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BRIEF REPORT

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Prototype of an evidence-based tool to aid individualized treatment for type 2 diabetes

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Abstract

Data-driven tools are needed to inform individualized treatment decisions for people with type 2 diabetes (T2D). To show how treatment might be individualized, an interactive outline tool was developed to predict treatment outcomes. Individualized predictions were generated for change in HbA1c and body weight after initiation of newer antidiabetes drugs recommended by current guidelines. These predictions were based on data from randomized controlled trials of glucose-lowering drugs. The data included patient demographics and clinical characteristics (sex, age, body mass index, weight, diabetes duration, HbA1c level, current diabetes treatment and renal function). Predicted outcomes were determined using prespecified statistical models from original trial protocols and estimated coefficients for selected baseline characteristics. This prototype illustrates how evidence-based individualized treatment might be facilitated in the clinic for people with T2D. Further and ongoing development is required to improve the tool's prognostic value, including the addition of disease co-morbidities and patient-orientated outcomes. Patient engagement and data-sharing by sponsors of clinical trials, as well as real-world evidence, are needed to provide reliable predicted outcomes to inform shared patient–physician decision-making.

KEYWORDS
antidiabes drug, type 2 diabetes

1 | INTRODUCTION

Current standards of medical care for type 2 diabetes (T2D) promote individualized treatment according to co-morbidities, individual preferences and treatment goals.[1–3] The American Diabetes Association (ADA) Standards of Care guidelines offer examples of important considerations for selecting a T2D therapy for any particular individual, including: the estimated reduction in HbA1c; adverse-event profile; risk of hypoglycaemia; impact on body weight; ease and frequency of administration; cost and availability; adherence to and persistence with therapy; and prevalent complications and co-morbidities.[1] The updated (2020) consensus report by the ADA and the European Association for the Study of Diabetes further emphasizes co-morbidities such as atherosclerotic cardiovascular disease (ASCVD), heart failure (HF) and chronic kidney disease (CKD) as key priorities for individualized care.[3] All these resources promote shared decision-making between patient and physician.[1–3] Clinical practice guidelines clarify how treatment selection can be directed

by high-risk co-morbidities, such as established ASCVD, CKD or HF,[1–3] but are less clear on how patient characteristics, treatment goals and preferences should direct treatment selection, and how this may vary among individuals. Another challenge is the lack of data to help predict potential outcomes in a specific individual. Current guidelines offer summaries of the efficacy, risk of hypoglycaemia, effect on body weight, and cardiovascular (CV) and renal events of the major classes of glucose-lowering treatment, but these are based on pooled outcomes from intention-to-treat analyses, so do not represent expected outcomes for a specific individual.[4] An expert perspective on precision medicine in T2D emphasized that for most people without high-risk co-morbidities, there is often no clear choice to suggest the 'best' antihyperglycaemic medication.[4]

Clinical tools for individualized care have been developed and implemented for other diseases. For example, the Framingham Cardiovascular Risk Score allows for the input of a range of patient-specific characteristics, and provides a risk score for developing heart disease over the next 10 years, with associated indications for different preventative strategies.[5] Drawing inspiration from tools such as this, we have developed a prototype tool to estimate patient-specific outcomes via a user-friendly web interface.

2 | METHODS

2.1 | Data sources

The tool was developed to represent a broad range of treatment regimens by integrating clinical trial data from patients post-treatment (after approximately 6 months). The trials included head-to-head and placebo-controlled comparisons of glucagon-like peptide-1 receptor agonists (GLP-1RAs), insulin, insulin and GLP-1RA combinations, dipeptidyl peptidase-4 inhibitors (DPP-4is), sodium-glucose co-transporter-2 inhibitors and sulphonylureas (Table **S1**). Trials that focused on specific co-morbidity–related endpoints (e.g. CV or renal) were not included. Table **S1** contains a brief description of these randomized clinical trials (RCTs), including the number of patients enrolled, background medication, trial length and study arm or interventions.

2.2 | Inputs and predicted outcomes

Inputs to the tool included a person's sex, age, body mass index (BMI), body weight, diabetes duration, HbA1c (in mmol/mol and %), current antidiabes/glucose-lowering treatment class, renal function (as defined by estimated glomerular filtration rate [eGFR]: normal function ≥90 mL/min/1.73 m^2, mild impairment eGFR 60 to <90 mL/min/1.73 m^2, moderate impairment eGFR 30 to <60 mL/min/1.73 m^2 and severe impairment eGFR <30 mL/min/1.73 m^2), and possible treatment options (Figure 1). The predicted treatment outcomes in the tool were estimated based on data from the listed RCTs (Table **S1**). These are changes in HbA1c and body weight after 26–30 weeks of treatment. After entering specific inputs, the tool is able to select an appropriate trial from the database to show predicted treatment outcomes.

2.3 | Statistical methods

The predicted treatment outcomes were determined using the prespecified mixed models for repeated measurements from the original trial protocols for the chosen efficacy endpoints, which are changes in HbA1c level and body weight. Both endpoints are quantified on a continuous scale and were therefore analysed using a linear normal model. This is also in line with how these endpoints were analysed according to the protocols for all the individual RCTs included. The model has been adopted and modified only by the inclusion of additional covariates and interaction terms. Additional covariates (e.g. renal function) were specified in some trials to represent individuals' characteristics, where available. The predictions used the estimated coefficients for the baseline characteristics determined in the model using the totality of the data. For example, in the interface illustrated in Figure 1—for a 55-year-old woman who has had T2D for 5 years, with an HbA1c of 9% (75 mmol/mol), BMI between 30 and 35 kg/m^2, and normal renal function—the estimated reduction in HbA1c was determined using a mixed model for repeated measurements nested within treatment visits. Thus, there is an intercept, main effects for all input variables, as well as interaction terms with visits, and also between HbA1c at baseline and diabetes duration.

3 | RESULTS

We have developed an interactive, online prototype tool based on high-quality data from RCTs of glucose-lowering therapies in individuals across the spectrum of T2D treatment (Figure 1). This tool can be accessed at https://t2-treatment-effect-estimator-prototype.com/treatment_app. This tool is a prototype, is not suitable for clinical use, and is provided only to show how an individualized treatment tool might help to support decision-making for patients with T2D.

To use the tool, an individual or healthcare provider enters an individual's specific data and selects a treatment from the list of choices available on the tool. Rather than reporting the change in the effect estimate for the average trial participant, the tool shows the predicted outcomes for a specific individual with T2D. Predicted outcomes may be generated in series for any number of treatment options represented in the tool's databases.

Figure 2 and Table S2 show the estimated changes in treatment outcomes (changes in HbA1c and body weight) in four individual scenarios with different characteristics, after different treatment options have been chosen. These examples are based on actual participants from the RCTs, and on fictional variations in these participants' characteristics, to provide an overview of typical scenarios that physicians may encounter in the clinic.

4 | DISCUSSION

This prototype individualized treatment selection tool was developed to illustrate how data-driven instruments might be used in the future for the management of people with T2D in the clinical setting.

A key strength of the prototype is that person-specific information can be inputted to drive treatment-outcome predictions. Thus, the output is based on the individual characteristics of an individual presenting in the clinic who may be similar to a particular trial participant, rather than an average trial participant. Several existing web-based tools support shared decision-making for people with T2D, including the Diabetes Medication Choice Decision Conversation Aid (CompareDiabetesDrugs.com)[6] and the clinical trial simulator feature of CompareDiabetesDrugs.com.[7] However, the Diabetes Medication Choice Decision Conversation Aid does not include all approved T2D treatment classes, and neither tool offers estimations on an individual basis. Other possible strengths of our prototype tool include its potential to support T2D healthcare providers in elucidating the benefit–risk profile for a given treatment in a specific individual. The magnitude and quality of data in the current version of the tool are based on similarly designed studies conducted under closely comparable conditions, which were subsequently used to generate the patient-specific outputs. Data integrated into the prototype tool are from rigorously conducted RCTs with well-defined protocols and ongoing data-quality monitoring for a large number of recruited participants (Table **S1**). The studies included were broadly selected among phase 3 programmes to reflect larger patient populations and longer duration of follow-up from among the sponsor's portfolio of antihyperglycaemic therapies broadly relevant in T2D.

Patient characteristic	Range of options that can be selected
Age, years	20–90
BMI, kg/m²	18–60
Diabetes duration, years	0–30
HbA1c, %	5.5–18.0
HbA1c, mmol/mol	30–180
Current treatment class	Diet and exercise GLP-1RA Insulin (long-acting) 1–2 OGLDs*
Sex	Male Female
Renal function†	Normal Mild impairment Moderate impairment Severe impairment
Treatment options	DPP-4i GLP-1RA Insulin (long-acting) + GLP-1RA Insulin (long-acting) Metformin SGLT2i SU

Visual representation of prototype tool user interface

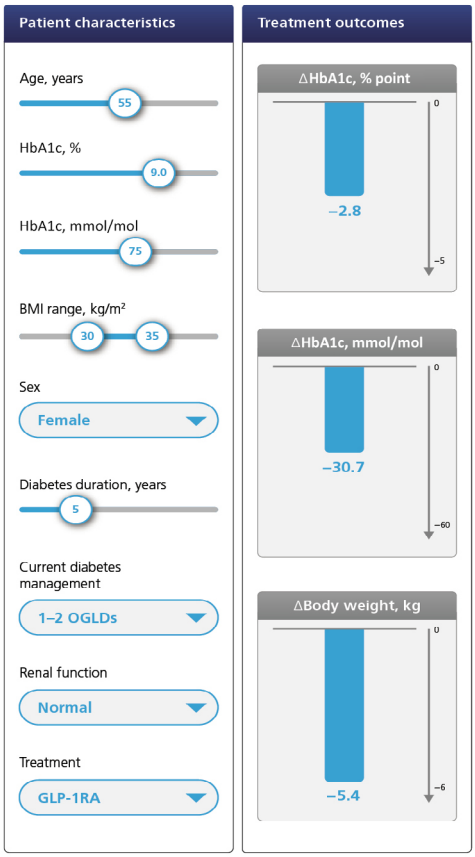

FIGURE 1 Inputs to the data-driven individualized treatment tool for people with type 2 diabetes (T2D). *Oral glucose-lowering drugs (OGLDs) include metformin, thiazolidinediones, sulphonylurea (SU), sodium-glucose co-transporter-2 inhibitors (SGLT2is), glinides, dipeptidyl peptidase-4 inhibitors (DPP-4is) and alpha-glucosidase inhibitors. †Mild, moderate and severe renal impairment was defined by estimated glomerular filtration rates, respectively, of 60–<90, 30–<60 and <30 mL/min/1.73m^2. BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist

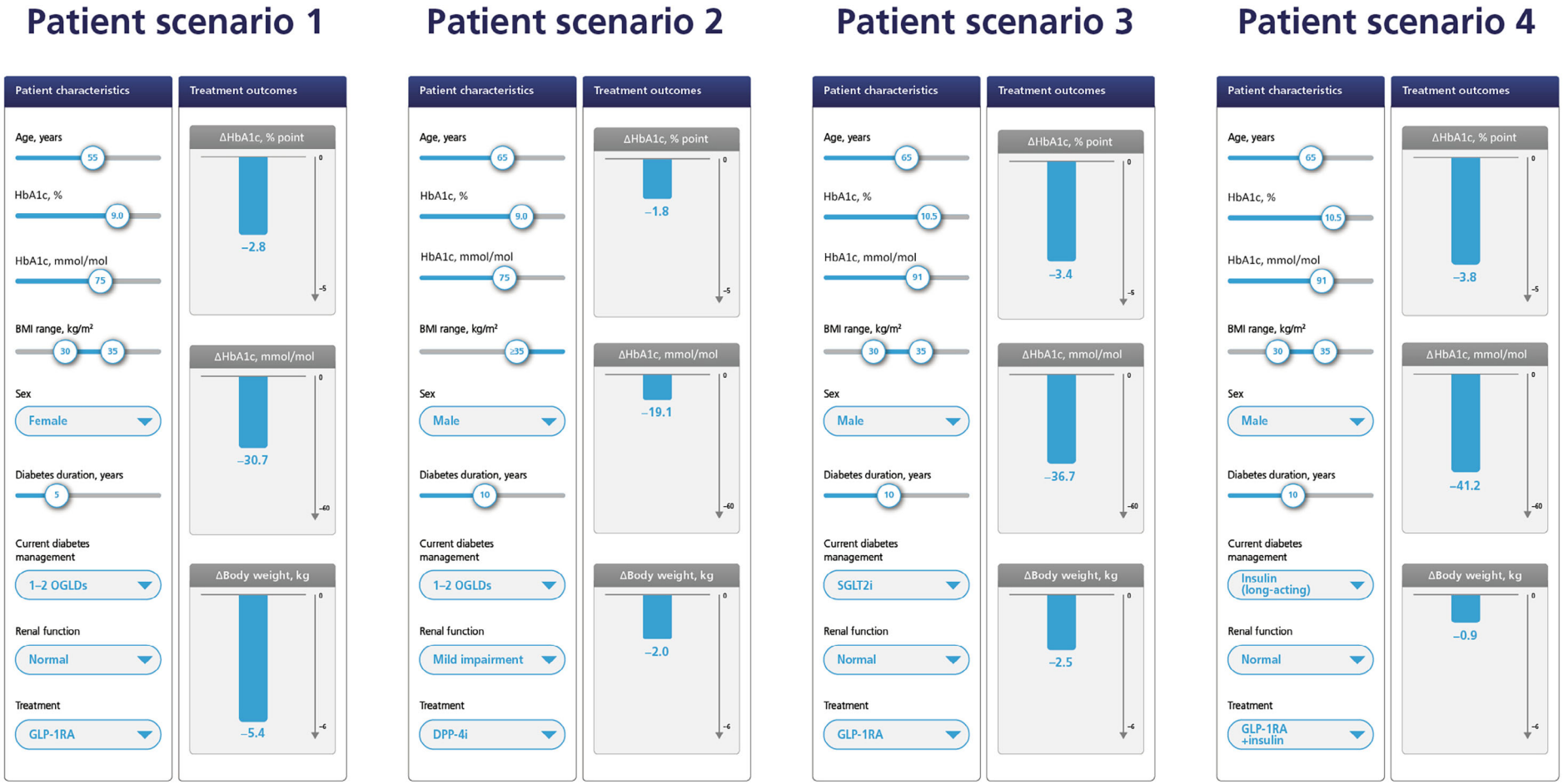

FIGURE 2 Examples of the prototype tool display for four different individual scenarios. The user inputs a person's characteristics, such as age, body mass index (BMI) and type 2 diabetes (T2D) duration, using the sliders on the left; the tool then estimates outcomes with the selected treatment option, in this case once-weekly subcutaneous glucagon-like peptide-1 receptor agonist (GLP-1RA) for 26 weeks. In scenario 1, if a person with an HbA1c of 9.0% (75 mmol/mol) receives treatment of once-weekly subcutaneous GLP-1RA, such as semaglutide 1.0 mg, the predicted outcomes would be HbA1c reduction of 2.7% and body weight reduction of 5.3 kg. This figure shows an example with only a selection of a person's characteristics across four separate scenarios. The final tool could allow for additional patient characteristics to be inputted and additional predicted treatment outcomes to be displayed. Outcomes are generated from different datasets, so it is not valid to compare directly effects across medication regimens. However, estimates may still be evaluated for individual, specific therapies with respect to patient treatment goals and values to select an optimal therapy. The examples shown here are based on data from participants from the SUSTAIN trials, and on hypothetical variations of these patients' characteristics. DPP-4i, dipeptidyl peptidase-4 inhibitor; OGLD; oral glucose-lowering drug; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Some limitations of this prototype tool are a result of the RCT data used to build it, all of which were from trials conducted by Novo Nordisk. Bias in participant enrolment for RCTs limits the generalizability of outcomes to all people with T2D. For example, an RCT may enrol participants receiving a specific treatment and with few treatment-related complications, which may under-represent certain groups of people with T2D in real-world clinical settings, such as older, frail individuals, and racial and ethnic minorities. Furthermore, the data used to generate the treatment-outcome predictions derive only from treatments investigated in a specific and controlled clinical trial development programme, with prespecified follow-up times. The trials included are from multiple development programmes within Novo Nordisk and were designed to meet the requirements of registration studies. These data are therefore not wholly reflective of individuals seen in daily practice. Another limitation is its incapability to make direct comparisons between potential treatments and therefore to display results for more than one treatment option at a time. This limitation may be addressed by building a platform for data sharing, particularly of studies representing a larger number of comparators for any given treatment (e.g. for DPP-4is, which have been well studied in multiple comparator trials). In addition to making treatment comparisons, the reliability of the tool could be increased if clinical trial sponsors were to share individual participant data with the tool developer to produce a more robust data platform. The scope and utility of the tool could be augmented by international collaborations and by using other data sources, such as real-world evidence studies and studies of CV, renal and HF outcomes, to create a broad, fully relevant and applicable evidence base.[8] Finally, development of a refined tool to predict treatment outcomes requires both internal and external validity,[9] as well as reproducibility and transportability.[10]

There are multiple opportunities for enhancements to this prototype. First, the range of inputs could be extended, for example, to include treatment targets. Second, outcome estimations could be broadened to include adverse events, such as CV outcomes, hypoglycaemia risk where relevant, and cost or coverage for users based on country and/or insurance coverage, with appropriate specifications for each outcome model.[4] Third, people with T2D could be engaged as part of the development process to ensure that the patient perspective is represented in the tool.[8] Fourth, individualized treatment decisions may be improved by the collection and inclusion of patient characteristics currently under-represented, such as comorbid HF, ASCVD or CKD, as well as specific patient-oriented information such as treatment-modality preference, short-term versus long-term treatment goals, socioeconomic considerations and health literacy. Patient preferences are not routinely collected in trials or observational studies, although a tool such as the prototype shown can facilitate patient–provider exploration of preferences in shared decision-making based on predicted individualized outcomes. Characteristics of the treatments of interest (e.g. oral administration vs. subcutaneous injection) can also be considered. As research continues to advance the goal of offering probabilistic, individualized predictions for diabetes treatment, there may be opportunities to integrate novel statistical methods to maximize robustness while minimizing bias.[4]

In conclusion, this prototype illustrates how evidence-based individualized treatment selection may be realized in the clinic for people with T2D. Such an instrument would be welcomed to assist physicians in optimizing individualized treatment for their patients.

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CONFLICT OF INTEREST

JBB's contracted consulting fees and travel support for contracted activities are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Dexcom, Eli Lilly, Fractyl, GI Dynamics, Intarcia Therapeutics, Lexicon, MannKind, Metavention, NovaTarg, Novo Nordisk, Orexigen, PhaseBio, Sanofi, Senseonics, vTv Therapeutics and Zafgen; he reports grant support from AstraZeneca, Eli Lilly, Intarcia Therapeutics, Johnson & Johnson, Lexicon, Medtronic, NovaTarg, Novo Nordisk, Sanofi, Theracos, Tolerion and vTv Therapeutics; he is a consultant to Cirius Therapeutics Inc., CSL Behring, Fortress Biotech, Mellitus Health, Moderna, Neurimmune AG, Pendulum Therapeutics, Praetego, Stability Health and Zealand Pharma; and he holds stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio and Stability Health. IH is an employee of Novo Nordisk. FKK reports grants, personal fees and non-financial support from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Carmot Therapeutics, personal fees and non-financial support from Eli Lilly, grants from Gubra, personal fees from MedImmune, personal fees and non-financial support from MSD/Merck, personal fees from Norgine, grants, personal fees and non-financial support from Novo Nordisk, grants and personal fees from Sanofi, grants and personal fees from Zealand Pharma, personal fees from Bayer, outside the submitted work. KK and DT are employees of Novo Nordisk and own stock in the company. RP reports non-financial support from Pfizer Inc. and Merck & Co., Inc. during the conduct of the study; consulting fees from AstraZeneca; consulting fees from Glytec, LLC; grants from Hanmi Pharmaceutical Co.; grants and consulting fees from Janssen; consulting fees from Merck; consulting fees from Mundipharma; grants, speaker fees and consulting fees from Novo Nordisk; consulting fees from Pfizer; grants from Poxel SA; grants and consulting fees from Sanofi; consulting fees from Scohia Pharma Inc.; consulting fees from Sun Pharmaceutical Industries;

and personal consulting fees from Sanofi US Services, Inc., outside the submitted work. Except for consulting fees in February 2018 and June 2018 from Sanofi US Services, Inc., RP's services were paid for directly to AdventHealth, which is a non-profit organization.

AUTHOR CONTRIBUTIONS

All authors contributed to conception, drafting, editing and approval of the final manuscript for publication. KK developed the model for the prototype tool and had full access to the data.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14381.

DATA AVAILABILITY STATEMENT

The data that support this brief report are openly available from the website for the prototype tool: https://t2-treatment-effect-estimator-prototype.com/treatment_app/

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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