates among all

subgroups (Supplementary Figure 8.3). Even at high rates of complication, complication costs are low when life expectancy is low.

After adjusting for sex and age, a standardized 62-year-old male and 63-year-old-female in DCS were predicted to accrue 9.98 and 11.12 QALYs and \$154,000 and \$176,000 in complication costs respectively. For data-driven subgroups, the lowest standardized QALYs were seen in RHAP-MOD for males (10.02) and RHAP-SIDD for females (10.88). For risk-driven subgroups, the ranking remained the same as before standardization, with the lowest standardized QALYs seen in H2S2 (male 8.73; female 10.22). The U.K. and U.S. settings featured similar outcomes, except that the absolute values of the U.K. setting were lower due to higher discounting rates and lower complication costs (Supplementary Figure 8.1 and Supplementary Table 8.2).

#### *The Maximum Annual Price of Stratification and Intensive Management*

Table 3 shows the incremental complication costs, QALYs and maximum prices of guideline-based treat-to-target strategy in the U.S. setting (threshold of \$100,000 per QALY). The outcomes of the remaining scenarios are provided in Supplementary Appendix 9.

Treat-to-target strategies led to an average reduction of 0.2% or 2.5 mmol/mol (2.7%) in HbA1c, 0.5 mmol/l (14.7%) in LDL, and 5.0 kg/m<sup>2</sup> (15.0%) in BMI (14.9 kg in weight) (Supplementary Tables 2.4 and 2.5). In the base case, without stratification into subgroups, treat-to-target of HbA1c could cost up to \$169 additionally per year while remaining below the \$100,000/QALY threshold. Furthermore, treating to the target of LDL and BMI in addition to HbA1c could cost up to \$1,499 per year and remain cost-effective.

For RHAPSODY data-driven subgroups, intensive management interventions targeting HbA1c resulted in the largest gains in QALYs (0.019) in the RHAP-SIDD subgroup and

could cost up to \$368 per year and remain cost-effective, which indicates RHAP-SIDD can spend \$199 more on diabetes management than overall type 2 diabetes while remaining cost-effective.

Compared to focusing on HbA1c only, treating to the target of HbA1c, BMI, and LDL in combination achieved 10 times higher gains in QALYs and could cost substantially more per year while remaining cost-effective, ranging from 0.044 QALYs and \$799 per person in the RHAP-MD subgroup to 0.112 QALYs and \$1,973 per person in the RHAP-MOD subgroup. On average, for individuals in high-risk subgroups (RHAP-SIDD, RHAP-SIRD and RHAP-MOD) the maximum annual price of intensive management could be 30.7% higher, compared to the no stratification scenario, while remaining cost-effective in the U.S. setting.

For risk-driven subgroups, intensive management solely targeting HbA1c resulted in the largest gains in QALYs in the subgroups with high HbA1c levels (0.017 for H2S1 and 0.012 for H2S2) and could cost up to \$270 and \$323 per year respectively and remain cost-effective. Compared to solely targeting HbA1c, treating to the target of BMI and LDL additionally achieved more than 10 times the gains in QALYs and could cost substantially more, up to 0.114 QALYs and \$2,578 per person in the H2S2 subgroup. On average, for individuals in high-risk subgroups (H2S1, H1S2, and H2S2) the maximum annual price of intensive management could be 31.2% higher, compared to a no stratification scenario, while remaining cost-effective in the U.S. setting.

### *Sensitivity Analyses*

Replicating the current analyses by following the subgroups of Ahlqvist et al. (1) led to robust findings about discrimination (Supplementary Appendix 10). BMI and C-peptide values in RHAP-MOD (37.82 kg/m<sup>2</sup>; 1.43 nmol/L) are significantly higher compared to MOD (33.51 kg/m<sup>2</sup>; 1.04 nmol/L) (Supplementary Table 10.2). Although, we observed

RHAP-SIRD to have significantly higher BMI compared to other RHAPSODY subgroups (Supplementary Figure 6.2), this difference was less pronounced than the BMI difference observed between SIRD and other subgroups in the study by Ahlqvist et al. (Supplementary Figure 10.2). MARD had the lowest absolute simulated QALYs, but after standardization, SIRD had the lowest QALYs (Supplementary Figures 10.7 and 10.8). SIRD and MARD generally had the highest risk of complications, except for SIDD, which had the highest risk of amputation (Supplementary Figure 10.9).

The scenario of a 5%-improvement led to similar findings as the treat-to-target scenario, while with a less substantial reduction in risk factors (Supplementary Tables 2.4 and 2.5), and therefore less difference in results (Supplementary Tables 9.1-9.4). Overall, considering both scenarios, compared to homogenous type 2 diabetes, treatment for individuals in high-risk subgroups could cost on average 22.0% and 25.3% more and still be cost-effective for data-driven and risk-driven subgroups respectively.

A longer treatment period implied lower maximum annual prices of intensive management while remaining cost-effective (Supplementary Figures 9.1-9.3). Allowing the treatment effect to extend beyond the hypothetical treatment period (Scenario 1) led to more incremental QALYs and higher maximum annual prices of intensive management among subgroups. In all scenarios, intensive management could cost significantly more in high-risk subgroups compared to no stratification and remain cost-effective.

## Conclusions

The data-driven subgroups were able to stratify individuals with diverse prognosis, displaying significant differences in simulated lifetime QALYs and complication costs. However, risk-driven subgroups showed somewhat larger differences between high and low risk subgroups than the data-driven subgroups. Both data-driven subgroups and risk-driven subgroups could support stratifying individuals and demand more healthcare resources. For the individuals in high-risk subgroups, higher than average resources could be committed for treat-to-target strategies while remaining cost-effective. This difference in maximum annual prices indicates substantial financial incentives to identify and treat more intensively individuals in high-risk groups.

About two-thirds of individuals with diabetes fail to achieve HbA1c targets (7%) (17; 29), and we show the potential gains and value of targeting HbA1c only. However, targeting LDL and BMI, in addition to HbA1c, offered significant benefits in contemporary populations like the DCS. This is important ~~significant~~—when more than 90% of individuals with type 2 diabetes are overweight or obese (30) and less than half reach LDL targets (31). Our predicted gains may partly reflect that current targets for BMI and LDL are quite ambitious when compared to actual risk factor levels observed in populations (32-34). Rather than treat-to-target, using 5%-reductions of risk factor levels has produced similar findings but of smaller magnitude. Furthermore, The RHAP-SIRD, RHAP-SIDD, RHAP-MOD and H2S2 subgroups benefited most from jointly targeting HbA1c, LDL, and BMI. These subgroups had the largest simulated QALY gains from a combined intervention. This highlights an opportunity to target specific subgroups of individuals more intensively. Specifically, in a contemporary care-as-usual setting, the RHAP-SIRD and H2S2 subgroups had the lowest predicted lifetime QALYs and the highest risk of complications among all subgroups – in

part driven by their advanced age.

The findings regarding differences in baseline characteristics were in line with previous studies (1; 19). In addition, our paper presents that across all RHAPSODY data-driven subgroups, a guideline-based five-year comprehensive intervention to lower HbA1c, BMI, and LDL could cost up to \$799-\$1,973 per year in the U.S. and £196-£463 per year in the U.K. at \$100,000 per QALY and £20,000 per QALY cost-effectiveness thresholds, respectively. Thus, the costs of measuring any clustering indicators and intensifying treatment must be lower than these values for a subtype-specific treatment strategy to be cost-effective. For risk-driven subgroups, the intervention could cost up to \$930-\$2,578 per year in the U.S., and £230-£515 per year in the U.K. to be cost-effective. The range indicates the financial incentives and potential benefits resulting from stratification of type 2 diabetes. The higher the range in annual prices, the more helpful stratification could be to inform treatment prioritization.

Comparing two stratification methods, risk-driven subgroups discriminated individuals better between mild and severe conditions than data-driven subgroups in the care-as-usual setting. Data-driven clustering better identified individuals who would benefit from more intensive glucose treatment alone. Risk-driven subgroups better identified individuals who would benefit from more intensive treatment targeting lipids, weight and HbA1c together. In general, also considering their more straightforward implementation, risk-driven subgroups seem better suited than data-driven subgroups for stratifying individuals with different risks and guiding comprehensive treatment.

Consistent with previous findings (19), RHAPSODY subgroups resembled Ahlqvist's subgroups, except that RHAP-SIRD were older, less obese and less insulin-resistant compared to SIRD, while RHAP-MOD were more obese and more insulin-resistant

compared to MOD. Although differences exist in their characteristics, using either of these two methods of data-driven clustering led to the same conclusion that classifying type 2 diabetes according to cut-offs for HbA1c and cardiovascular risk may better identify individuals for treatment intensification compared to data-driven clustering. Furthermore, MOD is being recognized as a mild diabetes subgroup, but this recognition is highly influenced by the young age of individuals in that subgroup. In both RHAPSODY and Ahlqvist's subgroups, after age-~~sex~~ standardization, the MOD subgroup has similar or even lower lifetime QALYs compared to other severe subgroups, including SIDD and SIRD. This indicates that despite this group's "mild" designation, this high BMI ~~obese~~ population still requires careful management.

This study had several limitations. First, despite the generally good fit of the linear dynamic models (Supplementary Appendix 4), they slightly underestimated eGFR, leading to overestimated kidney damage and underestimated QALYs. However, this likely had minimal impact on relative subgroup differences. Second, UKPDS-OM2 simulations predict complications using risk factor trajectories and pre-existing complications. The prediction of risk factor trajectories was specified by subgroup, based on subgroup-specific prediction models, while the prediction of complications was not specific to subgroups. The treatment intensification scenarios investigated were hypothetical and based on changes to risk factors to meet treatment targets. Our results provide a benchmark for stratified treatment strategies, allowing to compare different stratification approaches. They warrant further research to investigate how to best reach the treatment goals. Third, individuals with less favorable prognosis (e.g., individuals with a less-than-5-year life expectancy) might fall under the HbA1c <8% recommendation (17) rather than 7%, indicating lower incremental QALYs. However, our simulation cohort's average age (62.8) is around 18 years less than the mean life expectancy in the Netherlands (81 measured in 2020 (35)), therefore we believe our

finding is relevant. Finally, two clustering indicators, namely C-peptide and fasting glucose, are not captured in the UKPDS-OM2, which might underestimate the discrimination ability of data-driven subgroups. However, C-peptide is found to be relatively stable over time (1), and HbA1c, for which within-patient reproducibility is superior to that of fasting glucose (36), is included in the UKPDS-OM2. Therefore, we believe our findings will not be largely affected.

This study indicates several potential directions for future research. We suggest that cholesterol-lowering medicine and weight control interventions warrant further investigation for all diabetes individuals (37; 38), with special attention regarding their impact in specific subgroups (2; 39). For example, as expected, treating-to-target of HbA1c alone is not very cost-effective for SIRD individuals, given their already low HbA1c levels and the possibility that complications are primarily driven by hyperinsulinemia or insulin resistance (40). Treatment options targeting the latter are currently limited (39); while lifestyle programs may help reduce insulin resistance through weight loss, long-term sustainability is challenging (39). The high maximum annual price (around \$2000) we found in the combined intervention for SIRD suggests a significant potential return on investment, which could support the further development of therapeutic options specifically targeting them. Furthermore, ~~we found simpler risk-driven subgroups to slightly outperform novel data-driven clustering in terms of clinical utility and treatment prioritization. Therefore,~~ future data-driven clustering of diabetes subtypes may benefit from incorporating some elements of the risk-driven approach, such as smoking status, SBP, and total cholesterol. This may help refine the current clustering and indicate some etiology pathways that might have remained unnoticed at the current clustering indicators.

In summary, stratification approaches examined in this paper were successfully able to distinguish among type 2 diabetes individuals in terms of lifetime QALYs and costs. Both

subgroup stratification methods suggest that research and investment in personalized care are attractive from an individual and economic perspective. Using a data-driven clustering approach, we estimated that especially the RHAP-SIDD, RHAP-SIRD, and RHAP-MOD subgroups would potentially benefit in a cost-effective way from treat-to-target strategies. However, a more straightforward stratification using risk-driven cut-off values for risk factors, did slightly better than the novel data-driven clustering in identifying priority groups of individuals. With maximum prices of up to \$3,786 or £815 per individual per year, strong economic incentives exist to research and identify the best ways to achieve established treatment targets, especially in high-risk individuals.

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## Tables

	Abbreviation (Full Name)	Characteristics or Cut-offs	Proportion
<b>RHAP-SODY data-driven subgroups</b>	RHAP-SIDD (RHAPSODY - Severe Insulin Deficiency Diabetes)	High HbA1c	12.44%
	RHAP-SIRD (RHAPSODY - Severe Insulin Resistance Diabetes)	High C-peptide and age	21.70%
	RHAP-MOD (RHAPSODY - Mild Obesity-related Diabetes)	High BMI and C-peptide	17.72%
	RHAP-MD (RHAPSODY - Mild Diabetes)	Moderate in clustering indicators	29.30%
	RHAP-MDH (RHAPSODY - Mild Diabetes with high HDL)	High HDL	18.84%
<b>Risk-driven subgroups</b>	H1S1 (Low HbA1c and Low SCORE)	HbA1c<7% and SCORE<5%	43.41%
	H1S2 (Low HbA1c and High SCORE)	HbA1c<7% & SCORE≥5%	18.47%
	H2S1 (High HbA1c and Low SCORE)	HbA1c≥7% and SCORE<5%	28.65%
	H2S2 (High HbA1c and High SCORE)	HbA1c≥7% and SCORE≥5%	9.47%

Table 1 Subgroup characteristics

SCORE, Systematic COronary Risk Evaluation (15).

	RHAPSODY data-driven subgroups						Risk-driven subgroups				
	RHAP-SIDD	RHAP-SIRD	RHAP-MOD	RHAP-MD	RHAP-MDH	p	H1S1	H1S2	H2S1	H2S2	p
N (%)	365	637	520	860	553 (18.84)		1274	542 (18.47)	841	278 (9.47)	

	(12.44)	(21.70)	(17.72)	(29.30)			(43.41)		(28.65)		
Age, years	61.39 (9.74)	70.74 (7.41)	55.90 (8.05)	57.56 (8.20)	68.79 (7.76)	<0.001	59.08 (8.15)	72.75 (6.54)	58.18 (8.56)	73.58 (6.67)	<0.001
Duration of diabetes, years	4.46 (3.29)	2.30 (2.74)	3.05 (3.21)	3.26 (3.40)	2.80 (3.18)	<0.001	2.82 (3.22)	2.19 (2.69)	3.94 (3.38)	3.32 (3.21)	<0.001
LDL cholesterol, mmol/liter	2.72 (0.91)	2.64 (0.89)	2.68 (0.90)	2.79 (0.94)	2.80 (0.91)	0.005	2.76 (0.93)	2.82 (0.90)	2.61 (0.89)	2.80 (0.92)	<0.001
HDL cholesterol, mmol/liter	1.16 (0.31)	1.08 (0.22)	1.06 (0.26)	1.10 (0.23)	1.56 (0.34)	<0.001	1.19 (0.32)	1.25 (0.33)	1.12 (0.31)	1.20 (0.33)	<0.001
HbA1c, mmol/mol	61.51 (19.34)	47.87 (7.99)	51.17 (10.93)	49.47 (9.33)	46.90 (7.85)	<0.001	45.87 (6.86)	45.76 (6.04)	58.21 (14.44)	56.92 (13.26)	<0.001
HbA1c, %	7.78 (1.78)	6.53 (0.73)	6.83 (1.00)	6.68 (0.85)	6.44 (0.72)	<0.001	6.35 (0.63)	6.34 (0.55)	7.48 (1.32)	7.36 (1.22)	<0.001
eGFR based on CKD-EPI, mL/min/1.73 m <sup>2</sup>	84.35 (18.02)	71.50 (15.94)	88.06 (16.84)	87.54 (16.12)	77.97 (14.83)	<0.001	84.59 (16.25)	72.80 (15.50)	87.21 (17.37)	71.67 (16.13)	<0.001
BMI, kg/m <sup>2</sup>	29.50 (4.59)	29.89 (3.51)	37.82 (4.98)	28.90 (3.38)	27.15 (3.54)	<0.001	30.87 (5.54)	29.10 (4.55)	31.06 (5.47)	29.24 (4.10)	<0.001
Systolic blood pressure, mmHg	142.17 (19.84)	146.75 (19.99)	141.69 (17.87)	137.56 (17.56)	145.60 (18.57)	<0.001	137.23 (16.16)	155.01 (19.70)	138.36 (17.36)	153.48 (18.33)	<0.001
Male, n (%) [rest=female]	218 (59.7)	397 (62.3)	256 (49.2)	474 (55.1)	297 (53.7)	<0.001	629 (49.4)	347 (64.0)	490 (58.3)	176 (63.3)	<0.001
Smoking status [rest=never]						<0.001					0.017
Current, n (%)	76 (21.1)	86 (13.9)	108 (21.1)	204 (24.8)	72 (13.4)		197 (16.1)	105 (20.0)	182 (21.8)	62 (22.9)	
Former, n (%)	170 (47.1)	364 (58.9)	251 (48.9)	365 (44.3)	276 (51.3)		632 (51.6)	269 (51.2)	394 (47.3)	131 (48.3)	

Table 2 Selected baseline simulation characteristics of subgroups

RHAP-SIDD, Severe Insulin Deficiency Diabetes by RHAPSODY clustering; RHAP-SIRD, Severe Insulin Resistance Diabetes by RHAPSODY clustering; RHAP-MOD, Mild Obesity-related Diabetes by RHAPSODY clustering; RHAP-MD, Mild Diabetes by RHAPSODY clustering; RHAP-MDH, Mild Diabetes with high HDL by RHAPSODY clustering; H1S1, Low HbA1c and Low SCORE; H1S2, Low HbA1c and High SCORE; H2S1, High HbA1c and Low SCORE; H2S2, High HbA1c and High

SCORE; SCORE, Systematic COronary Risk Evaluation.

Mean (one standard deviation) are presented unless otherwise stated. Chi-square tests were applied to check for significant differences between subgroups.

		Treat-to-target hypothetical intensive management			
		HbA1c		HbA1c+LDL+BMI	
		Max annual price of intervention (\$)	Δ QALY vs CAU	Max annual price of intervention (\$)	Δ QALY vs CAU
	Overall*	169 (97-222)	0.008 (0.005-0.011)	1499 (1132-1776)	0.073 (0.058-0.09)
RHAPSODY data-driven subgroups	RHAP-MOD	221 (150-296)	0.012 (0.008-0.015)	1973 (1444-2603)	0.112 (0.083-0.146)
	RHAP-MD	116 (67-167)	0.006 (0.004-0.009)	799 (666-966)	0.044 (0.036-0.052)
	RHAP-SIDD	368 (248-477)	0.019 (0.013-0.024)	1504 (1233-1779)	0.079 (0.065-0.092)
	RHAP-MDH	58 (6-111)	0.003 (0-0.005)	1267 (986-1566)	0.061 (0.047-0.075)
	RHAP-SIRD	96 (48-148)	0.004 (0.002-0.007)	1902 (1519-2335)	0.087 (0.069-0.106)
	Range†	309	0.016	1174	0.068
Risk-driven subgroups	H1S1	82 (42-117)	0.004 (0.002-0.006)	930 (723-1182)	0.052 (0.041-0.066)
	H2S1	323 (235-416)	0.017 (0.012-0.021)	1247 (990-1546)	0.069 (0.055-0.084)
	H1S2	69 (23-120)	0.003 (0-0.005)	2356 (1897-2894)	0.105 (0.085-0.129)
	H2S2	270 (164-396)	0.012 (0.007-0.017)	2578 (2080-3100)	0.114 (0.093-0.137)
	Range†	253	0.014	1647	0.062

Table 3 Outcomes of five-year guideline-based intensive management targeting HbA1c, BMI and LDL, and targeting only HbA1c respectively compared to care-as-usual by subgroups in base case U.S. setting

CAU, Care as usual; RHAP-SIDD, Severe Insulin Deficiency Diabetes by RHAPSODY clustering; RHAP-SIRD, Severe Insulin Resistance Diabetes by RHAPSODY clustering; RHAP-MOD, Mild Obesity-related Diabetes by RHAPSODY clustering; RHAP-MD, Mild Diabetes by RHAPSODY clustering; RHAP-MDH, Mild Diabetes with high HDL by RHAPSODY clustering; H1S1, Low HbA1c and Low SCORE; H1S2, Low HbA1c and High SCORE; H2S1, High HbA1c and Low SCORE; H2S2, High HbA1c and High SCORE, SCORE, Systematic COronary Risk Evaluation.

\*Overall refers to a homogenous type 2 diabetes group. (Results were generated based on extrapolations of subgroup-specific linear dynamic models and summarized by subgroup information. The overall result is summarized by the assumption that every individual was within this homogenous type 2 diabetes group. Each extrapolation from either RHAPSODY data-driven subgroups' or risk-driven subgroups' linear dynamic models led to an overall result, and the final overall result was taken as the average

value).

†Range is defined as the maximum – minimum of the mean maximum annual cost-effective price of intervention or incremental QALY.

## Figure Legends

Figure 1 Non-standardized and standardized mean simulated lifetime QALYs and costs with 95% CI (in U.S. setting) for data-driven and risk-driven subgroups.

The horizontal solid line and dashed line indicated the average value and its 95% confidence interval.

QALYs, Quality-Adjusted Life-Years; RHAP-SIDD, Severe Insulin Deficiency Diabetes by RHAPSODY clustering; RHAP-SIRD, Severe Insulin Resistance Diabetes by RHAPSODY clustering; RHAP-MOD, Mild Obesity-related Diabetes by RHAPSODY clustering; RHAP-MD, Mild Diabetes by RHAPSODY clustering; RHAP-MDH, Mild Diabetes with high HDL by RHAPSODY clustering; H1S1, Low HbA1c and Low SCORE; H1S2, Low HbA1c and High SCORE; H2S1, High HbA1c and Low SCORE; H2S2, High HbA1c and High SCORE; SCORE, Systematic COronary Risk Evaluation