Towards a personalized medicine approach in diabetes type 2 secondary care:

implementation of personalized medicine approach in Dutch diabetes secondary care, from the perspectives of healthcare professionals

Faculty: Science and Technology

Student: Iana Pazenko, 2716135

Supervisors:

Dr. Janine van Til

Dr. Ria Wolkorte

Abstract

Introduction

Currently, the management of T2DM is driven by international guidelines. However, these guidelines do not offer guidance to individualized or personalized management. Not every patient with diabetes with the same age, duration of disease, body mass index, and Hemoglobin A1c (HbA1c) will respond the same way to a given treatment. Therefore, there is a need for personalization in medicine. Personalized medicine in diabetes care takes into account comorbidities, personal factors, biomarkers, genetic factors, healthcare resources, medication usage, diabetes phenotype. This study aimed to gain insight on whether different components of personalized medicine are currently integrated in Dutch diabetes type 2 secondary care, from the perspectives of healthcare professionals. Additionally, the study also intended to identify the facilitating and impeding factors that influence the implementation of the personalized approach in diabetes secondary care.

Methods

Semi-structured interviews with Dutch diabetes healthcare professionals were conducted. Topics addressed during the interviews included the elements that can be tailored within a personalized approach in type 2 diabetes care. Interviewees were 5 professionals working in secondary care, including 4 internists-endocrinologists and 1 diabetes nurse. Deductive coding was used to analyze the interviews. Coding frames were developed prior to coding based on theoretical frameworks. To answer each research question, different codes and different frameworks were used.

Results

The study revealed that diabetes healthcare professionals in Dutch secondary care partially integrate personalized medicine into their care delivery. While they already actively use such components of the personalized approach, as comorbidities, medication usage, diabetes phenotype, and personal factors, other components, such as genetic factors, biomarkers, and healthcare resources are not effectively used. Factors as high evidence, the lack of limitations in healthcare resources, skills of healthcare professionals that allows them to involve patients in decision making, were identified as facilitating factors. Meanwhile, factors including limited healthcare resources, low evidence of the effectiveness of personalizing care based on genetic factors, outdated guidelines that do not mention personalization, and resistance of healthcare professionals were identified as impeding factors.

Conclusion

This research gained insight on whether and how concepts of personalized medicine are currently integrated in Dutch diabetes type 2 secondary care, from the perspectives of healthcare professionals. Additionally, the study also revealed the impeding and facilitating factors that influence on the implementation. Further research should involve other stakeholders, such as patients, and focus on how to eliminate the impeding factors, to gain more insight into the effectiveness on using genetic factors. The guidelines that healthcare professionals currently use should be updated towards personalization, the promotion of using personalized approach in diabetes care should be conducted in medical institutions.

List of content

1 Introduction

Diabetes Mellitus (DM) is a multifactorial chronic disease caused by genetic and/or environmental factors [1]. The global prevalence of Type 2 Diabetes Mellitus (T2DM) is rapidly growing; its prevalence has quadrupled in the last decades, and the number of T2DM patients is expected to exceed 510 million by 2030 [2]. Diabetes affects around 1.1 million people in the Netherlands (2020). Every year, more than 50.000 new cases of DM are diagnosed throughout the country [3].

For many years, T2DM has been called as non-insulin dependent diabetes, characterized by progressive insulin resistance [1]. Insulin is a pancreatic hormone that controls blood sugar levels (glycemia). The main characteristic of T2DM is high blood sugar levels due to low concentration or activity of insulin [4]. Medication therapy and insulin are used to keep blood glucose levels close to normal. Such treatment also helps to delay or even prevent the development of comorbidities associated with diabetes [5]. Moreover, a healthy diet and sufficient physical activity help to manage the disease. Type 2 diabetes is often mitigated through lifestyle changes and preventative measures such as diet change, increased exercise, and overall holistic integration of health [6]. Without management, the disease may cause such complications as cardiovascular diseases, hyperglycemia, insulin-resistance, low-grade inflammation and accelerated atherogenesis, diabetic kidney disease [7].

Currently, the management of T2DM is driven by international guidelines. Management aimed at lowering glycemia consists of the gradual adding drugs to lifestyle changes for reducing weight and increasing the amount of physical exercises. Pharmacotherapy starts with one oral agent and progress to combination of such agents with insulin, depending on the progressive inability of the drugs to sustain target glycemic levels. This approach is uniform [8]. Until recently, international guidelines did not consider presence of comorbidities and individual characteristics of patients as drivers of treatment choice. These guidelines describing recommended treatment options are based on population-based studies and evidence from Phase 3 clinical trials. Although these recommendations have significantly changed the approach to diabetes care, they do not offer guidance to individualized and personalized management. However, recent recommendations of the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) include tailoring therapy taking into account life expectancy, risk of hypoglycemia, patient attitudes, comorbidities, disease duration, and resources [9].

Even if patients with diabetes have the same Hemoglobin A1c (HbA1c) levels, age, body mass index, and duration of the disease, there is no guarantee that they react similarly on the specific treatment [10]. The healthcare professional has to assess each patient to determine the treatment that will most likely be effective. This can be a difficult endeavor for the physician. Average outcomes on the group level obtained in clinical trials represent the particular ratio of patients that will respond to a specific treatment. However, these outcomes may be not necessarily applicable to a given patient. The problem is that physicians do not know what treatment can help a particular patient. Currently, the first choice of healthcare professionals is the therapy that has a high chance to be effective for the biggest amount of patients, despite the fact that this therapy will not work for some individuals [10].

Therefore, there is a need for personalization in medicine.

Personalized medicine is the tailoring of medical treatment to the individual characteristics of each patient [11]. This includes prescribing a specific treatment to particular patients based on specific information about them, increasing the capacity to estimate which treatment options will be helpful and safe for each individual and which will not. Advancements in quantitatively predicting responses to various therapy alternatives, properly analyzing patient preferences, understanding genetic basis of the disease, and quantifying individual risk are necessary to apply personalize medicine [2]. This may provide the opportunity to overcome two potential reasons of the ongoing morbidity and mortality associated with T2DM. These are 1) the suboptimal application of evidence-based therapies (e.g., due to lack of

medication intensification or insufficient lifestyle interventions or medication adherence by patients) and 2) inadequate efficacy of current therapies when used optimally [9].

Generally, personalized medicine in diabetes care might include a lot of complex factors: medical factors (including diabetes-related complications), patient personal factors (such as patient preferences), social, genetic, biochemical, and phenotypic factors (Figure 1). These factors are described in more detail below.

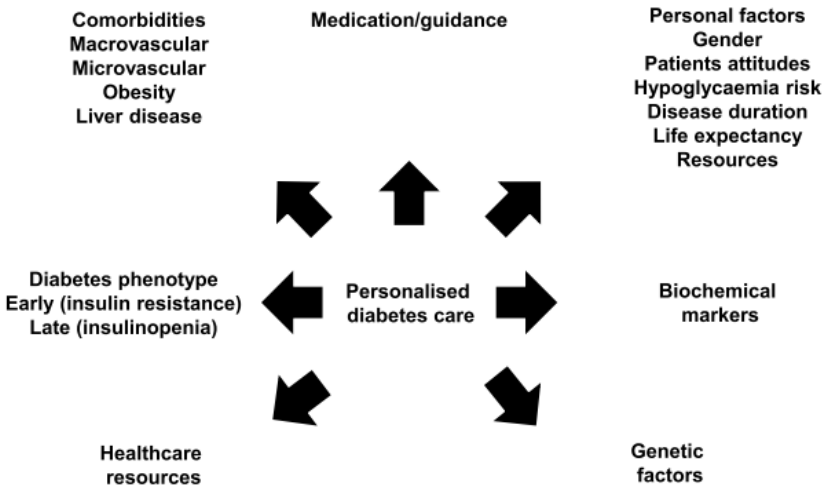

Figure 1. *Personalized diabetes care. This figure summarizes the key considerations that are needed when contemplating the choice of diabetes pharmacotherapy for a patient with T2DM* [9].

The first factor based on which diabetes treatment could be personalized is **comorbidity.** Medical comorbidities such as cardiovascular disease, diabetes kidney disease (DKD), liver disease, obesity and hypertension could impact the physician's choice of medication. Furthermore, existing diabetes risk engines could estimate cardiovascular risk based on key diabetes-related parameters such glycemia, blood pressure, dyslipidemia, smoking status, age, gender, and family history. Kidney function and other parameters may be included in more complicated tools [12].

Next, **personal factors** could also influence treatment intensity and medication selection. Patients' treatment preferences, expectant life span and age, duration of diabetes, hypoglycemia risk, psychological and social settings are all factors to take into account [9]. Patients with comparable demographic and comorbidity characteristics may distinguish in their personal goals and values of outcomes. These goals and preferences can impact the choice of adding lifestyle interventions, with or without health technologies, or starting pharmacotherapy and using insulin [12]. Latest developments in healthcare delivery technologies such as smartphone applications, telemedicine, mHealth, device connectivity (for example Continuous Glucose Monitoring (CGM) devices to continuously measure glucose values), machine-learning technology, and artificial intelligence, provide a significant opportunity to improve diabetes management efficiency. Also, they allow to increase patient engagement in diabetes self-management, that ultimately could reduce diabetes-related healthcare costs [13].

Biochemical markers can be used in clinical practice help with diabetes diagnosis and management. For example, antibody testing (e.g., Glutamic acid decarboxylase antibodies (GADA), anti-tyrosine phosphatase (anti-IA-2), islet cell autoantibodies (ICA)), and urinary C-peptide to differentiate between T1DM and T2DM. Higher antibody titers indicate a higher risk of underlying autoimmune diabetes and, as a result, the necessity for insulin therapy now or in the future. Lower urine C-peptide levels indicate decreased endogenous insulin production and, consequently, an increased requirement for exogenous insulin treatment. The urinary C-peptide level can also help to place a patient with T2DM in the latter

phases of the diabetic spectrum, indicating the necessity for insulin therapy. Nevertheless, the presence (or lack) of these biomarkers correlates with response to non-insulin- and insulin-based T2DM therapy, and frequently drives personalized treatment decisions in contemporary clinical practice [9].

Also, diabetes care could be personalized based on **genetic factors.** Healthcare professionals already use genetic testing to differentiate (Maturity onset diabetes of the young) MODY. However, it is used for the diagnostics, but not for personalization. Significant research has been conducted in the last decade to examine the genetics of T2DM. One of personalized medicine's long-term aims is to uncover genetic markers that will allow to tailor treatments to the individual. One of the difficulties in this area is that several genes and genetic variations can impact the T2DM phenotype. The situation is multifaceted, as is the "efficacy" of genetics in determining responders and non-responders to specific therapy. Although there is a link between genetic make-up and response to diabetes treatments in individual patients, few researches have shown significant pharmacogenomics in this regard [9].

Diabetes phenotype could also be a key consideration. Due to the complexity of physiologic pathways and the underlying genetic variation that determines different phenotypes (e.g., in insulin production, insulin resistance, and lipid processing), there is a strong case to be made for treating T2DM as a broad definition for a wide range of slightly distinct pathophysiologic problems with closely related final metabolic processes. This framework is the primary rationale for genetic dissection and the hope for personalized therapy [8].

Current medication prescriptions could influence the choice of the treatment for a specific patient. Physicians need to take into account the current use of medications by patients due to possible drug incompatibilities and the following consequences. For instance, certain kinds of medicine should be avoided by individuals with DKD, either because they are linked with a higher likelihood of side effects or because they have a lower efficacy for blood sugar level control [14].

Factors connected to **healthcare resources** may also have a negative influence on achieving target glycemic control. An absence of integrated care in many health systems, as well as clinical conservatism among health professionals, are two healthcare variables that may have an impact on patients. Higher expenditures for outpatient care, emergency department visits, hospitalization, and managing diabetic complications may have an impact on treatment personalization and therapy selection [15].

In general, the ideal of personalized medicine is that each patient receives the management plan best suitable to them. This entails implementing a treatment approach that is in line with the patient's goals and preferences, as well as individual risks and the patient's unique underlying illness pathophysiology and medication metabolism profile.

There is currently a little widespread implementation of personalized medicine in diabetes mellitus care and a limited evidence for how to effectively implement truly personalized care [12][16]. There are still several impediments to effective implementation in practice. Implementation requires involvement of different stakeholders, such as patients and patient advocates, basic scientists and clinical academic researchers, pharmaceutical industry representatives, pharmaceutical regulators, health technology assessors (HTAs) and healthcare professionals (HCPs). To implement personalized medicine successfully, early participation and goal alignment among stakeholders are critical [17]. Identification of obstacles to implementation of personalized medicine in diabetes care can later be used to develop strategies that would assist patients and healthcare institutions in overcoming barriers to implementation [18]. Moreover, there are still a number of problems that have to be solved before this approach may be used generally. These are, according to the literature, a paucity of data on the nature of diabetes in different populations, as well as inequalities in the availability and cost of various diagnostic and treatment modalities [9].

2 Research objective

About 17% of Dutch patients with type 2 diabetes are treated in secondary care, by a medical specialist, due to the complexity of their condition. Complex diabetes cases include patients who cannot reach glycaemic control in primary care or patients who need a more intricate treatment for complications or risk factors (e.g., treatment resistant cardiovascular risk factors, diabetes kidney disease, insulin-resistance) under management of a medical specialist [19]. Personalized medicine is even more important for these complex patients because their health condition is more severe than that of patients treated in primary care, and they have more need for using medical technology (e.g. CGM), as well as for taking into account already present comorbidities when developing the treatment plan.

The aim of the study is to gain insight on whether and how concepts of personalized medicine are currently integrated in Dutch diabetes type 2 secondary care, from the perspectives of healthcare professionals. Moreover, in this study we aim to identify the facilitating and impeding factors that influence on the implementation. The objective of obtaining this information is to provide recommendations for the further implementation on this approach.

This leads to the following research questions:

To what extent do diabetes healthcare professionals in Dutch secondary care integrate personalized medicine into their care delivery?

Which facilitating and impeding factors influence the implementation of the personalized medicine approach in Dutch T2DM secondary care?

In the next chapter, the theoretical framework behind the study approach is explained. In chapter 4, the methodological approach is described.

3 Theoretical framework

This chapter describes the definition of implementation. SWOT (Strengths, Weaknesses, Opportunities, and Threats) framework, CFIR (Consolidated Framework for Implementation Research), and PARiHS (Promoting Action on Research Implementation in Health Services) are represented as potential frameworks.

3.1 Implementation

In this study, we use the definition of Zorg Onderzoek Nederland (ZON) as they described implementation in 1997 as: “a process-based and systematic introduction of renewal and/or improvements (of proven value) with the aim that these are given a structural place in (professional) practice, in the functioning of the organization(s) or in the structure of healthcare” [20]. To begin, the assumption is that process-based and planned implementation is inherent in innovation. There is the claim that in order to achieve change, innovation requires a plan that anticipates multiple drivers. Then, it refers to innovations or enhancements that are thought to be newer, better, or distinct from the gold standard. Next, innovation becomes structurally embedded in professional practice, and finally, innovations can emerge at many levels within an organization or setting. As a result, 'implementation' entails far more than simply putting an innovation to use.

De Vries et al investigated different aspects for implementing of the personalized approach in treatment of diabetes and diabetes kidney disease (DKD) (from the perspective of patients, payers and global perspective (Figure 2).

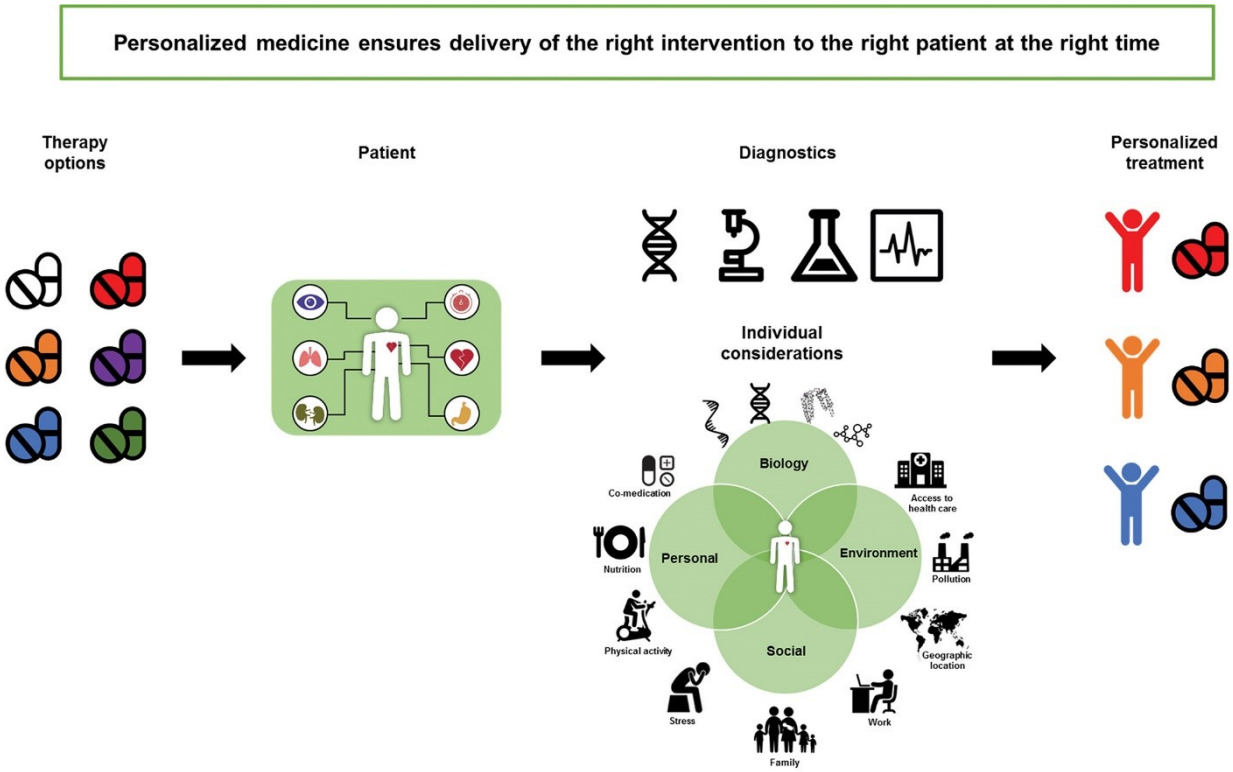

Figure 2. *Implementing personalized medicine includes suitable therapy options for a single patient's-specific illness and stage (co-morbidities), using appropriate diagnostic tools and tailoring therapy to the patient's individual circumstances including underlying biology of the disease, environmental, social and personal factors (indicated by the green circles in the figure)* [21].

According to patients, payers and global perspective, clinical practice guidelines should incorporate more accurate risk stratification and more precise treatment alternatives [21]. It is critical to treat the patients as an individual with their own specific social and environmental circumstances. Culture, resources, access

to healthcare, and prevalence vary widely around the globe, therefore the sociological and environmental context must be explored. The economic efficiency of personalized medicine must be evaluated, since not only the cost of new therapies but also the cost of diagnosis using novel methodology and complications must be considered. All of these factors have to be taken into account while implementing personalized medicine [21].

3.2 SWOT analysis

The SWOT analysis (Figure 3) is a tool for the identification of environmental relationships and complex strategic decision making and has been applied in the health care sector to identify internal and external subthemes and their interdependencies. Internal strengths and weaknesses have to be considered, as well as external opportunities and threats. SWOT analysis helps in the discovery of environmental relationships and the building of appropriate pathways [22].

Figure 3. *Model of SWOT-analysis*

SWOT analysis is commonly defined as a set of guidelines used to compare internal resources and capabilities against external developments. It consists of the following phases in its simplest basic form:

- (1) Identify external developments as opportunities or threats;
- (2) Identify internal means and capabilities as strengths or weaknesses.
- (3) Contrast strengths and weaknesses with opportunities and threats;
- (4) Apply the findings to develop strategic choices.

A conflict of stakeholder expectations, resources, and changes in contextual elements has to be involved in a strategic analysis in healthcare. This confrontation also makes it much easier to recognize what are the strengths, weaknesses, opportunities, and threats [23].

The SWOT approach is well-structured and enables qualitative, descriptive, and cross-sectional analysis. Data saturation can be achieved by including all available participants, by interviewing participants who had different perspectives and by exploring the insights and experiences of the stakeholders. The SWOT-analysis has already been used to qualitatively analyze the strengths, weaknesses, opportunities, and threats influencing the implementation of the health care intervention [24], [25].

3.3 CFIR

The Consolidated Framework for Implementation Research (CFIR) multilayered framework for substantiating an innovation's implementation process. The framework includes a taxonomy that may be used to identify facilitators and barriers to implementation. The taxonomy may be used in a variety of health settings, ranging from clinical treatment implementation to public health activities. The intervention is easily adaptable to fit the intended implementation setting. The taxonomy is composed of several domains and constructs that are based on the findings of several implementation studies [26].

The CFIR consists of five interactive domains: 1) intervention characteristics, 2) outer setting, 3) inner setting, 4) characteristics of the individual, and 5) process of implementation.

- The first domain, 'intervention features,' refers to how well the intervention fits into the intended situation.

- The second domain, 'outer setting,' focuses on an organization's external context. This might refer to the social, economic, or political environment.

- The third domain, 'inner setting,' refers to the qualities of an organization's cultural, structural, and political setting.

- The fourth domain, 'individual characteristics,' is about the people engaged in the implementation.

- The final domain of 'process of implementation' is made up of several interconnected subprocesses. It refers to the change process required for intervention implementation.

Constructs further define the five domains (Table 1). The constructs work together to impact the implementation of an innovation. When using the CFIR, the researcher is not required to include all constructs but may select to include those that are important to the implementation process. The constructs assist the researcher in guiding an evaluation of the implementation context, assessing implementation advancement, and clarifying findings in science publications or quality improvement programs [26].

Table 1. *CFIR domains and constructs according to Damschroder, 2009* [26].

I. Intervention characteristics	
A. Intervention source B. Evidence Strength & Quality C. Relative advantage D. Adaptability	E. Trialability F. Complexity G. Design quality and packaging H. Cost
II. Outer setting	
A. Patient needs & resources B. Cosmopolitanism	C. Peer pressure D. External policy & incentives
III. Inner setting	
A. Structural characteristics B. Networks & communications C. Culture	D. Implementation climate E. Readiness for implementation
IV. Characteristics of individuals	

A. Knowledge & beliefs about the intervention B. Self-efficacy C. Individual stage of change	D. Individual identification with an organization E. Other personal attributes
V. Process	
A. Planning B. Engaging	C. Executing D. Reflecting & evaluating

3.4 PARiHS framework

The PARiHS (Promoting Action on Research Implementation in Health Services) framework views successful research implementation as a function of evidence, context, and facilitation. According to the framework, these aspects have a dynamic, simultaneous connection. The three factors, evidence, context, and facilitation, are all ranked from high to low. The notion is that in order for evidence implementation to be effective, there must be clarity regarding the sort of evidence being utilized, the quality of context, and the type of facilitation required to support a successful change process [27].

According to Rycroft-Malone, 2004 [27] *evidence* should be considered as "knowledge derived from a variety of sources that has been subjected to testing and has found to be credible." The PARIHS framework specifies them as research, clinical experience, patient experience, and local data/information.

The term *context* is used in the PARIHS framework to refer to the environment or setting in which individuals receive healthcare services, or, in the context of putting research evidence into practice, the environment or setting in which the proposed change is to be implemented.

In the context of the PARIHS framework, *facilitation* refers to the process of facilitating (making simpler) the implementation of evidence into practice. Thus, facilitation is achieved by an individual performing a specific function (a facilitator) with the goal of assisting others. This implies that facilitators are those who have the necessary abilities, skills, and expertise to assist individuals, teams, and organizations in putting evidence into practice.

Implementation is more likely to be effective if each sub-element is deemed to be toward high. Therefore, when all of the factors are toward high (Table 2), effective implementation is more likely. As a result, evidence must be strong, match professional agreement, and, when applicable, contain local data (high evidence). When there are supportive cultures, competent leadership, and suitable evaluating mechanisms, the context will be more responsive to change (high context). Finally, sufficient facilitation should be provided to aid implementation (high facilitation). The goal for implementers then is to shift toward the right side of the continuum, where evidence, context, and facilitation are high.

Table 2. *Elements of the Promoting Action on Research Implementation in Health Systems (PARiHS) framework according to Rycroft-Malone, 2004* [27].

Sub-elements		
Elements	Low	High
Evidence		
Research	• Poorly conceived, designed, and/or executed research • Seen as the only type of evidence	• Well-conceived, designed, and executed research, appropriate to the research question • Seen as one part of a decision • Valued as evidence

	• Not valued as evidence • Seen as certain	•Lack of certainty acknowledged •Social construction acknowledged • Judged as relevant • Importance weighted • Conclusions drawn
Clinical expertise	• Anecdotal, with no critical reflection and judgment • Lack of consensus within similar groups • Not valued as evidence • Seen as the only type of evidence	• Clinical experience and expertise reflected upon, tested by individuals and groups • Consensus within similar groups • Valued as evidence • Seen as one part of the decision • Judged as relevant • Importance weighted • Conclusions drawn
Patients expertise	• Not valued as evidence • Patients not involved • Seen as the only type of evidence	• Valued as evidence • Multiple biographies used • Partnerships with healthcare professionals • Seen as one part of a decision • Judged as relevant • Importance weighted • Conclusions drawn
Local data/information	• Not valued as evidence • Lack of systematic methods for collection and analysis • Not reflected upon	• No conclusions drawn • Valued as evidence • Collected and analyzed systematically and rigorously • Evaluated and reflected upon • Conclusions drawn
Context		
Culture	• Unclear values and beliefs • Low regard for individuals • Task-driven organization • Lack of consistency • Resources not allocated • Well integrated with strategic goals	• Able to define culture(s) in terms of prevailing values/beliefs • Values individual staff and clients • Promotes learning organization • Consistency of individual's role/experience to value Relationship with others Teamwork Power and authority Rewards/recognition • Resources—human, financial, equipment – allocated • Initiative fits with strategic goals and is a key practice/patient issue
Leadership	• Traditional, command, and control leadership	• Transformational leadership • Role clarity • Effective teamwork

	• Lack of role clarity • Lack of teamwork • Poor organizational structures • Autocratic decision-making processes • Didactic approaches to learning/teaching/managing	• Effective organizational structures • Democratic-inclusive decision-making processes • Enabling/empowering approach to teaching/learning/managing
Evaluation	• Absence of any form of feedback • Narrow use of performance information sources • Evaluations rely on single rather than multiple methods	• Feedback on Individual Team System performance • Use of multiple sources of information on performance • Use of multiple methods Clinical Performance Economic Experience evaluations
Facilitation		
Purpose	Task	Holistic
Role	Doing for others	Enabling others
	• Episodic contact • Practical/technical help • Didactic, traditional approach to teaching • External agents • Low intensity—extensive coverage	• Sustained partnership • Developmental • Adult learning approach to teaching • Internal/external agents • High intensity—limited coverage
Skills and attributes	Task/doing for others	Holistic/enabling others
	• Project management skills • Technical skills • Marketing skills • Subject/technical/clinical credibility	• Cocounselling • Critical reflection • Giving meaning • Flexibility of role • Realness/authenticity

3.5 Choice of the model

In the process of research, several models were considered, which in theory could be suitable as the main theoretical framework. However, none of the considered models was entirely suitable for studying the implementation of a personalized approach in the treatment of type 2 diabetes in secondary care. However, the SWOT and CFIR models proved to be the most suitable, but not enough to be fully used. Since a personalized approach is not really an intervention, but more a new paradigm/trend that we see coming up, CFIR does not suit fully. At the same time, using only SWOT framework may cause missing of important aspects of implementation. To summarize, using these models does not make possible to answer research questions.

Therefore, the PARiHS model was chosen to answer the second research question, to identify facilitating and impeding factors. However, the elements and sub-elements in our study are not ranked from high to low. Facilitating and impeding factors have been identified through the elements and sub-elements of this model (see chapter 5 Results).

4 Methods

The study used the qualitative design. Interviews with diabetes healthcare professionals were conducted.

4.1 Design

Semi-structured interviews were used for this study. Semi-structured interviews were the selected method both because of their explorative nature and the opportunity to gain insight on specific topics. Interviews with diabetes healthcare professionals were conducted between October 1 and October 13.

4.2 Members and Recruitment

Dutch health care professionals involved in the care of patients with T2DM in secondary care settings were eligible to participate in the interview. These professionals included internists, diabetes nurses, and medical technicians. Inclusion criteria for participants selected for interviews were to be involved in the treatment of patients with T2DM in the Netherlands, and to be fluent in English.

The respondents for the interviews were asked to participate via their work e-mail addresses that were found in open access on the medical centers websites. If the respondents for the interviews agreed to participate, they received an invitation to a meeting.

The informative letter and informed consent form were distributed to participants, which included information such as the aim, content, information about the use and storage of their data (Appendix 1).

4.3 Ethical approval

Approval for this investigation has been granted by the ethical committee of the Faculty of Behavioural, Management and Social Sciences of the University of Twente under request number 221033.

4.4 Interview guide

The interview guide included open ended questions about:

1) Comorbidities;
2) Personal factors;
3) Biomarkers;
4) Genetic factors;
5) Healthcare resources;
6) Medication usage;
7) Diabetes phenotype.

These are the elements that can be tailored within a personalized approach in type 2 diabetes care [9]. Also, questions about eHealth, mHealth technologies as facilitators; definition, using and vision of the personalized approach were included. To start the conversation, the respondents were asked the question on how they define personalized medicine in type 2 diabetes secondary care. The interview guide can be found in Appendix 2.

4.5 Data collection

Interviews were conducted online. To conduct interviews, the program Microsoft Teams was used. The records of interviews were directly transferred to the server of the University of Twente and deleted from the personal computer. The average duration of the interview was 21 minutes (18 min, 25 max).

4.6 Data analysis

Recordings were transcribed; interview transcripts were stored under an anonymous number. The Amber Scripts server was used to transcribe the interview recordings. Interviews transcription was conducted using Amber Script and then manually adjusted by the researcher. The transcripts were analyzed by using an open coding thematic analysis with the program ‘Atlas.ti’.

To answer both research questions, deductive coding was chosen because of the previously defined themes. Codes were used to answer research questions. Since we used the deductive approach, coding frames were developed prior to coding based on theoretical frameworks. For each research questions, different codes and different frameworks were used. The transcripts were read and split into small samples, and developed codes were applied to them.

First, to answer the first research question, we began with a list of codes derived from the conceptual framework used in introduction. We used William's [9] framework to develop deductive codes for identifying findings that supported respondents' opinions on each aspect of the personalized approach (see Table 3). The main and sub-codes for this part can be found in Table 4, as well as the definition of the code and the participants in whose interview this code was identified. Explanations of all codes are provided underneath the table. The main codes (bold) represent the factors that could be taken into account while applying personalized medicine in diabetes care. The sub-codes address the reasons why do healthcare professionals use these factors or do not.

To answer the second research question, the list of codes was derived from the PARiHS framework described in Theoretical framework chapter. We used this framework to develop deductive codes useful for to identify facilitating and impeding factors of the implementation of the personalized approach in diabetes care (see Table 5). The main and sub-codes for this part can be found in Table 5, as well as the definition of the code and the participants in whose interview this code was identified. Explanations of all codes are provided underneath the table. The main codes (bold) represent the key factors of successful implementation of evidence-based practice in healthcare: evidence, context, facilitation. The sub-codes address the high and low levels of these factors. High levels serve as facilitating factors, low levels as impeding factors.

5 Results

This section is divided in two parts. Each part respectively provides answers to the first and second research questions of this study:

To what extent do diabetes healthcare professionals in Dutch secondary care integrate personalized medicine into their care delivery?

Which facilitating and impeding factors influence the implementation of the personalized medicine approach in Dutch T2DM secondary care?

5.1 Characteristics of respondents

5 respondents, 4 internists (males), 1 diabetes nurse (female) participated in the interviews. The number, function and medical institution of respondents are represented in the Table 3.

Table 3. *Characteristics of respondents*

N	Function	Medical Institution
1	Internist-endocrinologist	LUMC
2	Diabetes nurse	LUMC
3	Internist-endocrinologist	AMC
4	Internist-endocrinologist	UMCG
5	Internist-endocrinologist	ZGT

5.2 Identifying the extent of implementation of the personalized approach in Dutch T2DM secondary care

The results are represented in Table 4.

Table 4. *Deductive codes in data analysis to identify the extent of implementation*

Main and sub-codes	***Definition of code***	***HCP*** [a]
Comorbidities (CB)	Whether stakeholders take into account comorbidities when personalize therapy	7(5)
Personalized based on CB	Why do they (here and further they = healthcare professionals) take comorbidities into account	7(5)
Not personalized based on CB	Why they do not take comorbidities into account	0
Personal factors (PF)	Whether stakeholders take into account personal factors when personalize therapy	21(5)
Personalized based on PF	Why do they take personal factors into account when personalize therapy	11(5)
Not personalized based on PF	Why they do not take personal factors into account when personalize therapy	1(1)
Preferences and goals	Using patients preferences and goals when personalize therapy	9(5)
Biomarkers (BM)	Using biomarkers (C-peptide, GADA-test etc.) when personalize therapy	13(5)
Reason to use BM	Why do they use biomarkers when personalize therapy	10(5)
Reason not to use BM	Why they do not use biomarkers when personalize therapy	3(3)
Genetic factors (GF)	Using genetic markers when personalize therapy	12(5)
Reason to use GF	Why do they use genetic factors when personalize therapy	4(4)
Reason not to use GF	Why they do not use genetic factors when personalize therapy	8(5)
Healthcare resources (HR)	Whether stakeholders take into account healthcare resources when personalize therapy	8(5)
Personalized based on HR	Why do they take healthcare resources into account when personalize therapy	4(2)
Not personalized based on HR	Why they do not take healthcare resources into account when personalize therapy	4(3)
Medication usage (MU)	Whether stakeholders take into account medication usage when personalize therapy	5(5)
Personalized based on MU	Why do they take medication usage into account when personalize therapy	4(4)
Not personalized based on MU	Why they do not take medication usage into account when personalize therapy	1(1)
Diabetes phenotype (DP)	Whether stakeholders take into account diabetes phenotype when personalize therapy	7(5)
Personalized based on DP	Why do they take diabetes phenotype into account when personalize therapy	6(4)
Not personalized based on DP	Why they do not take diabetes phenotype into account when personalize therapy	1(1)
Technologies (TL)	Using eHealth, mHealth technologies as facilitators when personalize therapy	12(5)

Reason to use TL	Why do they use technologies when personalize therapy	7(4)
Reason not to use TL	Why do not they use technologies when personalize therapy	5(4)

a - Total amount of times a code was mentioned by healthcare professionals (HCP) and (#) the number of different healthcare professionals that mentioned it.

Comorbidities (CB)

All 5 respondents find comorbidities an important factor to personalize therapy, because comorbidities affect choice of medications and lifestyle interventions.

"It's very obvious, actually, that we do that because someone who had a myocardial infarction, for example, it needs medication that is different from someone who didn't have a myocardial infarction", participant 1, internist-endocrinologist

2 respondents, including the author of the above quotation, also emphasized that for them, as the doctors, the use of comorbidities in the personalization of therapy is obvious.

Personal factors (PF)

This main code refers to personalization of therapy based on the personal factors of patients with T2DM. Such factors included age, duration of the disease, hypoglycemia risk. Also, they included patients' preferences and goals.

All the respondents mentioned that they do take into account the age of the patients. They choose more intensive therapy for younger patients then for older ones.

"In younger patients I tend to be more, how should I put it, like aggressive, you know, that in older patients I tend to primarily prevent side effects including hypo's", participant 3, internist-endocrinologist

All the respondents try to consider the personal situation of the patient, and individualize to what the patient needs. Sometimes the focus is on lifestyle intervention, sometimes on medication.

3 respondents mentioned taking into account the risk of hypoglycemia in patients. 2 of them attribute this to the age of the patients: the older the patient, the higher is the risk of hypoglycemia. 1 doctor uses CGM to monitor hypoglycemia events.

1 respondent, a diabetes nurse, explicitly mentioned that she does not take into account the duration of the disease because of her strong belief in possible remission, if patients follow the plan that they develop together. Others did not mention the duration of the disease.

All the respondents personalize therapy based on patient preferences and goal. The goals should be set up 'step-by-step' to be able to achieve them. Goals can depend on the age and the lifestyle of the patients. Patient preferences influence the choice of medication and lifestyle interventions.

Biomarkers (BM)

All the participants do use C-peptide to personalize therapy, to determine if patients are insulin deficient or insulin resistant. One participant, diabetes nurse, also uses GADA-test to personalize therapy. In contrast, two internists-endocrinologists emphasized that they do it rarely, only when they have doubts on what is the major problems of the patient.

Genetic factors (GF)

4 respondents use MODY-testing, but only to exclude T2DM and only for diagnostic purposes, not for personalization of treatment.

Regarding other genetic factors, including genetics risk scores, none of the 5 respondents use them because of 3 different reasons. First, lack of enough knowledge on this topic. Second, the lack of such tests in the current guidelines. Third, based on present knowledge that they have, they do not find them helpful.

Healthcare resources (HR)

2 healthcare professionals (diabetes nurse and internist-endocrinologist) find healthcare resources important when personalize therapy. They refer to the health insurances which normally do not include all the necessary components for personalization, for example, continuous glucose monitoring devices for some patients with T2DM. 3 other internists-endocrinologists, however, do not take healthcare resources into account, explaining this with the fact that they have all the necessary facilities.

Medication usage (MU)

Most of the respondents (4) do take into account current medication usage of the patient when personalize therapy. The reason to do that is to avoid possible negative interaction between drugs. The healthcare professionals check what medications the patient already uses before prescribing new ones.

"Because you always have to take into account interactions between drugs. So it really is something to consider. The drugs that are used already by a patient do determine which drugs he or she can add. So in that sense, I think it is one of the determinants of personalized approach", participant 1, internist-endocrinologist

One participant mentioned that in case of medications for glucose regulation, it does not influence that much because these drugs do not really interact with the others.

Diabetes phenotype (DF)

Most of the participants (4) use diabetes phenotype to tailor therapy, because it strongly influences on medication choice.

"*Yes, I definitely do. So if I think that there is more insulin resistance, what can lead to obesity for example. So in this case I'll go for a weight losing agent. And if I think there is more insulin secretion deficit like lean patients, then I'll switch to insulin earlier on*", participant 3, internist-endocrinologist

Meanwhile, participant 5, internist-endocrinologist, mentioned that he does not personalize therapy based on diabetes phenotype, because they mostly take into account glucose values.

Technologies (TL)

This main code refers to using technologies (glucose sensors, eHealth, mHealth) in personalization of therapy. Although technologies themselves are not defined as a part of personalized approach, they can be used as facilitators.

4 respondents use technologies in their practice. They emphasize the utility of glucose sensors, because they can provide patients and healthcare professional with a lot of data. These data can help to personalize therapy. For example, they can see all glucose values throughout the whole day and based on those values, to give patients personalized advice.

Regarding eHealth and mHealth technologies, these respondents also find them useful and encourage patients to use them. For example, participant 5 uses remote consultations via videoconferencing and finds them very convenient, because they can reduce visitations of patients who are doing good with their diabetes self-management. However, the same respondent mentioned the disadvantages of such technology. These are time-consuming emailing with some patients, the lack of arrangements on how to use the technology.

"And also when emailing patients, for instance, you have to write a long story. So, it's hard to describe in words what you mean", participant 5, internist-endocrinologist

One respondent does not support using technology as a facilitator to personalize treatment. He explains that with a lack of perceived need, since he is mostly focusing on medication usage, meanwhile eHealth and mHealth technologies act mostly as facilitators in lifestyle interventions.

5.3 Identifying facilitating and impeding factors that influence the implementation of the personalized approach in Dutch T2DM secondary care

The results are represented in Table 5. The definitions of codes are based on the concepts represented in Chapter 3, 3.4 PARiHS framework, and in Table 2.

Table 5. *Deductive codes in data analysis to identify the extent of implementation*

Main and sub-codes	***Definition of code***	***HCP***
Evidence	Knowledge of personalized approach derived from a variety of sources that has been subjected to testing and has found to be credible	26(5)
Facilitating in evidence	High evidence in Research, Clinical expertise, Patients expertise, Local data/information related to the personalized approach	16(5)
Impeding in evidence	Low evidence in Research, Clinical expertise, Patients expertise, Local data/information related to the personalized approach	10(5)
Context	The environment or setting in which the personalized approach has to be implemented, Dutch diabetes secondary care institutions	25(5)
Facilitating in context	High context in Culture, Leadership, Evaluation	7(3)
Impeding in context	Low context in Culture, Leadership, Evaluation	18(5)
Facilitation	Process of enabling (making easier) the implementation of evidence into practice	27(5)
Task purpose (impeding)	Providing limited help and support for patients to achieve a specific task	1(1)
Holistic purpose (facilitating)	Holistic process of enabling patients to analyze, reflect, and change their own attitudes, behaviors, and ways of working	2(1)
Doing for others (impeding)	Role of the facilitator (HCP) in practice, when the HCP is the main actor in the process	3(3)
Enabling others (Facilitating)	Role of the facilitator (HCP) in practice, when the HCP involve the patient in care process	4(3)
Task/Doing for others (impeding)	Skills and attributes of the facilitator (HCP), Project management skills, Technical skills, Marketing skills, Subject/technical/clinical credibilit	2(1)
Holistic/Enabling others (facilitating)	Skills and attributes of the facilitator (HCP), including Cocounselling, Critical reflection, Giving meaning, Flexibility of role, Realness/authenticity	15(5)

a - Total amount of times a code was mentioned by healthcare professionals (HCP) and (#) the number of different healthcare professionals that mentioned it.

Evidence

Facilitating factors in evidence

All respondents confirm high level of evidence for personalized approach factors such as taking into account comorbidities, biomarkers, diabetes phenotype, current medication use, and patient personal factors. The evidence of these factors, according to the respondents, is confirmed by many years of

research and clinical expertise. Thus, high evidence of most components of a personalized approach can act as a facilitating factor in the implementation of a personalized approach.

Impeding factors in evidence

However, according to respondents, the lack of evidence of effectiveness currently makes it impossible to use genetic factors in a personalized approach to the treatment of T2DM. The respondents stated that additional research has to be done in this area to be able to use it in practice. Therefore, the lack of evidence of genetic factors can be an impeding factor.

Context

Facilitating factors in context

Some respondents (3) report the availability of good material and technological equipment in their medical institutions. They emphasize that, for them, lack of resources are not a reason to limit personalization.

Impeding factors in context

At the same time, 2 other respondents report that they sometimes lack resources and cannot apply a personalized approach to all patients equally. In particular, CGM devices are not covered by insurance for all patients.

A further impeding contextual factor, mentioned by 3 of the respondents, is the lack of support for personalization in the guidelines. According to them, some of the guidelines are very outdated and need to be refined towards a personalized approach.

Facilitation

Facilitating factors in facilitation

One of the facilitating factors is good skills and attributes of facilitator (HCP), such as cocounseling, critical reflection and flexibility of role. All respondents mentioned the importance of dialogue with the patient, during which the healthcare professional needs to understand the whole picture of the patient's health, lifestyle and preferences. 4 respondents emphasized the necessity of taking a look into the holistic picture of the patient’s condition. 2 respondents mentioned the importance of regular meetings with a patient and adapting the treatment based on current progress.

Impeding factors in facilitation

1 respondent mentioned the resistance of some healthcare professionals to use the personalized approach, their lack of flexibility in following the guidelines.

6 Discussion

This study aimed to gain insight on whether and how concepts of personalized medicine are currently integrated in Dutch diabetes type 2 secondary care, from the perspectives of healthcare professionals. Additionally, the study also intended to identify the impeding and facilitating factors that influence on the implementation.

The study revealed that diabetes healthcare professionals in Dutch secondary care *partially* integrate personalized medicine into their care delivery. While they already actively use some components of the personalized approach, such as comorbidities, medication usage, diabetes phenotype and personal factors, other components, such as genetic factors, biomarkers and healthcare resources are not effectively used.

The use and implementation of personal factors as a part of the personalized approach was also described in a study by Rutten et al. [28]. That study indicates that Dutch healthcare professionals actively use personal factors during personalization of therapy, which supports our findings. This means that healthcare professionals take into account such factors as age of the patient and patients' preferences and goals when personalize therapy. For younger patients they choose more intensive therapy than for older ones. Goals of the patients depend on their age and lifestyle. Preferences of the patients influence the choice of medication and lifestyle interventions.

Such component of personalized approach as taking comorbidities into account was mentioned by all participants in this study. Moreover, the respondents emphasized that it is very obvious for them to use this component, since as healthcare professionals they do it on routine basis. The positive effect of personalization in treating patients with comorbid type 2 diabetes based on comorbidities have also been previously described in a study by Schmieder et al. [29]. This positive effect is achievement in 6 months of personalized glucose and blood pressure targets.

From the data obtained from the interviews in this study, it becomes clear that the healthcare professionals personalize therapy based on existing medication usage of the patients to avoid possible negative interactions between drugs. Another study by Davies et al. [30] confirms the importance of this component for the personalization, especially for patients with hyperglycemia. For example, according to Davies et al. [30], dose adjustment or discontinuation of background medications may be required to avoid hypoglycemia when adding a new agent to a regimen containing insulin, sulfonylurea, or glinide therapy, particularly in patients at or near glycemic goals.

Regarding genetic factors, none of the 5 respondents use them because of their lack of enough knowledge on this topic, the lack of such tests in the current guidelines, and because they do not find them helpful. Even though genetic factors are seen as a potential breakthrough in the personalization of T2DM treatment, widespread adoption of this approach will probably occur only when the identification of risk factors through genotype is accompanied by effective therapy [10].

The second research question focused on identifying facilitating and impeding factors that influence the implementation of the personalized medicine approach in Dutch T2DM secondary care. The study revealed the following factors:

1. Facilitating factors.
    - High evidence of most components of a personalized approach.
    - Enough material and technological equipment of the medical institutions, no limitations in resources.
    - Skills of the healthcare professional, allowing him to involve patients in the decision making and to encourage them.
2. Impeding factors.

- Low evidence of genetic factors of the personalized approach.
- Lack of resources to personalize therapy for every patient.
- Outdated guidelines without personalization.
- Resistance of some healthcare professionals to use the personalized approach.

The facilitating factors identified in this study overlap with those mentioned in previous studies. For HCPs it was very important that treatment is evidence-based. For several of the options to personalize treatment, including comorbidities, existing medication usage and personal factors, strong evidence exists [12][28][29][30]. This supports the personalization of treatment for these factors. On the other hand, the low level of evidence for the effect of treatment adaptations based on genetic factors results in the lesser use of this factor for personalization. In the future, when more evidence becomes available, HCPs may be more inclined to base treatment decisions on genetic factors [10]. At our study, we found out that the low evidence of genetic factors is an impeding factor that negatively influence the implementation of the personalized medicine approach. The low evidence of genetic factors was also previously described in a study by Williams et al. [9].

The implementation would be aided by clear guidelines supporting personalization on all evidence-based factors and the training of physicians in the benefits and correct practice to personalize treatment. So far, according to the respondents, the guidelines are outdated and do not include the personalization, which is an impeding factor. The respondents mentioned that they try to personalize the treatment as much as they can, even if the guidelines are outdated. One respondent mentioned that some of the healthcare professionals (among colleagues) are too much adherent to these guidelines, and do not even put any efforts to personalize treatment. The need to include personalized medicine in clinical practice guidelines was previously described in a study by de Vries et al. [21], although this need was not literally considered as an impeding factor of implementation of the personalized approach in diabetes care. Also, such a facilitating factor as the importance of the communication skills of healthcare professionals that allows them to involve patients in decision-making process was previously proven by Heisler et al. [31].

Such a contextual factor as sufficient material equipment of medical institutions was not mentioned earlier. The lack of resources has not previously been considered as an impeding factor, however, in a study by Rutten et al. [28] the importance of sufficient resources for the implementation of a personalized approach was mentioned. Few respondents emphasized the importance of using CGM-devices to personalize therapy, however, it is not reimbursed for every patient with T2DM. According to respondents, unlimited insurance coverage for such devices would allow them to continuously monitor patients' glucose levels 24 hours a day, and based on this, personalize therapy. Moreover, it would improve patient self-management as they, too, could track these changes in glucose levels and adjust their diet and physical activity accordingly to reach their target glucose levels. The importance of using CGM-devices to personalize therapy was also proven in the study by den Braber et al. [32], as well as importance of them to be reimbursed and available.

Strengths and limitations

The main strength of this study is a narrow field focusing on the Dutch healthcare system. The Dutch healthcare system is specific and therefore the involvement of local health professionals can be a strength. Another strength of the study is including HCPs from different hospitals, both university centers and general hospitals. Oftentimes the physicians in one hospital work by a similar scheme, so by conducting interviews with people from multiple hospitals a broader view of the Dutch T2DM treatment was received. Using semi-structured interviews as a method is also a strength of this study, because it made possible to explore participants' thoughts and beliefs regarding the personalized approach in more detail.

This study has its limitations as well. The main limitation is the language barrier, since the interviews with Dutch healthcare professionals were performed in English. During the interviews, some of the participants

found it difficult to translate some terms into English, because in their practice they operate in Dutch. Because of this, the interviews took longer and there is a possibility that more insights would have been obtained if the interviews had been conducted in Dutch. Moreover, several potential respondents (2) refused to be interviewed, referring to their insufficient level of English. Another limitation was the short timeframe during which interviews had to be conducted. If more time was available, we would be able to attract more participants for interviews and get more information. Finally, among participants, self-selection can be a bias. All healthcare professionals included entered this study because of their enthusiasm, interest, or curiosity for a personalized approach to managing diabetes. If participants who do not believe in or are not interested in personalization were included, a broader and more complete representation could be established. However, as a first step in research into the implementation of a personalized approach to secondary care for diabetes, it would be sufficient to include only the perspective of active healthcare professionals in the study in order to obtain a general overview.

Implications for further research

The results of this study can be used to develop recommendations for the further implementation of a personalized approach in Dutch diabetes secondary care. Also, in the course of the study, facilitating and impeding factors influencing the implementation of a personalized approach were identified. Further research can be done to find out how to eliminate the impeding factors. In addition, respondents mentioned that the practical benefits of using genetic factors in personalization are not yet clear. A more detailed study of the potential use of genetic factors in personalization would be helpful. Implementation of personalized approach in diabetes secondary care is a very complex area with many elements intertwined, and different stakeholders involved. Since only healthcare professionals acted as stakeholders in the study, a multi-level perspective should be explored. Consideration of the implementation of a personalized approach from the patients' point of view could be carried out.

Implications for clinical practice

Some of respondents indicated that there is a lack of personalization in guidelines, which is an impeding factor that influence the implementation of the personalized approach in diabetes care. Therefore, guidelines could be updated towards personalization. Since the resistance of healthcare professionals is another impeding factor, promotion of a personalized approach among healthcare professionals can be carried out on the basis of medical institutions.

Conclusion

This study showed that diabetes healthcare professionals in Dutch secondary care use such components of the personalized approach, as comorbidities, medication usage, diabetes phenotype and personal factors, but do not much use genetic factors, biomarkers and healthcare resources to personalize therapy. Such factors as high evidence, the lack of limitations in healthcare resources, skills of healthcare professionals that allows them to involve patients in decision making, were identified as facilitating factors. Meanwhile, such factors as limited healthcare resources, low evidence of genetic factors, outdated guidelines without personalization, and resistance of healthcare professionals were identified as impeding factors. Further research should involve other stakeholders, such as patients, and focus on how to eliminate the impeding factors, to gain more insight on effectiveness on using genetic factors. The guidelines that healthcare professionals currently use should be updated towards personalization, the promotion of using personalized approach in diabetes care should be conducted in medical institutions.

Literature

[1] Artasensi A, Pedretti A, Vistoli G, Fumagalli L. Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs. Molecules. 2020 Apr 23;25(8):1987. doi: 10.3390/molecules25081987. PMID: 32340373; PMCID: PMC7221535.

[2] Basu S, Yudkin JS, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ, Sussman JB, Beran D. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabetes Endocrinol. 2019 Jan;7(1):25-33. doi: 10.1016/S2213-8587(18)30303-6. Epub 2018 Nov 21. Erratum in: Lancet Diabetes Endocrinol. 2019 Jan;7(1):e1. PMID: 30470520.

[3] 'Diabetes mellitus | Leeftijd en geslacht | Volksgezondheid en Zorg'. https://www.vzinfo.nl/diabetes-mellitus/leeftijd-en-geslacht (accessed Sep. 12, 2022).

[4] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013 Jan;36 Suppl 1(Suppl 1):S67-74. doi: 10.2337/dc13-S067. PMID: 23264425; PMCID: PMC3537273.

[5] Dhatariya K, Corsino L, Umpierrez GE. Management of Diabetes and Hyperglycemia in Hospitalized Patients. [Updated 2020 Dec 30]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279093/

[6] R. Alshammari, N. Atiyah, T. Daghistani, and A. Alshammari, 'Improving Accuracy for Diabetes Mellitus Prediction by Using Deepnet', *Online J. Public Health Inform.*, vol. 12, no. 1, Art. no. 1, Jul. 2020, doi: 10.5210/ojphi.v12i1.10611.

[7] Schlienger JL. Complications du diabète de type 2 [Type 2 diabetes complications]. Presse Med. 2013 May;42(5):839-48. French. doi: 10.1016/j.lpm.2013.02.313. Epub 2013 Mar 23. PMID: 23528336.

[8] R. J. Smith, D. M. Nathan, S. A. Arslanian, L. Groop, R. A. Rizza, and J. I. Rotter, 'Individualizing Therapies in Type 2 Diabetes Mellitus Based on Patient Characteristics: What We Know and What We Need to Know', *J. Clin. Endocrinol. Metab.*, vol. 95, no. 4, pp. 1566–1574, Apr. 2010, doi: 10.1210/jc.2009-1966.

[9] D. M. Williams, H. Jones, and J. W. Stephens, 'Personalized Type 2 Diabetes Management: An Update on Recent Advances and Recommendations', *Diabetes Metab. Syndr. Obes. Targets Ther.*, vol. 15, pp. 281–295, Feb. 2022, doi: 10.2147/DMSO.S331654.

[10] Klonoff DC. Personalized medicine for diabetes. J Diabetes Sci Technol. 2008 May;2(3):335-41. doi: 10.1177/193229680800200301. PMID: 19885196; PMCID: PMC2769744.

[11] 'Personalized Medicine Coalition - Precision Medicine Advocacy and Education.' https://www.personalizedmedicinecoalition.org/index.cfm (accessed Sep. 21, 2022).

[12] R. W. Grant and D. J. Wexler, 'Personalized medicine in Type 2 diabetes: what does the future hold?', *Diabetes Manag. Lond. Engl.*, vol. 2, no. 3, pp. 199–204, May 2012, doi: 10.2217/dmt.12.15.

[13] S. Ashrafzadeh and O. Hamdy, 'Patient-Driven Diabetes Care of the Future in the Technology Era', *Cell Metab.*, vol. 29, no. 3, pp. 564–575, Mar. 2019, doi: 10.1016/j.cmet.2018.09.005.

[14] 'Diabetic kidney disease: update on clinical management and non-glycaemic effects of newer medications for type 2 diabetes - PubMed'. https://pubmed.ncbi.nlm.nih.gov/34104399/ (accessed Oct. 13, 2022).

[15] W. H. Polonsky and R. R. Henry, 'Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors', *Patient Prefer. Adherence*, vol. 10, pp. 1299–1307, 2016, doi: 10.2147/PPA.S106821.

[16] J. W. Kleinberger and T. I. Pollin, 'Personalized medicine in diabetes mellitus: current opportunities and future prospects', *Ann. N. Y. Acad. Sci.*, vol. 1346, no. 1, pp. 45–56, Jun. 2015, doi: 10.1111/nyas.12757.

[17] E. Bakker *et al.*, 'Perspectives on a Way Forward to Implementation of Precision Medicine in Patients With Diabetic Kidney Disease; Results of a Stakeholder Consensus-Building Meeting', *Front. Pharmacol.*, vol. 12, p. 662642, May 2021, doi: 10.3389/fphar.2021.662642.

[18] B. Kulzer *et al.*, 'Integrated Personalized Diabetes Management (PDM)', *J. Diabetes Sci. Technol.*, vol. 10, no. 3, pp. 772–781, Dec. 2015, doi: 10.1177/1932296815617487.

[19] R. J. Geurten, A. M. J. Elissen, H. J. G. Bilo, J. N. Struijs, C. van Tilburg, and D. Ruwaard, 'Identifying and delineating the type 2 diabetes population in the Netherlands using an all-payer claims database: characteristics, healthcare utilisation and expenditures', *BMJ Open*, vol. 11, no. 12, p. e049487, Dec. 2021, doi: 10.1136/bmjopen-2021-049487.
[20] 'Welke implementatiestrategieën zet je in? - ZonMw'. https://www.zonmw.nl/nl/onderzoek-resultaten/palliatieve-zorg/implementatiepagina/welke-implementatiestrategieen-zet-je-in/ (accessed Sep. 12, 2022).
[21] J. K. de Vries, A. Levin, F. Loud, A. Adler, G. Mayer, and M. J. Pena, 'Implementing personalized medicine in diabetic kidney disease: Stakeholders' perspectives', *Diabetes Obes. Metab.*, vol. 20, no. S3, pp. 24–29, 2018, doi: 10.1111/dom.13412.
[22] M. M. Helms and J. Nixon, 'Exploring SWOT analysis – where are we now? A review of academic research from the last decade', *J. Strategy Manag.*, vol. 3, no. 3, pp. 215–251, Jan. 2010, doi: 10.1108/17554251011064837.
[23] J. D. H. van Wijngaarden, G. R. M. Scholten, and K. P. van Wijk, 'Strategic analysis for health care organizations: the suitability of the SWOT-analysis', *Int. J. Health Plann. Manage.*, vol. 27, no. 1, pp. 34–49, 2012, doi: 10.1002/hpm.1032.
[24] P. Ngassa Piotie *et al.*, 'Factors affecting the implementation of a complex health intervention to improve insulin management in primary care: A SWOT analysis', *Afr. J. Prim. Health Care Fam. Med.*, vol. 14, Jul. 2022, doi: 10.4102/phcfm.v14i1.3467.
[25] Horgan D, Jansen M, Leyens L, Lal JA, Sudbrak R, Hackenitz E, Bußhoff U, Ballensiefen W, Brand A. An index of barriers for the implementation of personalised medicine and pharmacogenomics in Europe. Public Health Genomics. 2014;17(5-6):287-98. doi: 10.1159/000368034. Epub 2014 Nov 15. PMID: 25401385.
[26] Damschroder, L.J., Aron, D.C., Keith, R.E. et al. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implementation Sci 4, 50 (2009). https://doi.org/10.1186/1748-5908-4-50
[27] J. Rycroft-Malone, G. Harvey, K. Seers, A. Kitson, B. McCormack, and A. Titchen, 'An exploration of the factors that influence the implementation of evidence into practice', *J. Clin. Nurs.*, vol. 13, no. 8, pp. 913–924, 2004, doi: 10.1111/j.1365-2702.2004.01007.x.
[28] Guy E.H.M. Rutten, Heidi A. van Vugt, Inge de Weerdt, Eelco de Koning; Implementation of a Structured Diabetes Consultation Model to Facilitate a Person-Centered Approach: Results From a Nationwide Dutch Study. Diabetes Care 1 April 2018; 41 (4): 688–695.
[29] R. E. Schmieder *et al.*, 'Achievement of individualized treatment targets in patients with comorbid type-2 diabetes and hypertension: 6 months results of the DIALOGUE registry', *BMC Endocr. Disord.*, vol. 15, no. 1, p. 23, May 2015, doi: 10.1186/s12902-015-0020-7.
[30] M. Davies *et al*., A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 1 December 2018; 41 (12): 2669–2701. https://doi.org/10.2337/dci18-0033
[31] M. Heisler, R. R. Bouknight, R. A. Hayward, D. M. Smith, and E. A. Kerr, 'The Relative Importance of Physician Communication, Participatory Decision Making, and Patient Understanding in Diabetes Self-management', *J. Gen. Intern. Med.*, vol. 17, no. 4, pp. 243–252, Apr. 2002, doi: 10.1046/j.1525-1497.2002.10905.x.
[32] N. den Braber *et al.*, 'Glucose Regulation Beyond HbA1c in Type 2 Diabetes Treated With Insulin: Real-World Evidence From the DIALECT-2 Cohort', *Diabetes Care*, vol. 44, no. 10, pp. 2238–2244, Oct. 2021, doi: 10.2337/dc20-2241.

Appendix 1. Consent form

Consent Form for Towards a personalized medicine approach in diabetes type 2 secondary care: implementation of personalized medicine approach in Dutch diabetes secondary care, from the perspectives of healthcare professionals

YOU WILL BE GIVEN A COPY OF THIS INFORMED CONSENT FORM

Please tick the appropriate boxes	**Yes**	**No**
Taking part in the study		
I have read and understood the study information dated [13/07/2022], or it has been read to me. I have been able to ask questions about the study and my questions have been answered to my satisfaction.	○	○
I consent voluntarily to be a participant in this study and understand that I can refuse to answer questions and I can withdraw from the study at any time, without having to give a reason.	○	○
I understand that taking part in the study involves an audio-recorded interview, audio recording will be transcribed as text.	○	○
Use of the information in the study		
I understand that information I provide will be used for the master's thesis report	○	○
I understand that personal information collected about me that can identify me, such as [e.g. my name or where I live], will not be shared beyond the study team.	○	○
I agree that my information can be quoted in research outputs	○	○
I agree that my real name can be used for quotes	○	○
Consent to be Audio/video Recorded		
I agree to be audio/video recorded	○	○
Future use and reuse of the information by others		
I give permission for the anonymized audio recording that I provide to be archived in P-drive server of the University of Twente so it can be used for future research and learning.	○	○
I give the researchers permission to keep my contact information and to contact me for future research projects.	○	○

Signatures

_____ _____ _____

Name of participant [printed]

Signature Date

I have accurately read out the information sheet to the potential participant and, to the best of my ability, ensured that the participant understands to what they are freely consenting.

_____ _____ _____

Iana Pazenko Signature Date

Study contact details for further information: Iana Pazenko, i.pazenko@student.utwente.nl

Contact Information for Questions about Your Rights as a Research Participant

If you have questions about your rights as a research participant, or wish to obtain information, ask questions, or discuss any concerns about this study with someone other than the researcher(s), please contact the Secretary of the Ethics Committee/domain Humanities & Social Sciences of the Faculty of Behavioural, Management and Social Sciences at the University of Twente by ethicscommittee-hss@utwente.nl

Appendix 2. Interview guide

"Good afternoon, you are talking to Iana Pazenko. I'm calling you today for an interview for my graduation research on the implementation of personalized medicine approach in Dutch diabetes secondary care, from the perspectives of healthcare professionals. First of all, thank you for participating in this interview. Today I would like to discuss how personalized medicine is currently integrated in Dutch diabetes type 2 secondary care, and what are the main facilitators and barriers for the further implementation. With this information, we can provide recommendations for the further implementation on this approach.

With your approval, I would like to record this interview. By means of a recording, I can go through your feedback again at a later time. Your feedback will always remain anonymous and will only be used for the purposes of this research. I would like to know if you agree with this. Do you give me your permission to record the interview? Before we start the interview, do you have any questions that you would like to ask me? If not, I'll start recording and we'll start the interview.

START OF RECORDING

With your approval I started recording.

1. My first question is: How would you define personalized medicine in type 2 diabetes secondary care?

2. Can you describe when and where you currently use personalized medicine in patients with type II diabetes? And could you describe why you currently use it?

- If "I don't use it", "not really", then why not?

Now I would like to go through the specific aspects of the personalized approach which were drawn from literature, and learn more about whether you use them, and if so, when, where and why?

3. The first aspect is **comorbidity**.

Do you personalize therapy based on the presence of medical comorbidities? (eg, cardiovascular, renal diseases)

- If yes, how?
- If not, why? What has to be changed for you to use it?

4. The next aspect is **personal factors**. Do such factors as age, duration of disease, and hypoglycemia risk influence on personalization of therapy in your practice?

- If yes, how?
- If not, why? What has to be changed for you to use it?
- Do you take into account patient preferences and goals?

5. Okay, then the next aspect. Do you personalize therapy based on the **diabetes phenotype**?

- If yes, how?
- If not, why? What has to be changed for you to use it?

6. Let's talk about **biochemical markers.** Do you use biomarkers (eg, urinary C-peptide, GADA test) to personalize therapy?

- If yes, how?
- If not, why? What has to be changed for you to use it?

7. The next aspect is **genetic factors.** Do you use genetic markers (eg, MODY testing), or genetic risk scores to personalize the therapy?

- If yes, how?
- If not, why? What has to be changed for you to use it?

8. Regarding **medication prescription**. Does existing medication usage of the patient influence the choice, the personalization for T2DM treatment?

- If yes, how?
- If not, why? What has to be changed for you to use it?

9. Do you take into account **healthcare resources** when you personalize care?

- If yes, how?
- If not, why?

10. Do you use eHealth, mHealth technologies as facilitators in your practice?

11. We discussed a lot of aspects of personalized medicine. Could you please tell me about your own vision of the future of a personalized approach in diabetes care? What does it include?

This was the end of the interview. I would like to thank you very much for participating in this interview. Do you have any questions for me right now?

STOP RECORDING