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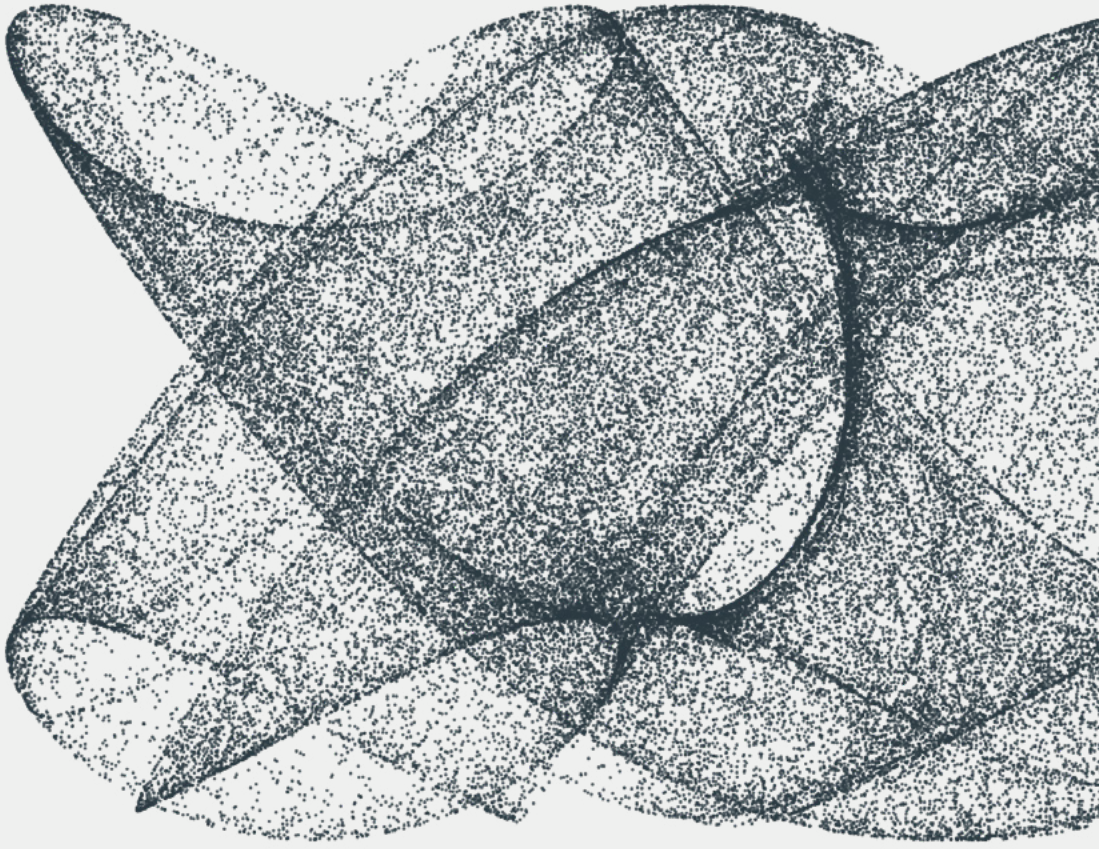
FOR HUMAN DATA SCIENCE

Advancing Glycemic Management in People with Diabetes

NEW APPROACHES AND MEASURES



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2019

Introduction

Diabetes is a leading cause of death in the United States, with 1.5 million individuals diagnosed per year and an estimated 30.3 million affected.[1] Sub-optimally managed diabetes can lead to psychosocial and physical health complications for people with diabetes (PwD) and creates a significant societal and economic burden. The cost to the U.S. healthcare system alone is estimated at $404 billion in medical expenditures and lost productivity across all diabetes types.[2] Recent advances in blood glucose management including continuous glucose monitoring and associated short-term metrics such as time in range (TIR), offer a new strategy to improve management beyond the current state and reduce complications in the U.S. PwD population.

This paper discusses blood glucose management for PwD, which is fundamental to diabetes care, and examines the benefits and shortcomings of finger stick self-monitoring of blood glucose (SMBG) and HbA1c — a lab test that indicates average blood glucose levels over a 12-week period.[3] As advances in digital technologies have given rise to continuous glucose monitors (CGM), which provide more than 50-times the number of glucose readings compared to self-monitoring of blood glucose per day, new approaches to care are being enabled.

For instance, CGM-derived data can be evaluated at specific time points to determine Time in Range (TIR) — the percentage of time a PwD spends in their glucose target range. This report aims to assess TIR and determine whether its management and incorporation into diabetes care paradigms can lead to meaningful reductions in complications and costs.

It additionally puts forth approaches to further the use of TIR in the U.S. PwD population and improve blood glucose management.

This study is based on research and analysis undertaken by IQVIA Real World & Analytics Solutions with support and funding from Eli Lilly and Company.

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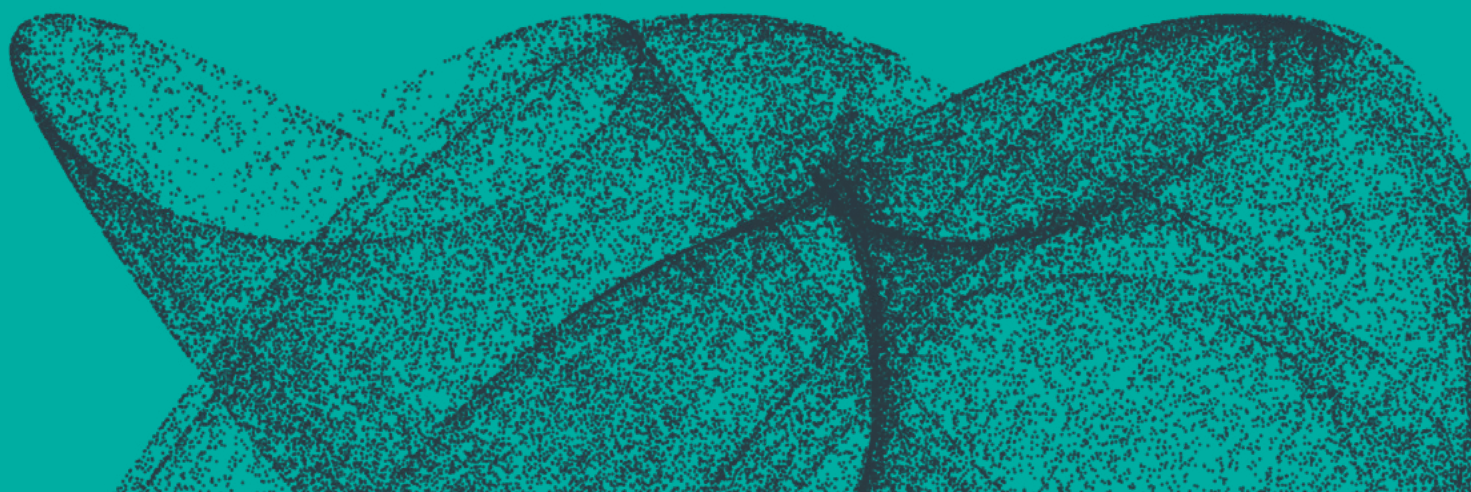


Executive summary

Advances in diabetes care have resulted in improved technologies for monitoring glucose along with refined insulins and novel non-insulin therapies for people with diabetes (PwD). However, there still exists a gap in managing blood glucose in the United States, as evidenced by the significant societal and economic burden placed on PwD and the healthcare system as a whole.

HbA1c, an important long-term and indirect measure of blood glucose management, is used by clinicians to determine the success of blood glucose management, and also to understand the risk of developing diabetes-related complications. Despite its relevance and position within the clinical paradigm, HbA1c carries with it several limitations, including its inability to identify daily fluctuations in blood glucose and periods of hyperglycemia and hypoglycemia.

Recent technological advances in continuous glucose monitoring have resulted in greater recognition of metrics beyond HbA1c, including time in range (TIR), time below range (TBR) and time above range (TAR). TIR is defined as the amount of time spent within a clinically acceptable glucose range, whereas TBR and TAR are defined as the amount time below or above a certain glucose range, respectively. Although improvements in TIR have not yet been definitively linked to long-term outcomes, recent evidence proposes a relationship between TIR, HbA1c, retinopathy and microalbuminuria. The incorporation of these metrics alongside HbA1c is expected to enhance the way in which diabetes is managed in the future, and subsequently, reduce the overall societal and economic burden. Indeed, recent efforts were made to solidify TIR during the 79th Annual American Diabetes Association Scientific Sessions, where recommendations for target TIR values were proposed by Advanced Technologies & Treatments for Diabetes (ATTD) working group. A minimum consensus target of 70% TIR for people with Type 1 and people with Type 2 diabetes was put forth.

Preliminary peer reviewed data indicates study cohorts had an average TIR of 50–60%. This level is below the minimum consensus target of 70% proposed by the ATTD working group. To assess the value of improving TIR management from its current average state to the minimum consensus target value and beyond, the IQVIA Core Diabetes Model was used to conduct the first estimation of reduction in complications and costs associated with improving TIR. Using this model, improvements in TIR were estimated to reduce the risk of developing diabetes-related complications, such as myocardial infarction, end-stage renal disease, severe vision loss and amputation, resulting in a conservative reduction of $6.7–9.7 billion in costs over a 10-year period, based on the relationship between TIR and HbA1c. This reduction in costs represents a conservative estimate as the TIR in the overall US population may be lower than the starting TIR of 58%, as seen in clinical trials.

To advance into a new era of care in diabetes — where all diabetes management tools including HbA1c and TIR, are optimized and personalized — there are various approaches to further the use of TIR that can help address the need for improved blood glucose management. There are three critical stages in this process: establishing the importance of TIR for blood glucose management across key stakeholders, advancing the use of this metric and promoting ease of use of technologies, and, lastly, perpetuating the use of TIR to sustain blood glucose management across all diabetes populations. Within this framework, approaches that can further the use of TIR are suggested from a PwD, healthcare policy, and healthcare delivery perspective, and consider issues such as advocacy, access and interoperability.

Type 1 and Type 2 diabetes in the United States

+ **Diabetes creates significant physical and psychosocial health challenges for PwD that affect their quality of life, productivity and life expectancy.**
+ **Both Type 1 and Type 2 diabetes can result in short- and long-term health issues including microvascular complications (e.g., vision loss, end-stage renal disease) and macrovascular complications (e.g., myocardial infarction, stroke), and are associated with higher rates of major depressive disorder, general anxiety disorder and panic disorder.**
+ **The high prevalence of diabetes and its associated complications create significant social and economic burdens for the healthcare system.**
+ **The economic burden of diagnosed and undiagnosed diabetes, prediabetes and gestational diabetes was nearly $404 billion in 2017 in the United States.[2]**
+ **The PwD health, societal and economic burdens tied to diabetes suggest a need to improve blood glucose management exists.**

OVERVIEW OF TYPE 1 AND TYPE 2 DIABETES AND ASSOCIATED COMPLICATIONS

Type 1 diabetes mellitus is an autoimmune disease characterized by the loss of insulin-producing pancreatic beta cells[10] and inability to regulate blood glucose levels. People with Type 1 diabetes must self-administer insulin to manage their blood glucose levels. Type 2 diabetes, on the other hand, is characterized by insulin resistance and the progressive dysfunction of insulin production that may also eventually require affected individuals to self-administer insulin.[4]

Poorly managed glucose levels in people with Type 1 or Type 2 diabetes can lead to both short- and long-term complications.[5] Over the long term, persistently elevated blood glucose levels are linked to a greater risk of microvascular complications (e.g., severe vision loss, end-stage renal disease) and macrovascular complications (e.g., myocardial infarction, stroke).[5] In the senior United States diabetes population (65 or older), 1.6 million individuals experienced visual impairment, 20,250 developed kidney failure, and 27,180 underwent leg amputations in 2010.[6]

Short-term complications associated with diabetes include low blood glucose levels, lethargy, poor wound healing, ketoacidosis and hyperosmolar hyperglycemic state. In 2014 alone, there were 14.2 million emergency room visits attributed to diabetes in the United States,[7] 245,000 of which were due to hypoglycemia and 207,000 from hyperglycemia. In addition to the physical manifestations, diabetes is also responsible for significant psycho-social impact on PwD, which includes complex environmental, social, behavioral and emotional factors.[8,9] Overall, PwD have a 60% higher rate of major depressive disorder, a 123% higher rate of general anxiety disorder and an 85% higher rate of panic disorder compared to the general population.[8] When taken together, the physical and psychosocial consequences of diabetes play a significant role in determining overall quality of life, productivity and life expectancy.[8]

Diabetes creates significant physical and psychosocial health challenges for PwD that affect their quality of life, productivity and life expectancy.

A MAJOR PUBLIC HEALTH CONCERN WITH SIGNIFICANT ECONOMIC AND SOCIETAL BURDEN

The existing societal and economic burden due to diabetes in the United States is significant and suggests a drastic need for improvement in blood glucose management. In 2015, diabetes was the seventh leading cause of death in the United States, with 1.5 million diagnoses per year and a total of 30.3 million individuals affected. This includes 23.1 million diagnosed cases of diabetes and an estimated 7.2 million remaining undiagnosed.[1] Type 1 diabetes accounted for 1.25 million (approximately 5%) of these cases, with a diagnosis rate of 40,000 cases per year.[10] The average age of diagnosis for Type 1 diabetes is 14 years, meaning that people with this form of diabetes are required to manage it for majority of their life.[11] Overall, there were 1.5 million new cases of Type 1 and Type 2 diabetes in the United States among adults over the age of 18 in 2015, for which non-Hispanic blacks and people of Hispanic origin had a higher age-adjusted incidence compared to non-Hispanic whites.[7] Of note, the percentage of adults with Type 2 diabetes increases significantly with age, reaching approximately 27% among individuals aged 65 or older.[12]

The high prevalence of diabetes and its complications, cost of therapy and loss of productivity, lead to direct and indirect costs. In 2017, the estimated cost of diagnosed Type 1 and Type 2 diabetes in the United States was $327 billion, representing a 33% increase from 2012.[13] Approximately 70% of the $327 billion was attributed to medical costs and the remainder to reduced workplace productivity.[13] When accounting for undiagnosed diabetes, prediabetes and gestational diabetes, the original $327 billion figure rose to $404 billion. Persons diagnosed with diabetes individually incur an average medical expenditure of $16,752 per year, which is 2.3 times greater than a person without diabetes,[13] and when hospitalized, spend on average an extra 1.1 days in care.[14]

The high prevalence of diabetes and its complications, cost of therapy and loss of productivity, lead to direct and indirect costs. In 2017, the estimated cost of diagnosed Type 1 and Type 2 diabetes in the United States was $327 billion.

Evolution of blood glucose management in diabetes

+ **Traditionally, blood glucose monitoring for PwD has included finger stick self-monitoring of blood glucose (SMBG) and use of a lab test, HbA1c, which indicates average blood glucose levels over a 12-week period.**

+ **Despite its relevance and position within the clinical paradigm, HbA1c also carries with it several limitations, including its inability to identify specific periods of hyperglycemia and hypoglycemia.**

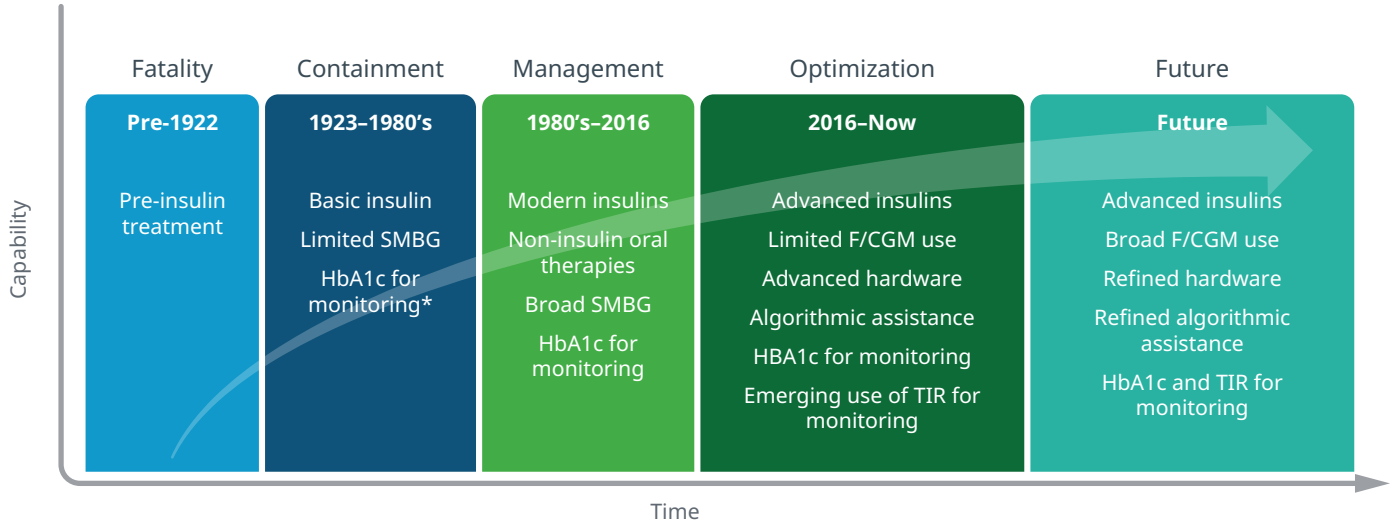
+ **Advances in technology have led to the creation of continuous glucose monitors and as a result, metrics, such as time in range (TIR), time below range (TBR) and time above range (TAR) are becoming increasingly utilized by PwD and healthcare providers to monitor glucose levels.**

+ **The incorporation of time in range metrics, alongside HbA1c, is expected to enhance how diabetes is managed in the future, and subsequently reduce the overall societal and economic burden.**

ERAS OF DIABETES MANAGEMENT

Diabetes care has gone through several eras of progress. Prior to 1922, there was a complete lack of therapies, but consistent advances made since that period including new non-insulin oral and injectable therapies, increasingly physiological next-generation insulins, and technological advances (such as CGMs, hybrid-closed loop insulin pumps with algorithmic assistance) have enhanced blood glucose management (see Exhibits 1 and 2).

Exhibit 1: Eras of Diabetes Management



Source: IQVIA, Aug 2019

Notes: SMBG = self-monitoring of blood glucose. F/CGM = flash/continuous glucose monitoring. *HbA1c measurements were available for monitoring in the latter part of this era. Fatality refers primarily to people with Type 1 diabetes. Advanced hardware includes various technologies such as smart insulin pens and hybrid closed loop pumps, which are an automatic insulin delivery system that regulates basal insulin levels and typically integrate a CGM data sensor, transmitter and insulin delivery system.

CURRENT APPROACH TO ASSESSING BLOOD GLUCOSE MANAGEMENT

For the majority of PwD, day-to-day blood glucose is measured via self-monitoring of blood glucose. Additionally, the current long-term clinical strategy for assessing PwD glucose management is through the measurement of glycated hemoglobin A1c (HbA1c), which reflects a person's average plasma glucose levels over a period of 12 weeks.[3] The fact that HbA1c tests can be performed at any time of the day, do not require special preparation, such as fasting, and can be done as an outpatient laboratory test, have made it the preferred test for assessing glycemic management in PwD. There is also a proven direct link between higher HbA1c levels and increased risk of developing diabetes-related microvascular and macrovascular complications.[15] This link was established following the completion of several milestone clinical studies, including the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS).[16,17] Moreover, these trials were responsible for establishing clinical practice guidelines around acceptable HbA1c levels for different PwD groups.

Despite advances in blood glucose management tools… the proportion of PwD achieving glycemic targets can still be improved.

LIMITATIONS OF HbA1c

The American Diabetes Association (ADA) recommends that HbA1c be measured twice per year for PwD who are meeting treatment goals, or quarterly for those who are not at goal or for whom therapy recently changed.[3] Although HbA1c is used extensively to track blood glucose management, it does have limitations. Specifically, it,

- Is unable to indicate intraday variations in glucose levels, thus making it ineffective in capturing periods of hyperglycemia, hypoglycemia, severe hypoglycemia and general glucose variability. Thus, healthcare professionals (HCPs) cannot be notified of these important blood glucose events that, if occurring frequently, may contribute to short- and long-term complications
- Cannot provide immediate glucose feedback associated with changes in medication, diet or exercise[18,19]

Despite advances in blood glucose management tools, such as next-generation insulins, advanced blood glucose monitoring capabilities, modern treatment guidelines and the long-standing measurement of HbA1c, the proportion of PwD achieving glycemic targets can still be improved. A recent study highlighted only 21% of adults with Type 1 diabetes achieve the ADA HbA1c goal of less than 7% and only 17% of adolescents (<18 years old) achieve an HbA1c of less than 7.5%. Moreover, the mean HbA1c of a cohort of adults with Type 1 diabetes increased from 7.8% to 8.4% between the years 2010–12 to 2016–18.[45]

HbA1c
A long-term indirect measure of blood glucose concentration that is used as a marker to evaluate the clinical status of the glucose management due to its direct correlation with microvascular and macrovascular complications in PwD[3]

EMERGING BLOOD GLUCOSE METRICS: TIME IN RANGES

Advances in glucose monitoring devices now enable PwD to receive a stream of up to 288 glucose measurements per day, drawn from interstitial fluid. As a result, metrics from these, such as time in ranges, are increasingly utilized. Though not fully established, focus on time in ranges is increasing since health providers and physician key opinion leaders (KOLs) recently reached consensus on its use.[20] Time in ranges is defined as the amount of time a person with diabetes spends within (or outside) a target glucose range. This metric includes three key measurements: percentage of readings and time per day within target glucose range (Time in range, i.e., TIR), time below target glucose range (Time below range, i.e., TBR) and time above target glucose range (Time above range, i.e., TAR). An important component of time in ranges is post-prandial glucose (PPG). The term 'post-prandial' means after a meal; therefore, PPG concentrations refer to plasma glucose concentrations after eating. Many factors contribute to post-meal glucose management and therefore, require significant attention to manage well.[21]

Ideally, identifying a person's target TIR should be both a collaborative and individualized process, dependent on several factors including age, long-term HbA1c target and pregnancy status.[3] In June 2019, the Advanced Technologies & Treatments for Diabetes (ATTD) released a consensus statement on TIR targets that was presented at the American Diabetes Association 79th Scientific Sessions.[20] The consensus recommends PwD (both Type 1 and Type 2 diabetes) over the age of 25 achieve at least 70% of the day within a glucose range of 70–180mg/dL. This target TIR and glucose range varies based on whether the PwD is pregnant or high-risk/elderly (see Appendix, Exhibit 11). This international consensus on TIR has led to updates in the ADA Standards of Medical Care which has now acknowledged that metrics such as TIR, TAR, TBR provide additional information from CGMs that can aid in blood glucose management.[22] Recent small cohort, peer-reviewed, studies show that current TIR for people with Type 1 diabetes ranges from 50–58%.[23,24] However, it should be noted that this may be an overestimate for the entire US population due to a clinical trial effect. The average HbA1C seen in recent research suggests that the TIR may be lower.[45]

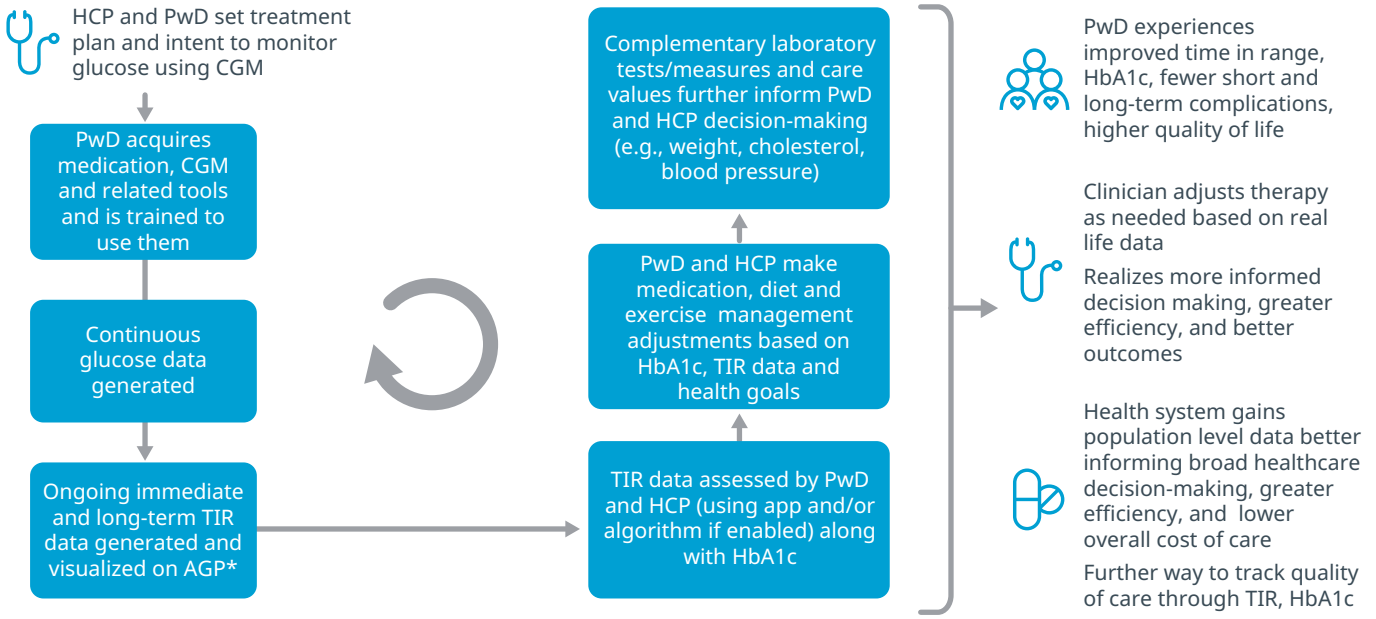
A consensus statement on TIR targets recommends PwD over the age of 25 achieve at least 70% of the day within a glucose range of 70–180mg/dL.... Recent small cohort, peer-reviewed studies show that current TIR for people with Type 1 diabetes ranges from 50–58%.

Digital health offerings in diabetes have increased in recent years, particularly with the advanced insulin pumps, continuous and flash glucose monitors (C/FGMs), and smartphone applications. As a result, there is now a significant amount of data generated, which often includes TIR, allowing for more regular monitoring of this metric by both the PwD and HCP (see Exhibit 2).

TIME IN RANGES

The metric includes three key measurements: percentage of readings and time per day within target glucose range, or time in range (TIR), time below target glucose range (TBR), and time above target glucose range (TAR). The primary goal for effective and safe glucose management with these metrics is to increase the TIR, while reducing the TBR.

Exhibit 2: The Ecosystem of Blood Glucose Management Incorporating Continuous Glucose Monitoring



Source: IQVIA, Aug 2019

Notes: The ecosystem of CGM and digital health apps for tracking TIR. *AGP or ambulatory glucose profile is a standardized, single page glucose report, developed by RS Mazze, D Lucido, O Langer, K Hartmann, D Robard and further developed by International Diabetes Center.[25] It is recommended by an ATTD consensus group as standard for visualization of CGM data (Petrie et al., 2017). In patients with T1DM, RT-CGM use is associated with lower health care costs, fewer hospital admissions, and better glycemic management (Gill et al., 2018). Use of RT-CGM in T1DM patients is associated decrease in HbA1c level and health care system utilization compared with traditional SMBG (Parkin et al., 2017). CGM measurements are taken from interstitial fluid and not directly from blood.

In contrast to HbA1c, TIR offers PwD with an understanding of what is taking place on a daily basis. The ATTD consensus report[20] states that TIR offers several unique benefits that HbA1c, including,

- Notifying both the PwD and HCP about the frequency and time spent in hypoglycemic/hyperglycemic range, with the ability to inform current and future therapy choices
- Leveraging algorithms to predict blood glucose excursions, thereby allowing for more precise insulin management when using a combined insulin pump/pen/CGM system
- Enabling healthcare providers and PwD to respond faster to blood glucose excursions that may otherwise result in severe hypoglycemic or hyperglycemic events
- Improving PwD quality of life and psychosocial well-being — e.g., PwD report TIR as an important factor for overall PwD wellbeing[26]

Despite these benefits however, there are also areas where measuring TIR using a CGM poses challenges, including the

- Requirement for consistent CGM use in order to accurately report TIR, TAR and TBR
- Potential for PwD to experience anxiety due to witnessing real-time glucose excursions

Reduction in complications and costs by improving TIR

+ **Recent small cohort, peer reviewed data indicates study population PwD experience an average TIR of 58%, which is below the minimum consensus recommended target value of 70%, enabling an assessment of potential complications and costs that can be reduced by improving TIR to consensus values and beyond.**

+ **Although improvements in TIR have not yet been definitively linked to long-term outcomes, recent evidence suggests an association between lower TIR and the development of microvascular complications, as TIR affects levels of HbA1c.**

+ **Using the IQVIA Core Diabetes Model to assess the complications and costs that can be reduced by improving TIR, over a 10-year period the risk of developing complications was predicted to decrease and costs were expected to decline by $6.7–$9.7 billion.**

To understand the impact of advances in care and the ability to better measure and manage short-term blood glucose management, the complications and costs that can be reduced by improving TIR were assessed. No known health or economic analyses currently illustrate the reductions in complications and costs associated with improving TIR from 58% (current average) to 70% (minimum consensus target). Although improvements in TIR have not yet been definitively linked to long-term outcomes, previous research efforts suggest a relationship between TIR and HbA1c, and the development of microvascular outcomes.[23, 24, 33, 34] It should be noted that this reduction in costs represents a conservative estimate as the TIR in the overall US population may be lower than the starting TIR of 58%, as seen in clinical trials. Additionally, further cost reductions may be possible due to reductions in hypoglycemia for people with Type 2 Diabetes.

Exhibit 3: Methodology for Assessing Reduction in Complications and Associated Costs Achieved by Improving TIR

1

- A relationship between HbA1c and TIR was needed as there is limited longitudinal TIR-claim data available and not yet a validated model using TIR as a primary input
- Two peer-reviewed articles indicating a mathematical relation ship between TIR percentage achievement and HbA1c were identified
  - $HbA1c = 9.65 - 0.041 \times TIR^{70\text{-}180}$ *
  - $HbA1c = 12.31 - 0.08 \times TIR^{70\text{-}180}$ **

2

- Based on selected peer-reviewed articles, a conservative average current TIR of 58% was used for the analysis*^^
- 70% TIR was used as the minimum consensus target based on the ATTD working group consensus paper***
- Additionally, 80% was used as a target for the analysis which has recently been demonstrated by advanced insulin pump-CGM-treatment algorithm combination****

3

- The HbA1c values associated with TIR of 58%, 70% and 80% were calculated using the peer-reviewed articles
- These were used as input for the IQVIA Core Diabetes Model, a validated, peer-reviewed model, which simulates clinical outcomes and costs for individuals with either Type 1 or Type 2 diabetes^ (For more details see Appendix and: https://www.core-diabetes.com/)
- Associated complications and costs were estimated by the model

Source: IQVIA, Aug 2019; *Beck et al., 2019; **Vigersky et al., 2019, ***Battelino T, Danne T, Bergenstal RM et al., 2019; ****Lewis DM, Swain RS and Donner TW, 2018; ^See endnotes 42,43. ^^The current average is based on clinical trials. The average TIR for the overall US population may be lower.

Notes: Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019.The model then takes HbA1c, in addition to other surrogate inputs such as blood pressure, weight and lipids, and generates long-term endpoints including life expectancy, incidence of macro/micro-vascular events and costs. Slope equations used to convert TIR into HbA1c were developed predominantly based on Type 1 Diabetes datasets per Beck et al., 2019, with a small Type 2 diabetes population derived from Vigersky and McMahon, 2019.

Currently, only HbA1c can be used as input for the IQVIA Core Diabetes Model. Therefore, before modeling, TIR values of interest were converted into HbA1c using the slope equations described by authors Beck et al. (2019)[24] and Vigersky and McMahon (2019)[23] (see Exhibit 3). The IQVIA Core Diabetes Model was then run using the current average TIR of 58% to the minimum consensus state of 70%, and beyond to 80%, which has recently been demonstrated by advanced insulin pump-CGM-treatment algorithm combination which are demonstrating an ability to achieve this level of TIR (see Exhibit 4 for the current and proposed alternate state of treatment for PwD).[27] Output from this model is shown as the 10-year cumulative incidence of developing diabetes-related complications, and the costs that accompany these complications.

In this assessment, improving TIR reduces the cumulative incidence of developing complications such as myocardial infarction, end-stage renal disease, severe vision loss and amputation (see Exhibit 5). For a more detailed breakdown of complications, please refer to Appendix Exhibit 16.

Exhibit 4: The Current and Proposed Alternate State of Treatment for People with Diabetes

CURRENT STATE

Key Statistics

Age	41 years	$TIR^{70\text{-}180}$ [23,24]	58%^
Indication	Type 1	$TAR^{>180}$ [23,24]	37%
Duration of Diabetes	20 years	$TBR^{<70}$ [23,24]	5%
HbA1c[23,24]	7.3–7.5%	No. of hypoglycemic[29] events/week	4.1

Current Management

- **Treatment:** Multiple daily injections of insulin
- **Blood Glucose Measurement:** SMBG using fingerstick and HbA1c; No CGM use

Key Complication Risks+

10-year cumulative incidence of developing complications

Myocardial infarction	3.29	Severe vision loss	9.12
End-stage renal disease	3.85	Amputation	3.96

Psychosocial Profile

Anxiety related to blood glucose levels and fear of hypoglycemia

ALTERNATE STATE

Key Statistics

Age	41 years	$TIR^{70\text{-}180}$	>70%
Indication	Type 1	$TAR^{>180}$	<25%
Duration of Diabetes	20 years	$TBR^{<70}$	<4%
HbA1c	6.5–7.0%	No. of hypoglycemic events/week	1.1

Current Management

- **Treatment:** Insulin pump delivery system of next-generation insulins*
- **Blood Glucose Measurement:** CGM-TIR. Ambulatory Glucose Profile** and HbA1c

Key Complication Risks

10-year cumulative incidence of developing complications

Myocardial infarction	2.65-2.97	Severe vision loss	7.99–8.44
End-stage renal disease	3.79-3.81	Amputation	3.73–3.82

Psychosocial Profile

Increased confidence in overall glucose management

Source: Beck et al., 2019; Vigersky and McMahon, 2019; Bosi et al., 2019; Battelino et al., 2019; + Estimated by IQVIA Core Diabetes Model, v9.0 2019

Notes: ^ Current average TIR is based on clinical trials, the TIR in the US population may be lower. PwD vignette illustrating the current and proposed alternate state for PwD. * Insulin pump systems may not be needed for all PwDs. ** AGP; ambulatory glucose profile is a standardized, single page glucose report, developed by RS Mazze, D Lucido, O Langer, K Hartmann, D Robard and further developed by International Diabetes Center.[25] This visual is produced automatically by CGM-supporting software and provides the individual with a summarized profile of their glucose metrics over a set period of time, including TIR, TAR and TBR. The average TIR, TAR, TBR is based on Beck et al., 2019 where a masked baseline CGM was used to collect the baseline data, this data represents the best estimate of PwD currently not on CGMs. SMBG = self-monitoring of blood glucose. Hypo events refer to both severe and non-severe hypoglycemic events.

Exhibit 5: 10-year Cumulative Incidence of Developing Diabetes-Related Complications After Improving TIR in PwD with Type 1 and Type 2 Diabetes

TYPE 1 DIABETES

COMPLICATION	58% TIR	70% TIR	80% TIR
Myocardial infarction	3.29	2.65–2.97	2.25–2.70
End-stage renal disease	3.85	3.79–3.81	3.72–3.73
Severe vision loss	9.12	7.99–8.44	7.55–8.00
Amputation	3.96	3.73–3.82	3.57–3.73

TYPE 2 DIABETES

COMPLICATION	58% TIR	70% TIR	80% TIR
Myocardial infarction	12.76	11.99–12.39	11.37–11.97
End-stage renal disease	2.84	1.94–2.34	1.42–1.98
Severe vision loss	5.18	4.78–4.98	4.56–4.83
Amputation	1.00	0.97	0.95–0.96

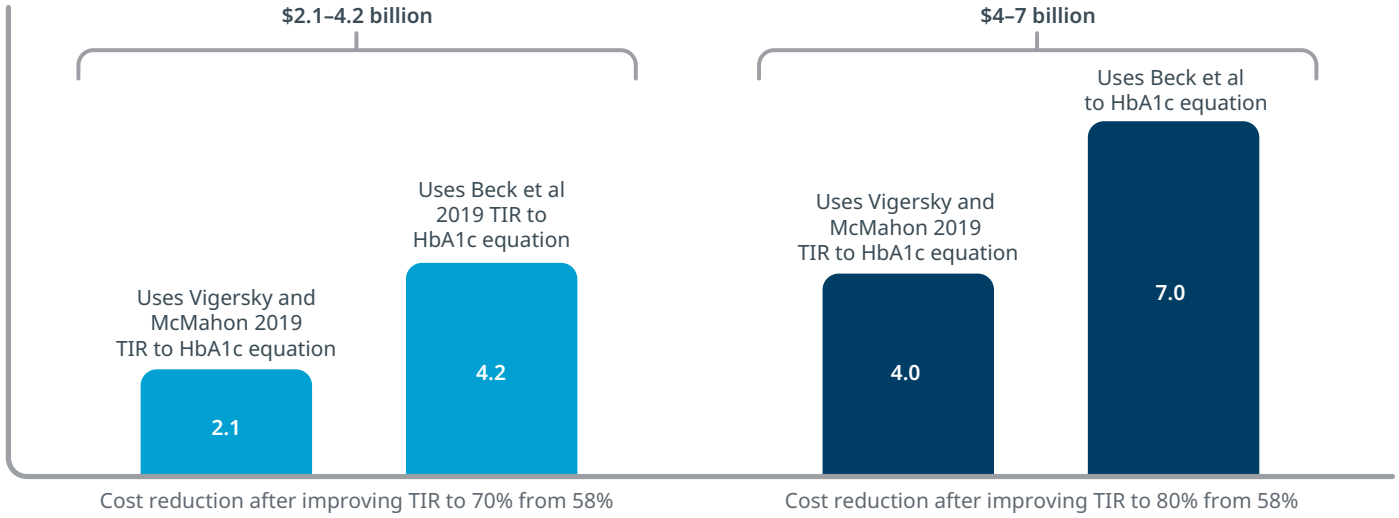
Source: IQVIA Core Diabetes Model, 2019

Notes: The IQVIA Core Diabetes Model was used to calculate the cumulative incidence of developing major diabetes-related complications over a 10-year time horizon in people with Type 1 and Type 2 diabetes. Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019. 10-year cumulative incidence refers to the percentage of patients having a complication over a ten-year period.

Improving TIR from 58% to 70% yielded $2.1–4.2 billion cost reduction. Improving TIR further to 80% yielded an additional $1.9–2.7 billion, resulting in a total of $4.0–6.9 billion cost reduction (see Exhibit 6).

Recent evidence suggests that digital advances, such as the combination of CGM with an insulin pump therapy with a "suspend-before-low" feature (that suspends insulin delivery before a PwD's glucose levels drop too low), have the ability to reduce the number of hypoglycemic events in people with Type 1 diabetes.[25] In general, improvements in HbA1c result in increases in hypoglycemic events as blood sugar levels drop at baseline, however, recent evidence suggests that these

Exhibit 6: 10-Year Cost Reduction by Improving TIR in People with Type 1 and Type 2 Diabetes to 70% and 80%, US$Bn



Source: IQVIA Core Diabetes Model, 2019

Notes: Shown is a summary of the 10-year cost ($Bn) reduction after improving TIR from the current average of 58% to 80% in people with Type 1 and Type 2 diabetes. Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019. Outputs from the model are provided on a per PwD basis, and therefore required multiplying by the total number of U.S. insulin-dependent people with Type 1 and Type 2 diabetes to generate the figures shown. Population sizes used to make these calculations were 1.25Mn for Type 1 diabetes (per the ADA), and 5.86Mn for Type 2 diabetes (per the CDC National Diabetes Statistics Report, 2017). The total complication costs at different TIR values are as follows: At 58% = $207.4Bn; at 70% = $203.1-205.3Bn; at 80%= $200.4-203.4Bn.

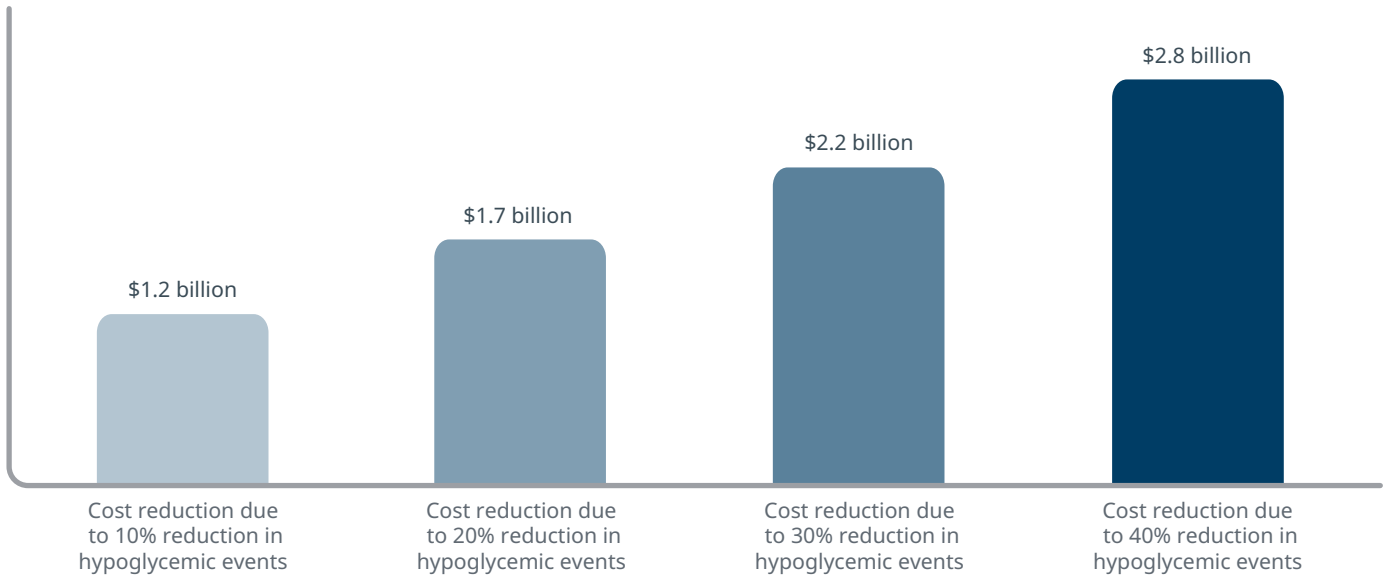
digital advances can overcome such issues. The previous analysis was therefore repeated, with the addition of incrementally reducing hypoglycemic events by up to 40% in people with Type 1 diabetes (see Exhibit 7). In doing so, this generated a total 10-year cost reduction of $6.7–9.7 billion (see Exhibit 8). Additional cost reductions may be possible due to reductions hypoglycemic events in people with Type 2 diabetes. This scenario is not covered in this analysis as data on these reductions is not currently available.

When analyzed at an individual level, people with Type 1 diabetes who start with an HbA1c of greater than 8% experienced the greatest reduction in costs, when incrementally improving TIR (see Exhibit 9).

Although PPG is widely considered to be a feature of TIR as it specifies glucose fluctuations at a specific time (e.g., post-meal), a separate analysis was carried out to determine the reduction in complications and costs associated with improving PPG from 200mg/dL to the consensus targets of 180mg/dL and 140mg/dL in people with Type 2 diabetes.[27,28] This additional analysis revealed reductions in the 10-year incidence of diabetes-related complications, that amount to a 10-year cost reduction of $1.7 billion (see Appendix, Exhibits 14 and 15 and Data Limitations and Modeling Caveats section).

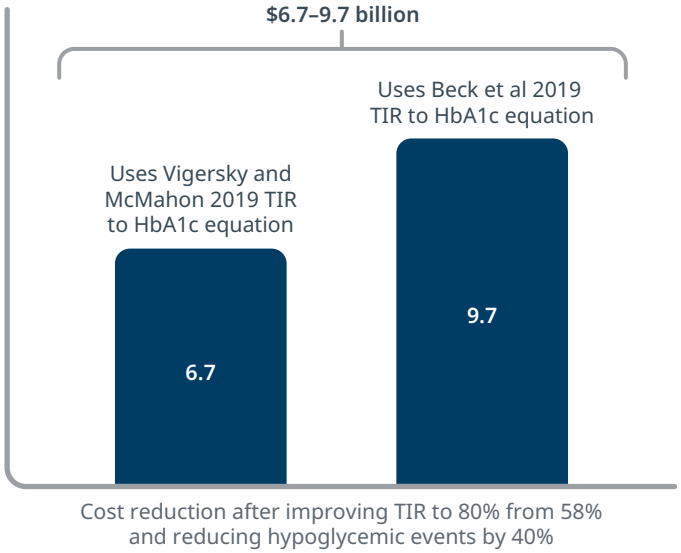
Taken together, these analyses demonstrate that improving TIR from its current state to the desired minimum consensus value has the potential to result in significant reductions in complications and costs over a 10-year period. These analyses are based on the most current information and represent the best understanding of how improvements in TIR may impact health outcomes (see Data Limitations and Modelling Caveats, Appendix). As more CGM and associated claims data are generated in the future, this understanding will be refined and further enhanced. For additional details on modeling methodology and further analyses, please refer to the appendix.

Exhibit 7: Incremental 10-Year Cost Reduction from Lowering the Rate of Hypoglycemic Events in People with Type 1 Diabetes as a Result of Improving TIR, US$Bn



Source: IQVIA Core Diabetes Model, 2019
Notes: The IQVIA Core Diabetes Model was used to determine the 10-year cost ($Bn) reduction after improving TIR from the current average of 58% to both the minimum consensus target of 70% (Battelino et al., 2019) or to 80% and incrementally reducing the rate of hypoglycemic events by 10%, 20%, 30% and 40% in Type 1 diabetes. Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019. Outputs from the model are provided on a per PwD basis, and therefore required multiplying by the total number of U.S. insulin-dependent people with Type 1 diabetes to generate the figures shown. Population size used to make this calculation was 1.25Mn for Type 1 diabetes (per the ADA).

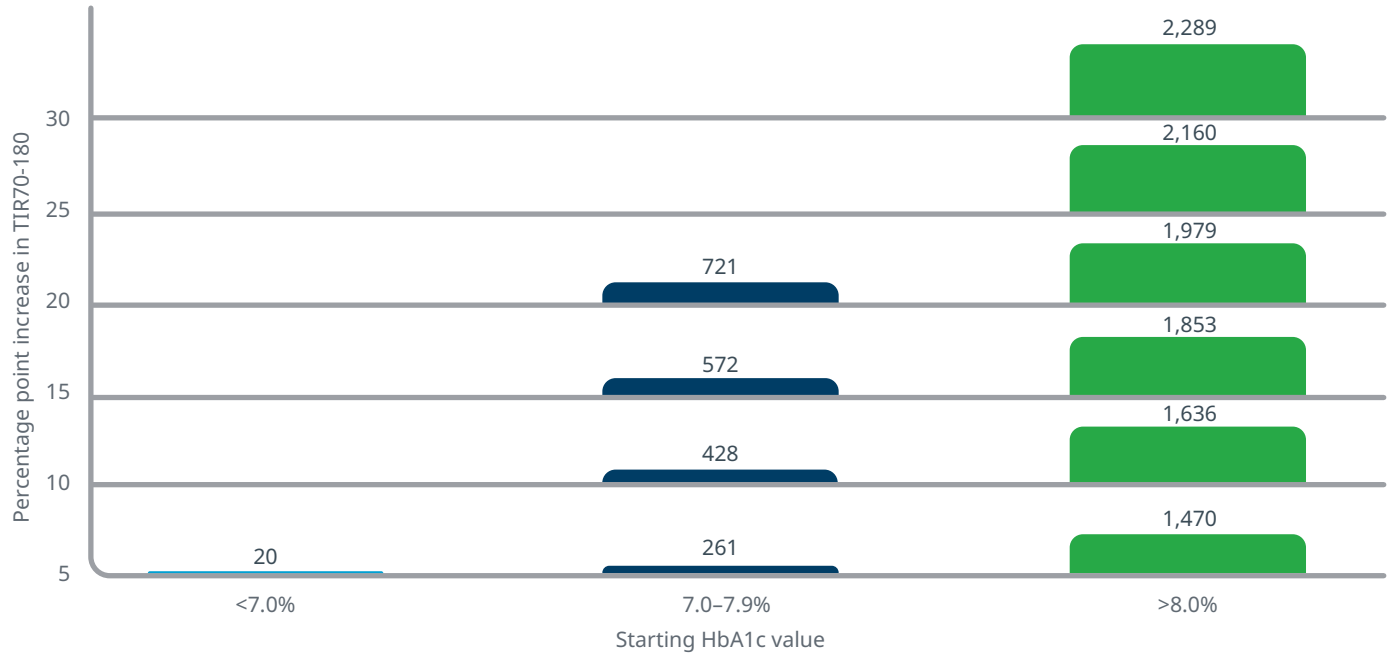
Exhibit 8: Summary of 10-Year Cost Reduction After Improving TIR to 80% and Reducing the Rate of Hypoglycemic Events, US$Bn



Source: IQVIA Core Diabetes Model, 2019

Notes: Shown is a summary of the 10-year cost ($Bn) reduction after improving TIR from the current average of 58% to 80% in people with Type 1 and Type 2 diabetes, as well as the costs reduced after reducing hypoglycemic event rate by 40% in people with Type 1 diabetes. Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019. The range of values shown are driven by the differences in equations linking HbA1c and TIR in Beck et al., 2019 and Vigersky and McMahon, 2019. Outputs from the model are provided on a per PwD basis, and therefore required multiplying by the total number of U.S. insulin-dependent people with Type 1 and Type 2 diabetes to generate the figures shown. Population sizes used to make these calculations were 1.25Mn for Type 1 diabetes (per the ADA), and 5.86Mn for Type 2 diabetes (per the CDC National Diabetes Statistics Report, 2017). The total complication costs at different TIR values were as follows: At 58% = $207.4Bn, At 80% = $200.4-203.4Bn, and with reduction in Hypoglycemic events = $197.7-200.6Bn.

Exhibit 9: 10-Year Per Person Cost Reduction Associated with Incrementally Improving TIR in Type 1 Diabetes, US$



Source: IQVIA Core Diabetes Model, 2019

Notes: The IQVIA Core Diabetes Model was used to determine the per person 10-year reduction in costs ($) associated with incrementally improving TIR at different starting HbA1c levels in people with Type 1 diabetes. Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019.

Approaches to further the use of TIR in the U.S. PwD population

+ **The management of blood glucose has advanced significantly through the advent of new technologies, advanced insulins and non-insulin therapies, however there is still room for improvement.**
+ **Potential approaches to further the use of TIR can help address this need for improved blood glucose management and enable a new era of diabetes care.**
+ **Three stages will be critical in this process: establishing the importance of TIR for blood glucose measurement and management across key stakeholders, advancing the use of this metric and promoting ease of use of associated technologies, and, lastly, perpetuating the use of TIR to sustain blood glucose management across all appropriate diabetes populations.**

The management of insulin-requiring Type 1 and insulin-managed Type 2 diabetes has improved significantly over time, through a combination of more precise and accessible glucose data, improved management tools, enhanced HCP management skills guided by diabetes care guidelines and broader support mechanisms for people with diabetes. Though there have been consistent improvements in glucose management, there is still significant room for improvement as measured through mean TIR and HbA1c. Based on the current research, the differential risk of improving TIR remains non-existent, suggesting that spending a greater amount of time in range carries no negative implications for PwD, and there is growing evidence of benefit from even modest improvement in TIR and increasingly so as TIR improves over 70%.[20]

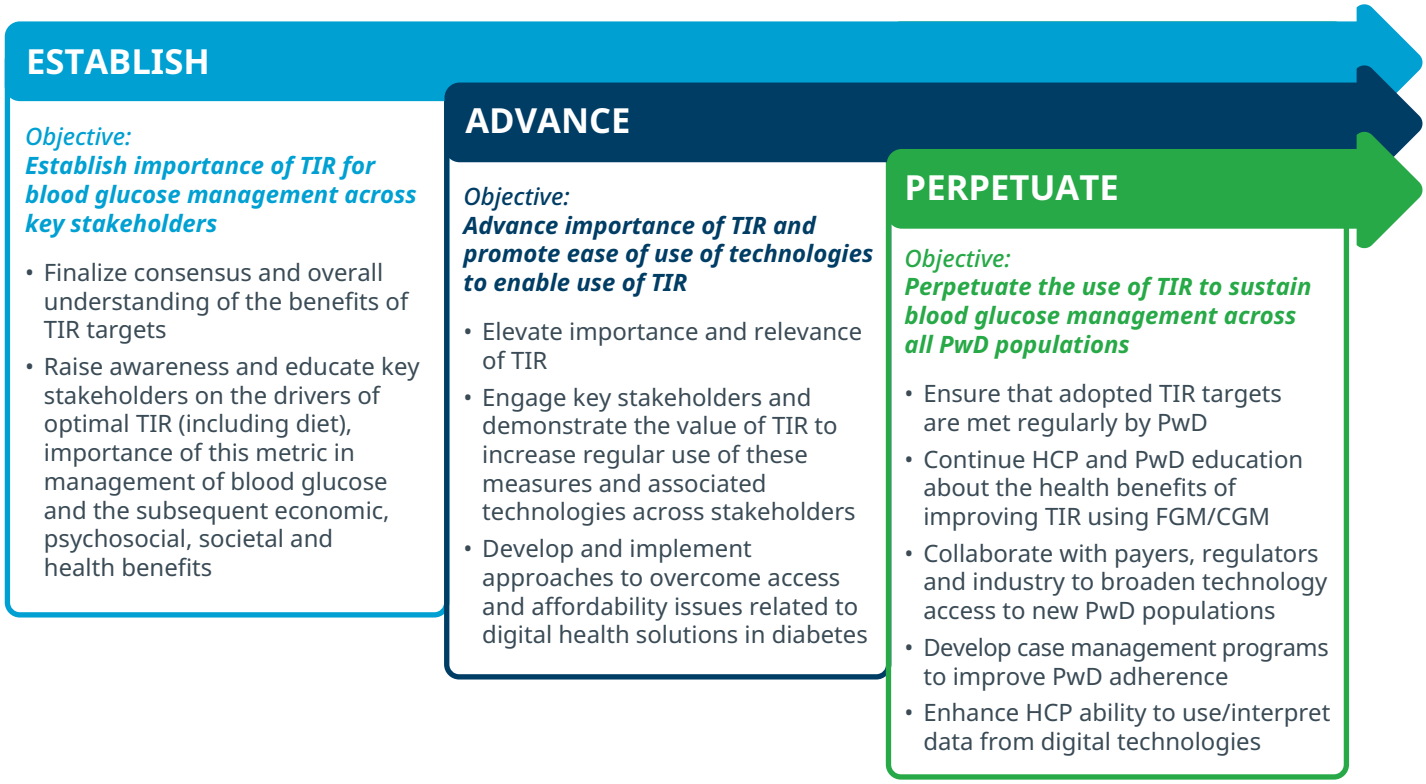
There is growing evidence of benefit from even modest improvement in TIR, and increasingly so as TIR improves over 70%.[20]

To advance into a new era of care in diabetes where all diabetes management tools including HbA1c and, increasingly, TIR, are optimized and personalized, a number of potential approaches can support a greater understanding and use of TIR across three stages of maturity (see Exhibit 10). These include activities from a healthcare policy, healthcare delivery and PwD perspective that can help establish, advance and perpetuate the use of TIR:

- **Diabetes Healthcare Policy** including actions regulators, CMS and/or commercial payers can enable
- **Diabetes Healthcare Delivery** including actions that can be taken by care providers, hospital systems, Integrated Delivery Networks (IDNs) to improve blood glucose management for PwD, along with guidelines for healthcare professionals and actions that involve their data systems or ability to conduct clinical research
- **People with Diabetes** including actions that can be taken by PwD advocacy groups and actions that can support PwD awareness and care decision making

The following approaches recognize voices from PwD, advocacy organizations and HCPs, on how to advance management and measurement tools to optimize insulin-managed diabetes.[20] Colloborative efforts between PwD, HCP, industry, and government stakeholders can accelerate access to and optimization of such new management and measurement tools. The following approaches therefore stand the greatest chance of advance and full implementation via such productive collaboration.

Exhibit 10: Approaches to Further the Use of TIR Across Three Stages of Maturity



Source: IQVIA, Aug 2019
Notes: Potential approaches to furthering the use of TIR as a diabetes management tool. FGM/CGM = Flash Glucose Monitoring/Continuous Glucose Monitoring.

ESTABLISH THE IMPORTANCE OF TIR IN SUSTAINING BLOOD GLUCOSE MANAGEMENT

Simplify TIR maintenance in PwD achieving glycemic targets and prioritize improvement in PwD that are not.

Key focus: Diabetes Healthcare Delivery

For those PwD already using CGMs, the first steps towards improving population-level TIR are to ensure that current glucose levels are maintained in those achieving targets and to develop approaches to improve TIR levels in those that are not. Even a 5% improvement in TIR provides benefit. Support for any advance in TIR is warranted. An evidence-based approach that simplifies management for PwD could be used to facilitate the process of maintenance, enabling the PwD to manage their TIR over time and to the best of their ability. In this regard, there is a need to continue refining the operation and utility of existing digital technologies (such as hybrid closed-loop insulin pumps) to make them more user-friendly, reduce the burden for PwD of optimizing their blood glucose, and improve adherence to therapy.[30]

With increasing analysis of data around TIR, there is a growing understanding of which PwD groups would benefit the most from a focus on these metrics. Moreover, analysis using the IQVIA Core Diabetes model demonstrated the greatest reduction in complications and costs could be achieved in PwD with the highest starting HbA1c value — a trend that has also been reflected, when incrementally improving TIR.[24] Irrespective of the starting point, PwD and HCPs should work towards improving TIR by 5% or more as this is viewed as clinically meaningful. Taken together, these findings suggest that certain PwD groups may require additional management than others (consisting of traditional approaches focused on diet

and exercise and next-generation advances in insulins or digital technologies) when seeking to use TIR as a tool for improving blood glucose. Prioritizing improvements in these populations and effectively managing them will be an important first step as other aspects of TIR continue to be established.

In addition to this, there are currently very few stakeholders, including digital health application developers and device manufacturers, that implement gamification to positively encourage and motivate PwD behavior.[31] Incentivizing PwD behavior through gamification may enhance blood glucose management, making individuals more aware of their condition and enhancing their understanding of the implications associated with variations in blood glucose levels.

Raise awareness of TIR in PwD, HCPs and diabetes support communities.

Key focus: PwD, Diabetes Healthcare Policy and Diabetes Healthcare Delivery

Awareness of TIR is currently limited to individuals that are either using, prescribing or advocating the use of CGMs. The majority of PwD are either unaware of these metrics or lack access to the medical devices required to effectively leverage TIR data. Therefore, raising the awareness of these metrics is critical for their future adoption and success as tools for managing blood glucose.

Several years ago, a "Know Your Number" campaign was run to raise awareness of HbA1c. An analogous campaign that builds off the success of this prior effort would be an effective means to raise awareness of TIR. Moreover, complimentary efforts from leading, trusted PwD and professional organizations such as the Juvenile Diabetes Research Foundation (JDRF), American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) would further bolster the effectiveness of such a campaign. To increase awareness at the PwD-level, it may be useful for stakeholders, such as professional and advocacy organizations, to update their training curriculum to include contemporary information around the utility of, and means to improve, TIR. Additionally, working groups consisting of PwD, HCPs, advocacy, and professional organizations can continue to advance understanding and raise awareness of management practices leading to achievement of TIR targets.

CGM and insulin pump use is currently limited. To raise awareness of these technologies, endocrinologists, diabetologists, specialist primary care physicians (local/regional KOLs), centers of excellence and innovative health systems can consider pioneering the regular use and monitoring of TIR in those PwD with access to CGMs to assess their usefulness to the wider HCP community. Lastly, a government organization, such as the National Clinical Care Commission (NCCC), could be engaged to evaluate and provide recommendations on the coordination of federal programs related to diabetes, disseminate educational materials and consolidate any existing programs. As experience with, and confidence in, these metrics grow, these stakeholders, including physician groups and endocrinologists can generate awareness of them through conference presentations and peer-reviewed publications, and likewise, PwD advocacy groups can support the importance of TIR in policy.

Rapidly advance real world evidence and randomized controlled studies to further inform optimal use and accelerate attainment of current consensus TIR levels.

Key focus: Diabetes Healthcare Delivery

There is limited but growing information demonstrating a relationship between TIR and long-term health outcomes.[32,33] However, there is still a need for more directed studies that demonstrate the causal relationship and benefits of achieving this metric.

To overcome this lack of information, an effort to develop, collect, and utilize real world evidence (RWE) and/or clinical trial data is needed to understand and demonstrate the positive impact that improving TIR has on health, societal, psychosocial and economic outcomes. One way to achieve this could be through the creation of a TIR registry that contains and gathers

longitudinal holistic data including, but not limited to, demographics, care methodology, short- and long-term outcomes. This type of registry could then be leveraged to demonstrate to HCPs and PwD the appropriate role for this metric when managing diabetes. Moreover, engaging companies who are currently leading behavior-focused studies, may allow stakeholders to redouble efforts to advance understanding of the psychosocial benefits linked to improved TIR.

There are however several pre-requisites, the most important being the availability of, or financial backing to generate such datasets. Several stakeholders are expected to play a pivotal role in making this solution possible, including device/pharmaceutical manufacturers, existing data holders, healthcare providers and academics. To overcome this, a working group or coalition of stakeholders, consisting of multiple manufacturers, academics, PwD, physician KOLs and HCPs, may be necessary. Assuming positive data is generated, the role of this group would be to create a research agenda that demonstrates and advocates the benefits of TIR. Academics and physician KOLs would be encouraged to analyze existing datasets generated by healthcare providers and be involved in the design of new studies. An artificial intelligence-based approach could also be leveraged for data mining purposes, with the aim of providing an understanding of TIR and its validity as a diabetes care measure in the short-term. Pilot partnerships between payers and integrated delivery networks could also be created to understand the value of improving TIR in targeted PwD populations. Together, these steps could help generate data on health and economic outcomes, solidify the value of TIR and subsequently reduce the risk for payers and manufacturers.

Encourage collaboration with the FDA to assess the clinical meaningfulness of TIR and consider establishing it as an accepted primary endpoint.

Key focus: Diabetes Healthcare Policy

Several steps by manufacturers, clinicians and the research community can ensure the FDA is provided the necessary evidence to support TIR and its clinical importance, and whether it can be appropriately leveraged as a primary endpoint or included in product labeling. For example, collaborative efforts can be made between device manufacturers and the Center for Devices and Radiological Health (CDRH) on a pilot basis to optimize study designs seeking to incorporate TIR as a primary endpoint and assess their outcomes. Moreover, both medical device and biopharmaceutical manufacturers could further progress in this direction by convening a Critical Path Innovation Meeting, which addresses the issues around medical device developments and their associated metrics, including TIR. This could also be coupled with collaboration alongside the Center for Drug Evaluation and Research to demonstrate the broader usefulness and clinical importance of TIR for diabetes management. The overall goal of these collaborative efforts with various FDA departments would be to encourage the FDA to assess the appropriateness of TIR as a primary outcome and consider it for inclusion as a primary outcome in Phase II and Phase III clinical trials.

Develop further consensus on ideal TIR targets for specific populations and propose inclusion of these targets in clinical care guidelines.

Key focus: Diabetes Healthcare Delivery

Currently, there is a consensus by Advanced Technologies & Treatments for Diabetes (ATTD) working group that states at least 70% of a PwD's time should be spent within a glucose range of 70–180mg/dL. Updates in the ADA Standard of Medical Care have, also, recently acknowledged that metrics such as TIR, TAR, TBR from CGMs are providing additional information that can

aid in blood glucose management.[22] The targets set for TIR in the general PwD population, based on ATTD consensus, is predominantly due to 70% TIR being equivalent to an HbA1c of 7%, which is the general, international consensus minimum target value for PwD. There are, however, scenarios in which this number is not appropriate and requires personalization, as has been the case with HbA1c targets. For example, women that are pregnant experience greater red blood cell turnover and are therefore recommended to maintain an HbA1c of 6-6.5% or lower.[34] Elderly PwD with few coexisting chronic illnesses and intact cognitive function are recommended to maintain an HbA1c of less than 7.5%, whereas those with significant co-morbidities should have HbA1c goals between 8–8.5% or lower.[3]

Building on existing data analyses, physician KOLs and HCPs can help ensure appropriate stratification of PwD and promote TIR in those individuals that would benefit the most. Once these populations have been defined, efforts can be made to achieve TIR targets for greater blood glucose management.

The aim of building a consensus for TIR in different populations is to create clarity for HCPs and PwD when setting realistic, safe and achievable blood glucose targets. However, before doing so, there are several prerequisites including clinical data that justifies the use of certain targets and an overall agreement on which targets are the most appropriate. To finalize the optimal target values, engagement of academics and physician key opinion leaders would help ensure that existing datasets are analyzed appropriately using methods, such as artificial intelligence, to identify accurate TIR values for different populations, along with what tools/approaches have worked best for achieving better TIR in different populations. PwD stratification will also be important when individualizing TIR targets, allowing for more apt and achievable targets. Once both general and individualized targets have been established, engagement with stakeholders including academics, leading physicians, manufacturers and policy makers, can help form an international consensus.

Another key step in establishing TIR as a tool for blood glucose management is through its inclusion into clinical guidelines, such as those produced by the American Diabetes Association (ADA) and American Associate of Clinical Endocrinologists (AACE). Recent updates in the ADA Standard of Medical Care acknowledging metrics such as TIR, TAR, TBR represent an important first step in this process. As more robust data continues to be generated, physician KOLs, academics and manufacturers could help ensure that the clinical benefit of TIR is demonstrated to the ADA or AACE. By putting forth TIR and corresponding evidence for inclusion into guidelines, its use as a tool for managing blood glucose is expected to grow significantly. Moreover, its inclusion and advocacy by PwD groups, is likely to legitimize the benefits and usefulness offered by such a measure.

Previous efforts by Advanced Technologies & Treatments for Diabetes (ATTD) have aimed to generate TIR consensus target values for different PwD populations. These targets are now widely endorsed by a number of different organizations, including the American Diabetes Association. FDA support may also be needed for inclusion to occur, which will depend on the availability of outcomes data demonstrating the clinical benefits of TIR. Lastly, inclusion of TIR into the U.S. government run "Healthy People 2030 Objectives and Measures", with advocacy from the ADA and JDRF, would significantly enhance the positioning of TIR as an effective diabetes management tool.

ADVANCE THE USE OF TIR

Support endocrinologists, PCPs, payers and PwD by demonstrating the benefits of improving TIR.

Key focus: PwD and Diabetes Healthcare Delivery

The benefits of improving TIR is currently appreciated by a select few stakeholders, including academics, physician key opinion leaders and endocrinologists. This is due largely to the limited access to CGMs by the majority of PwD, who are treated predominantly by primary care physicians.[35] By raising awareness and demonstrating the value of TIR as a tool for blood glucose management to the wider spectrum of key stakeholders, acceptance and utilization is likely to increase significantly. Before achieving this however, access to CGMs would need to be expanded to a wider range of PwD, which additionally leads to considerations for care providers and institutions around the time and additional staff needed to download and analyze this data.

Physician KOLs and academics can submit their research on TIR to peer-reviewed clinical journal articles (i.e., JAMA, Lancet, NEJM) for dissemination to the wider community of HCPs. Distribution of these materials by the same stakeholders to educate other stakeholders (such as payers, policy makers, PwD) would also be important for advancing the use of TIR and could be achieved through conferences, such as the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) or the annual American Diabetes Association Scientific Sessions. Enhanced coverage for Diabetes Care and Education Specialist within CMS and commercial insurance plans will still be needed in order to further enhance PwD education and could be discussed with the American Association of Diabetes Educators (AADE) and the Center for Medicare and Medicaid Services (CMS). PwD involvement at each step will ensure that the materials produced focus on key aspects relevant to PwD (such as quality of life, psychosocial benefits, etc.). Moreover, these materials can be updated as required, ensuring that the most up-to-date information is presented and available.

Establish an appropriate reimbursement framework to promote collaboration between insurers, PwD and HCPs to leverage and utilize CGMs data and blood glucose management tools to optimize TIR.

Key focus: Diabetes Healthcare Policy and Diabetes Healthcare Delivery

Short-term metrics, such as TIR, are not widely used amongst HCPs. Initial steps towards further supporting the use of CGMs through development of current procedural terminology (CPT) codes for CGM training and data interpretation are taking place.[36,37] CMS has recently stated that policies will be revised to support the use of CGMs.[38] Billing codes have been established for technical set-up and interaction with device and for HCP review and interpretation of data. However, more comprehensive reimbursement policies that consider the full set of time and efforts that HCPs put in and ensure that they are appropriately compensated would help with further adoption of these metrics.

Make advancements in electronic healthcare records to enable them to capture TIR data and guide care improvements for PwD.

Key focus: Diabetes Healthcare Policy and Diabetes Healthcare Delivery

Electronic healthcare records provide ease of access to historic and current health data. Such access allows for informed decision-making at the patient and population level. TIR data generated by CGMs may not currently be optimally captured in electronic health records, resulting in loss of valuable PwD and population level care insight and learning. Ideally, TIR data capture in electronic health records would be accomplished remotely or locally via electronic or wireless transfer. As a practical matter, however, even enabling manual entry to live cells in an electronic health records would make claims data with TIR and HbA1c details accessible for care improvement and research at multiple levels. By harmonizing data collection and transfer protocols

(i.e., protocols for transferring data from a CGM to a readable software) across all CGMs, decision-making based on TIR values will likely become more efficient as data becomes more easily accessible, for example within an electronic health record (EHR). This can occur either through collaboration between health system stakeholders to develop an interoperable data protocol for CGM collection and transfer or by policymakers promoting interoperability or protocols through appropriate legislative changes. Recent efforts have been made by the Office of the National Coordinator for Health Information Technology (ONC) to promote a Shared Nationwide Interoperability Roadmap and are themselves engaged in developing and harmonizing domestic health information technology standards.[39] Existing players could further support efforts in CGM data standardization by collaborating to promote standardized data formats and data accessibility.

Consider value-based contracting agreements to further use of CGMs and improve TIR management and maintenance.

Key focus: Diabetes Healthcare Policy and Diabetes Healthcare Delivery

Agreements that pay based on the value generated by innovation are beginning to gain traction in the diabetes space.[40] CGMs and other diabetes care tools that improve TIR help advance the use of value-based agreements — an approach supported by institutes such as the University of Michigan Value-Based Insurance Design Center. As the utilization of metrics such as TIR is expected to grow, value-based agreements would provide a way to showcase the value of improving TIR by tying them to corresponding improvements such as PwD health outcomes and associated cost-savings, while simultaneously sharing risk between payers and manufacturers. Early work is happening and can be accelerated though analyses that demonstrate the value associated with improving TIR. These analyses are expected to be a part of the 'establish' phase discussed above and could be supported both by academics and health economists to estimate the healthcare budget savings due to improving TIR.

Empower and leverage nurses, diabetes educators, healthcare assistants, technology navigators and pharmacists to support PwD using TIR.

Key focus: Diabetes Healthcare Delivery

The clinical importance of TIR as a tool for managing blood glucose is currently promoted largely by thought-leading endocrinologists. However, endocrinologists are not easily accessible by all PwD, making adherence to TIR targets and follow-up potentially challenging. By engaging and educating a variety of clinical stakeholders (i.e., pharmacists, nurses, diabetes educators) about the importance of TIR and approaches to improve it, this could allow for a more holistic care approach to diabetes and ease the burden on physicians. In doing so, the likelihood of achieving TIR targets is also expected to improve.

To make this possible, care management organizations could help by designing trainings for a variety of clinical stakeholders (i.e., pharmacists, nurse, diabetes educators) that focus on describing the different role requirement in improving TIR and managing blood glucose. Clinical stakeholders can then be empowered to use this data and take appropriate decisions for PwD.

PERPETUATE THE USE OF TIR TO APPROPRIATE POPULATIONS

Foster an environment that encourages the development of increasingly simple-to-use, broadly accessible CGM and blood glucose management tools. Expand the use of such technology and tools.

Key focus: PwD, Diabetes Healthcare Policy and Diabetes Healthcare Delivery

CGMs make the process of measuring glucose levels more convenient for PwD but are also less accessible and largely confined to a small number of the Type 1 diabetes population.[41] By widening the access and affordability of CGMs to a larger Type 1 population and insulin-dependent Type 2, the use of metrics, such as TIR, is likely to increase significantly.

Making this solution possible likely requires involvement from stakeholders from across the healthcare delivery system. Payers and policymakers could enhance both insurance and Medicare coverage of CGMs, ensuring that eligibility for these devices is expanded. Moreover, PwD advocacy groups can disseminate the most up-to-date information about advances in diabetes management.

Professional and advocacy organizations, their associated members and all other Diabetes Care and Education Specialist networks/individuals may consider working alongside PwD to enhance the understanding and utility of CGM data, leveraging both in-person and internet-based strategies to disseminate information regarding diabetes management to those that are not physically able to access care. Easy-to-use, accessible software systems for physicians and PwD may need to be developed. Simplified decision-making using data for physicians — particularly primary care physicians — will help reduce operational burden. Lastly, the development of care pathways would be beneficial for enhancing the holistic management of PwD (including diet, exercise), as well as appropriate training for nurses and HCPs.

Include TIR among quality measures (e.g., HEDIS, STAR) used by health plans to benchmark care provision.

Key focus: Diabetes Healthcare Policy

TIR is not currently included as a quality measure among HEDIS and STAR Performance Metrics put forth by the National Committee for Quality Assurance (NCQA) and Centers for Medicare and Medicaid Services (CMS), respectively. Inclusion of this metric as a quality measure would further enhance its usefulness as a tool for managing blood glucose. To achieve this, academics, manufacturers and PwD advocate groups could help by demonstrating the health and economic benefits associated with TIR to CMS and NCQA. Action from diabetes groups could help ensure inclusion of TIR as a quality measure — for instance the Diabetes Advocacy Alliance through their 2020 Advocacy Priorities — to further legitimize the position of these metrics in diabetes management.

Collectively, these steps could help ensure that TIR is included among the quality metrics accepted to measure performance on importance dimensions of care and service. Finally, payers could help ensure HCPs regularly collect relevant data to monitor this measure through close collaboration.

Conclusion

The societal and economic burden of diabetes in the United States is significant and rising. In 2017 alone, diabetes cost the United States approximately $404 billion, with 1.5 million people diagnosed annually.[1,2] Advances in technology have allowed for improved blood glucose management through the use of new metrics, such as TIR, however several challenges still exist that limit its adoption in the wider diabetes population, such as access to technology. Once overcome, the benefits of using these metrics as tools for managing blood glucose are expected to lead to a reduction in complications and associated costs.

Considering this, a comprehensive and coordinated set of actions has been laid out in this paper to establish the awareness of TIR as a measure of glucose management, advance the use of this metric by the wider PwD population and finally perpetuate its use through empowerment, policy change and where required, widened technology uptake.

Appendix

ATTD CONSENSUS STATEMENT VALUES FOR TIR

A statement released by an Advanced Technologies & Treatments for Diabetes (ATTD) consensus group during the American Diabetes Association 79th Scientific Sessions outlined the recommended amount of time in, above or below recommended glucose ranges for different PwD groups (see Exhibit 11).[20] This consensus was released in response to what the group perceived to be "relatively low" adoption of CGMs that they attributed to a lack of clear guidelines for PwD glycemic targets.

IQVIA CORE DIABETES MODEL

The IQVIA Core Diabetes model (CDM) was utilized to model the complications and costs associated with improving TIR. The IQVIA Core Diabetes Model is a simulation model that predicts long-term health outcomes and costs associated with the management of Type 1 and Type 2 diabetes at the individual PwD level.[42] This model has been used extensively by health agencies and pharmaceutical manufacturers to determine reimbursement decisions, therapeutic cost-effectiveness and optimal patient management strategies.[43] Moreover, a validation exercise published in 2014 examined the predictive validity and robustness of the IQVIA Core Diabetes model by comparing the outputs generated against multiple published clinical trial endpoints.[43]

The IQVIA Core Diabetes model structure comprises 17 interdependent sub models that simulate numerous diabetes-related complications, including angina pectoris, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, nephropathy (comprising microalbuminuria, gross proteinuria and end-stage renal disease), neuropathy, foot ulcer and amputation, pulmonary edema, and depression, in addition to non-specific mortality. Inputs for the IQVIA Core Diabetes model are divided into four sections, including cohort, economics, treatment and clinical data, with the majority being derived from the DCCT, EDIC and UKPDS. More specifically, cohort data inputs include age, gender, duration of diabetes, race, HbA1c and baseline proportion of complications. Currently, the IQVIA Core Diabetes model cannot directly use TIR as an input variable.

Exhibit 11: Consensus Target Percentage of Readings in Different Ranges

	TIR		TBR		TAR	
	PERCENTAGE OF READINGS	TARGET RANGE (MG/DL)	PERCENTAGE OF READINGS	BELOW TARGET LEVEL (MG/DL)	PERCENTAGE OF READINGS	ABOVE TARGET LEVEL (MG/DL)
T1DM*/ T2D	>70%	70–180	<4% <1%	<70 <54	<25% <5%	>180 >250
Old/high risk T1DM/T2D	>50%	70–180	<1%	<70	<10%	>250
Pregnancy T1DM	>70%	63–140	<4% <1%	<63 <54	<25%	>140
Pregnancy T2D/GDM	Not included in consensus report due to lack of data					

Source: Battelino et al., 2019

Notes: Consensus target values for TIR for Type 1 and Type 2 diabetes populations. GDM = gestational diabetes mellitus; TIR= Time in Range, TBR= Time Below target glucose Range, TAR= Time Above target glucose Range; *For age <25 years, if the A1C goal is 7.5%, set TIR target to approximately 60%

Appendix

MODELING SCENARIOS AND METHODOLOGY

Given that the CDM cannot model based on TIR values, these were instead converted into HbA1c values. To do so, several recently published peer-reviewed articles were leveraged that establish a robust correlative relationship between TIR and HbA1c. These articles were then used to convert TIR into HbA1c (see Exhibit 12).

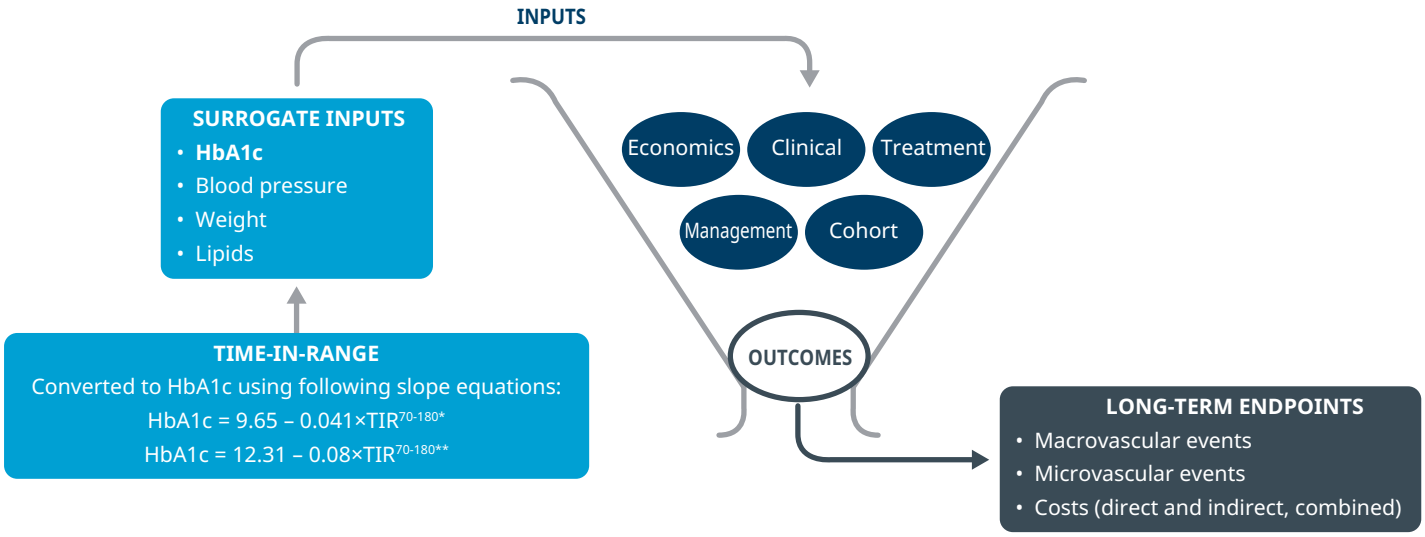
The correlative relationship between TIR and HbA1c was recently described in two publications, which both used different approaches to conclude this relationship. For example, Beck et al. (2019) reanalyzed data from four clinical trials that used CGM devices, whereas Vigersky and McMahon (2019) performed a meta-analysis of 18 articles.[23,24] In both articles, the majority of data was derived from people with Type 1, and not Type 2 diabetes. The conclusion from these studies was that for every 10 percentage change in TIR, HbA1c saw either a 0.5 or 0.8 percentage point improvement (see Exhibit 13).[23,24] The Beck paper also suggests that improvements in TIR have a greater impact on PwD with higher starting HbA1c values. Additionally, a recent paper looking at children and adolescents in Sweden also establishes a strong non-linear correlation between TIR and HbA1c.[44]

Exhibit 13: Impact of Improving TIR on HbA1c

STUDY	TIR IMPROVEMENT	HBA1C REDUCTION
Beck et al., 2019	10 p.p.	0.5 p.p.
Vigersky and McMahon, 2019	10 p.p.	0.8 p.p.

Source: Beck et al., 2019, Vigerksy and McMahon, 2019
Notes: Shown are the percentage point reductions in HbA1c associated with improvements in TIR, as described by Beck et al., 2019 and Vigersky and McMahon, 2019.

Exhibit 12: IQVIA Core Diabetes Model Inputs and Outputs



Source: IQVIA, Aug 2019; *Beck et al., 2019; **Vigersky et al., 2019
Notes: Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, TIR values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019 and Vigersky and McMahon, 2019.The model then takes HbA1c, in addition to other surrogate inputs such as blood pressure, weight and lipids, and generates long-term endpoints including life expectancy, incidence of macro/micro-vascular events and costs. Slope equations used to convert TIR into HbA1c were developed predominantly based on Type 1 Diabetes datasets per Beck et al., 2019, with a small Type 2 diabetes population derived from Vigersky and McMahon, 2019. Economic refers to medical costs and utilities of all complications and events considered in the model. Clinical refers to the settings for the clinical data in the model (event rates, risk adjustments, ethnicity adjustments etc.). Management refers to assumptions for screening procedures and primary and secondary prevention with concomitant medications. Treatment refers to all effects and adverse events of the treatment intervention being considered. Cohort refers to the PwD profiles used in the model.

ADDITIONAL COMPLICATIONS AND COSTS MODELING DATA

Exhibit 14: 10-Year Cumulative Incidence of Developing Diabetes-Related Complications After Improving PPG in T2D

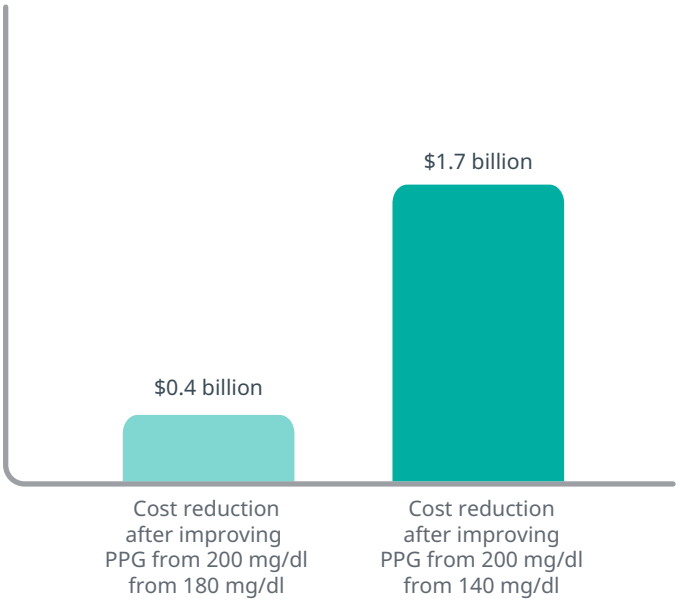
T2D

COMPLICATION	200MG/DL	180MG/DL	140MG/DL
Myocardial infarction	12.76	12.61	12.32
End-stage renal disease	2.84	2.62	2.29
Severe vision loss	5.18	5.05	4.912
Amputation	1.00	0.967	0.972

Source: IQVIA Core Diabetes Model, 2019

Notes: The IQVIA Core Diabetes Model was used to calculate the cumulative incidence of developing major diabetes-related complications over a 10-year time horizon in people with Type 2 diabetes. Major diabetes-related complications changed after improving PPG from 200mg/dL to 180mg/dL (ADA target value) and 140mg/dL (AACE target value). Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, PPG values are required to be converted into HbA1c prior to being modelled, per Valensi et al., 2018. Value of current average PPG levels in the U.S. population are not available, An approximate value of 200MG/DL is assumed for the purposes of this calculation based on El-Kebbi et al., 2004 and Borg et al., 2010.

Exhibit 15: 10-Year Costs Avoided by Improving PPG in People with Type 2 Diabetes, US$Bn



Source: IQVIA Core Diabetes Model, 2019

Notes: The IQVIA Core Diabetes Model was used to determine the 10-year cost ($Bn) reduction by improving PPG from 200mg/dL to 180mg/dL (ADA target value) and 140mg/dL (AACE target value) in people with Type 2 diabetes. Currently available risk equations do not include TIR as a variable but have HbA1c. As HbA1c is a core input of the model, PPG values are required to be converted into HbA1c prior to being modelled, per Valensi et al., 2018. Outputs from the model are provided on a per PwD basis and therefore required multiplying by the total number of US insulin-dependent people with Type 2 diabetes to generate the figures shown. Population size used to make this calculation was 5.86M (per the CDC National Diabetes Statistics Report, 2017) for Type 2 diabetes. Value of current average PPG levels in the U.S. population are not available. An approximate value of 200MG/DL is assumed for the purposes of this calculation based on El-Kebbi et al., 2004 and Borg et al., 2010. However, the actual US PPG may be higher as the average HbA1c associated with 200 mg/dl is lower than estimates of US averages. The total complication costs at different PPG values were as follows: At 200mg/dl = $174.3Bn, at 180mg/dl = $173.9Bn and at 140mg/dl = $172.6Bn.

Appendix

Exhibit 16: 10-Year Cumulative Incidence of Developing Diabetes-Related Complications After Improving TIR in Type 1 and Type 2 Diabetes

TYPE 1 DIABETES

COMPLICATION	58% TIR	70% TIR	80% TIR
Microalbuminuria	6.90	3.07–3.23	1.56–3.23*
Gross proteinuria	4.24	3.12–3.59	2.49–3.19
End-stage renal disease	3.85	3.79–3.81	3.72–3.73
Peripheral vascular disease	2.46	1.95–2.16	1.59–1.97
Heart failure	0.68	0.55–0.61	0.45–0.55
Angina	2.93	2.37–2.59	1.97–2.38
Stroke	0.57	0.45–0.51	0.38–0.47
Myocardial infarction	3.29	2.65–2.97	2.25–2.70
Proliferative diabetic retinopathy	6.67	2.92–4.41	1.46–3.10
Macular edema	7.33	3.21–4.83	1.64–3.35
Severe vision loss	9.12	7.99–8.44	7.55–8.00
Cataract	6.62	6.62–6.71	6.65–6.56
Ulcer	3.00	1.83–2.43	1.38–1.92
Recurrent ulcer	14.99	14.21–14.65	13.92–14.26
Amputation ulcer	3.96	3.73–3.82	3.57–3.73
Amputation recurrent ulcer	3.69	3.60–3.61	3.58–3.61
Neuropathy	14.38	8.32–10.93	5.24–8.65

Source: IQVIA Core Diabetes Model, 2019

Notes: Complete 10-year cumulative incidence of developing diabetes-related complications in type 1 and type 2 diabetes after improving TIR from 58% to 70% and 80%, as determined using the IQVIA Core Diabetes Model. *80% TIR is equivalent to an HbA1c value of 5.5%. The risk equations used for modeling are based on PwD with HbA1c values of greater than 7%. In several scenarios where HbA1c is less than 7% (such as in the case where TIR is 80%), the risk equations may be less robust in their predictive ability.

DATA LIMITATIONS AND MODELING CAVEATS

Despite the robustness of the analyses discussed throughout this whitepaper, there are also several data limitations and modeling caveats that need to be considered.

1. As HbA1c is a core input of the model, TIR and PPG values are required to be converted into HbA1c prior to being modelled, per Beck et al., 2019, Vigersky and McMahon, 2019 and Valensi et al., 2018. Studies linking HbA1c with TIR are growing but are still based on correlative relationships with high-levels of data variability.
2. Long-term trials linking TIR to clinical outcomes are yet to be conducted.

Exhibit 16: 10-Year Cumulative Incidence of Developing Diabetes-Related Complications After Improving TIR in Type 1 and Type 2 Diabetes

TYPE 2 DIABETES

COMPLICATION	58% TIR	70% TIR	80% TIR
Microalbuminuria	15.85	12.54 – 14.05	10.26 – 12.63
Gross proteinuria	9.55	7.36 – 8.33	5.94 – 7.49
End-stage renal disease	2.84	1.94 – 2.34	1.42 – 1.98
Peripheral vascular disease	9.05	8.11 – 8.54	7.29 – 8.15
Heart failure	7.55	7.51 – 7.58	7.43 – 7.52
Angina	8.57	8.69 – 8.58	8.64 – 8.63
Stroke	7.37	6.97 – 7.14	6.74 – 7.03
Myocardial infarction	12.76	11.99 – 12.39	11.37 – 11.97
Background diabetic retinopathy	9.01	6.98 – 7.91	5.68 – 7.06
Proliferative diabetic retinopathy	1.21	0.88 – 1.02	0.68 – 0.88
Macular edema	8.04	6.22 – 6.97	5.09 – 6.30
Severe vision loss	5.18	4.78 – 4.98	4.56 – 4.83
Cataract	4.07	3.59 – 3.82	3.27 – 3.61
Ulcer	1.12	1.01 – 1.06	0.92 – 1.03
Recurrent ulcer	2.85	2.79 – 2.79	2.74 – 2.80
Amputation ulcer	1.00	0.97 – 0.97	0.96 – 0.95
Amputation recurrent ulcer	0.82	0.78 – 0.78	0.80 – 0.78
Neuropathy	28.84	23.76 – 26.13	20.04 – 24.11

3. Data on TIR in people with Type 2 diabetes is limited to only one paper, with a relatively small sample size.[23] Further research is needed to establish an independent link between TIR and HbA1c in Type 2 diabetes populations. Data on PPG in people with Type 1 diabetes and the link with HbA1c is limited.

4. The risk equations used for modeling are based on PwD with HbA1c values of greater than 7%. In several scenarios, the CDM was run to HbA1c levels that were less than 7% (such as in the case where TIR is 80%), making the risk equations less robust in their predictive ability.

5. It is currently not clear whether PwD that experience persistently low TIR yield the same benefits when improving TIR, versus those that experience only acute episodes of low TIR.

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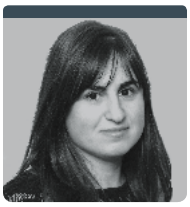

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About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

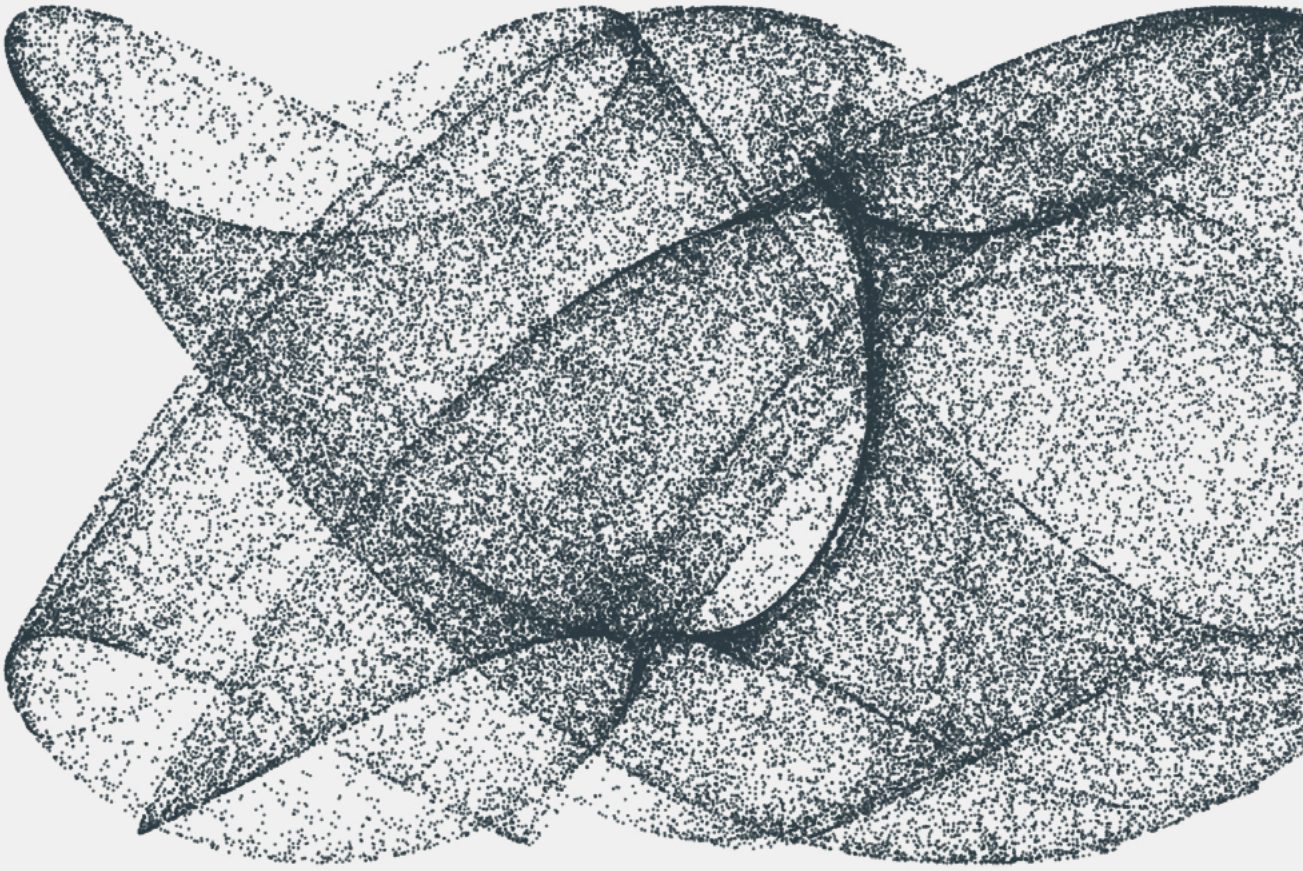
Guiding Principles

The Institute operates from a set of Guiding Principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

Artwork on the cover of this report represents the diabetes-related complications and costs avoided after improving glycaemic values from their current average to the minimum consensus statement and beyond, over a 10 year period in the United States.



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