Consensus Recommendations for the Use of Automated Insulin Delivery (AID) Technologies in Clinical Practice

Moshe Phillip, MD[1,2]*, Revital Nimri, MD[1,2]*, Richard M Bergenstal, MD[3], Katharine Barnard-Kelly, PhD[4], Thomas Danne, MD[5], Roman Hovorka, PhD[6], Boris P Kovatchev, PhD[7], Laurel H Messer, PhD[8], Christopher G Parkin, MSc[9], Louise Ambler-Osborn, MS,NP[10], Stephanie A Amiel,MD,FRCP[11], Lia Bally, MD[12], Roy W Beck, MD, PhD[13], Sarah Biester, RN[5], Torben Biester, MD[5], Julia E Blanchette, PhD[14,15], Emanuele Bosi, MD[16], Charlotte K Boughton, MD, PhD[17], Marc D Breton, PhD[7], Sue A Brown, MD[7,18], Bruce A Buckingham, MD[19], Albert Cai, BSE[20], Anders L Carlson, MD[3], Jessica R Castle, MD[21], Pratik Choudhary, MD,FRCP[22], Kelly L Close, BA[20], Claudio Cobelli, PhD[23], Amy B Criego, MD,MS[3], Elizabeth Davis, MD, PhD[24], Carine de Beaufort, MD, PhD[25], Martin I de Bock, FRACP, PhD[26], Daniel J DeSalvo, MD[27], J Hans DeVries, MD, PhD[28], Klemen Dovc, MD, PhD[29], Francis J Doyle III, PhD[30], Laya Ekhlaspour, MD[31], Naama Fisch Shvalb, MD[1], Gregory P Forlenza, MD[8], Geraldine Gallen, RGN[11], Satish K Garg, MD[8], Dana C Gershenoff, MS,RD,CDCES[3], Linda A Gonder-Frederick, PhD[7], Ahmad Haidar, PhD[32], Sara Hartnell, BSc[33], Lutz Heinemann, PhD[34], Simon Heller, MB,DM,FRCP[35], Irl B Hirsch, MD[36], Korey K Hood, PhD[37], Diana Isaacs, PharmD[38], David C Klonoff, MD[39], Olga Kordonouri, MD[5], Aaron Kowalski, PhD[40], Lori Laffel, MD,MPH[10], Julia Lawton, PhD[41], Rayhan A Lal, MD[42], Lalantha Leelarathna, PhD[43], David M Maahs, MD[19], Helen R Murphy, MD,FRACP[44], Kirsten Nørgaard, MD,DMSc[45], David O'Neal, MBBS,MD[46], Sean Oser, MD,MPH[47] Tamara Oser, MD[47], Eric Renard, MD, PhD[48], Michael C Riddell, PhD[49], David Rodbard, MD[50], Steven J Russell, MD, PhD[51], Desmond A

© The Author(s) 2022. Published by Oxford University Press on behalf of the Endocrine Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Schatz, MD[52], Viral N Shah, MD[8], Jennifer L Sherr, MD, PhD [53], Gregg D Simonson, PhD [3], R Paul Wadwa, MD[8], Candice Ward, BSc[54], Stuart A Weinzimer, MD[53], Emma G Wilmot, PhD [55]and Tadej Battelino, MD, PhD [29]

* Moshe Phillip and Revital Nimri contributed equally to the manuscript

[1]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

[2]Sacker Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

[3]International Diabetes Center, HealthPartners Institute, Minneapolis, MN, USA

[4]Southern Health NHS Foundation Trust, UK

[5]AUF DER BULT, Diabetes-Center for Children and Adolescents, Endocrinology and General Paediatrics, Hannover, Germany

[6]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK

[7]University of Virginia Center for Diabetes Technology, Charlottesville, Virginia, USA

[8]Barbara Davis Center for Diabetes, University of Colorado Denver - Anschutz Medical Campus, Aurora, Colorado, USA

[9]CGParkin Communications, Inc., Henderson, NV, USA

[10]Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

[11]King's College London, London, UK

[12]Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism, Bern University Hospital and University of Bern, Bern, Switzerland

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

[13]Jaeb Center for Health Research Foundation, Inc., Tampa, FL, USA

[14]University of Utah, College of Nursing, Salt Lake City, UT, USA

[15]University Hospitals Cleveland Medical Center, Cleveland, OH, USA

[16]Diabetes Research Institute, IRCCS San Raffaele Hospital and San Raffaele Vita Salute University, Milan, Italy

[17]University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK

[18]University of Virginia, Division of Endocrinology, Charlottesville, VA, USA

[19]Division of Endocrinology, Department of Pediatrics, Stanford University, School of Medicine, Stanford, California, USA

[20]The diaTribe Foundation / Close Concerns, San Diego, CA, USA

[21]Oregon Health & Science University, Harold Schnitzer Diabetes Health Center, Portland, OR, USA

[22]Diabetes Research Centre, University of Leicester, Leicester, UK

[23]Department of Woman and Child's Health, University of Padova, Padova, Italy

[24]Telethon Kids Institute, University of Western Australia, Perth Children's Hospital, Western Australia

[25]Diabetes & Endocrine Care Clinique Pédiatrique DECCP/Centre Hospitalier Luxembourg, and faculty of Sciences, technology and Medicine, University of Luxembourg, Esch sur Alzette, GD Luxembourg/Department of Paediatrics, UZ-VUB, Brussels, Belgium

[26]Department of Paediatrics, University of Otago, Christchurch, New Zealand

[27]Baylor College of Medicine, Houston, TX, USA

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

[28]Amsterdam UMC, University of Amsterdam, Internal Medicine, Amsterdam, the Netherlands

[29]Department of Pediatric Endocrinology, Diabetes and Metabolic Diseases, UMC - University Children's Hospital, Ljubljana, Slovenia, and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[30]Harvard University, Harvard John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA, USA

[31]Stanford University School of Medicine, Lucile Packard Children's Hospital - Pediatric Endocrinology, Palo Alto, CA, USA

[32]McGill University, Department of Biomedical Engineering, Montreal, Canada

[33]Cambridge University Hospitals NHS Foundation Trust, Wolfson Diabetes and Endocrine Clinic, Cambridge, UK

[34]Science Consulting in Diabetes GmbH, Kaarst, Germany

[35]Department of Oncology and Metabolism, University of Sheffield, UK

[36]University of Washington School of Medicine, Seattle, WA, USA

[37]Stanford University School of Medicine, Stanford Diabetes Research Center, Stanford, CA, USA

[38]Cleveland Clinic Endocrinology and Metabolism Institute, Cleveland, OH, USA

[39]Diabetes Research Institute, Mills-Peninsula Medical Center, San Mateo, California, USA

[40]JDRF International, New York, NY, USA

[41]Usher Institute, University of Edinburgh, UK

[42]Stanford University, Stanford, California, USA

[43]Manchester University Hospitals NHS Foundation Trust / University of Manchester, UK

[44]Norwich Medical School, University of East Anglia, Norwich, UK

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

[45]Steno Diabetes Center Copenhagen and University of Copenhagen, Gentofte, Denmark

[46]University of Melbourne Dept. of Medicine and Department of Endocrinology St Vincent's Hospital Melbourne, Australia

[47]Department of Family Medicine, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, USA

[48]Department of Endocrinology, Diabetes, Nutrition, Montpellier University Hospital, and Institute of Functional Genomics, University of Montpellier, CNRS, INSERM, Montpellier, France

[49]School of Kinesiology & Health Science, Muscle Health Research Centre, York University, Toronto, Canada

[50]Biomedical Informatics Consultants LLC, Potomac, MD, USA

[51]Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[52]University of Florida, Gainesville, FL, USA

[53] Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA

[54]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[55]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, England UK and University of Nottingham, Nottingham, England UK

Short Title: Automated Insulin Delivery Consensus

Key Words: Automated Insulin Delivery, Closed-Loop, Type 1 Diabetes, Consensus Recommendations

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Funding and Duality of Interest:

The consensus on the use of Automated Insulin Delivery (AID) meeting was held virtually and no reimbursement and/or honoraria were provided. ATTD congress supported the meeting and provided funding to Christopher G. Parkin, CGParkin Communications, Inc., for his medical writing and editorial support. Abbott Diabetes Care, Dexcom, Inc., Insulet Corporation, Medtronic, Novo Nordisk, Sanofi, Tandem and Roche Diabetes Care provided funding to the ATTD to support the consensus meeting.

MP's institute received grant support from Medtronic, Novo Nordisk, Roche, Eli Lilly, Sanofi, Pfizer, Insulet, Opko, Dexcom, Dompe, GWave, DreaMed–Diabetes, NG Solutions. MP received Honoraria or consultation fees from Sanofi, Medtronic, Novo Nordisk, Eli Lilly and Pfizer. MP participated in Medical Advisory Board of Sanofi, Medtronic, AstraZeneca, Eli Lilly, Insulet, Pfizer, Dompe. Stock shareholder: NG Solutions Ltd., DreaMed-Diabetes Ltd. Consultant: Qulab Medical. RN reports receiving grants from Helmsley Charitable Trust, Dexcom, Medtronic, Abbott Diabetes Care and Insulet; personal fees and other from DreaMed Diabetes Ltd; personal fees from Novo Nordisk and Eli Lilly; RN owns DreaMed Diabetes Ltd stock.

KB-K received Research support from Dexcom, Novo Nordisk, BD; speaker honoraria Roche, Lifescan; ad board member, Sanofi, Roche. RMB has received research support, has acted as a consultant, or has been on the scientific advisory board for Abbott Diabetes Care, DexCom, Eli Lilly, Insulet, Medtronic, Novo Nordisk, and Sanofi. RMB served as a consultant for Ascensia, Bigfoot Biomedical, Inc., CeQur, Hygieia, Onduo, and United Healthcare. RMB's employer, non-profit HealthPartners Institute, contracts for his services and he receives no personal income.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

TD received research support and speaker honoraria from AstraZeneca, Boehringer, DexCom, Insulet, Lilly, Medtronic, Novo Nordisk, Roche, Sanofi and is a shareholder of Dreamed-Diabetes Ltd. RH is a speaker for Eli Lilly, Dexcom and Novo Nordisk; Advisory Board: Eli Lilly; License and consultancy honoraria: B. Braun and Abbott Diabetes Care; Patents related to closed-loop; Director: CamDiab; Research support: Dexcom, Abbott Diabetes Care, Medtronic. BPK Speaker/consultant: Tandem; Patent royalties and handled by UVA: DexCom, J&J, Sanofi; research support handled by UVA: Dexcom Novo Nordisk. LHM Speaking/consulting honoraria from Tandem Diabetes and DexCom, Inc., consulting for Capillary Biomedical. LHM's institution receives research/project grants from Medtronic, Tandem Diabetes, Beta Bionics, Dexcom, Abbott, and Insulet Corporation. CGP has received consulting fees from Abbott Diabetes Care, CeQur, Dexcom, Mannkind, and Provention. LA-O declares that no conflict interest exists. SAA is on the advisory board for Medtronic and Novo Nordisk, speaker at educational symposia sponsored by Novo Nordisk and Sanofi. Co-investigator on EU IMI HypoRESOLVE program. LB received research support from Dexcom. RWB reports no personal financial disclosures but reports that his institution has received funding on his behalf as follows: grant funding and study supplies from Tandem Diabetes Care, Beta Bionics, and Dexcom; study supplies from Medtronic, Ascencia, and Roche; consulting fees and study supplies from Eli Lilly and Novo Nordisk; and consulting fees from Insulet, Bigfoot Biomedical, vTv Therapeutics, and Diasome. SB has served on Advisory Board Medtronic, Freelancer Diaexpert, Freelancer Medicolab. TB received speaker's honoraria Medtronic, Roche, Novo Nordisk, AstraZeneca, Sanofi, Member of EU EXPAMED Panel for Medical products. JEB Advisory board for Cardinal Health and Provention Bio; Consultant for WellDoc, Inc; Independent Contractor (pump trainer) for Insulet

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

and Tandem. EB is a speaker and received advisory board fees from Abbott, AstraZeneca, Eli Lilly, Novartis, Roche, Sanofi. Non-economic support from Medtronic. CKB Consultant for CamDiab. MDB receives research support from Tandem Diabetes, Dexcom, Novo Nordisk, and Arecor paid to his institution. MDB serves as a consultant for Dexcom, Adocia, Air Liquide, and Roche. MDB received speaker fees from Tandem and Arecor. SAB reports institutional grants and material funding from Dexcom, Insulet, NIH, Roche Diagnostics, UVA Strategic Investment Fund, Tandem Diabetes Care and Tolerion. BAB is a member of Advisory Board for Medtronic, Convatec, and Arecor. Received consulting fees from Insulet and Medtronic. Received grants support from Insulet, Medtronic, Beta Bionics, JDRF, and NIDDK. AC is employee for Biolinq Inc. ALC has received research support, has acted as a consultant, or has been on the scientific advisory board for Abbott Diabetes Care, DexCom, Eli Lilly, Insulet, Medtronic, Novo Nordisk, Sanofi, Senseionics, and UnitedHealth. ALC's employer, non-profit HealthPartners Institute, contracts for his services and he receives no personal income. JRC holds stock in Pacific Diabetes Technologies, a company that may have a commercial interest in closed-loop technologies. JRC has been on advisory boards for Novo Nordisk, Astra Zeneca, and Zealand. JRC's institution has received grant support from Dexcom and Medtronic. PC received personal fees from Medtronic, Abbott, Dexcom, Insulet, Roche, Sanofi, Lilly, Novo Nordisk, Astra Zeneca. Research support from Novo Nordisk, Sanofi, Abbott, Medtronic. KLC received grant support (diaTribe) from Abbott, Ascencia, Bigfoot Biomedical, Dexcom, Insulet, LifeScan, Lilly, Medtronic, Novo Nordisk, One Drop, Roche, Sanofi, Senseonics, Xeris, and Zealand; news service subscription revenue (Close Concerns) from Abbott, Agamatrix, Air Liquide, Ascencia, BD, Beta Bionics, Bigfoot Biomedical, Biolinq, Capillary Biomedical, Cecilia Health, Cequr,

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

DarioHealth, Dexcom, DreamED Diabetes, Glooko, Insulet, LifeScan, Lilly, MannKind, Medtronic, Metronom, Modular Medical, Novo Nordisk, Onduo, One Drop, Roche, Sanofi, Senseonics, Tandem, Xeris, Ypsomed, and Zealand. diaTribe.org/our-supporters, closeconcerns.com/disclosure/php. CC declares that no conflict interest exists. ABC has received research support from Abbott Diabetes Care, DexCom, Insulet, Medtronic, Sanofi and has been on the scientific advisory board for Insulet. ABC's employer, non-profit HealthPartners Institute, contracts for these services and she receives no personal income. ED received speaker honoraria from Lilly (paid to Institution). ED's institution receives research support from Medtronic and Dexcom. CdB declares that no conflict interest exists. MIdB received research support from Medtronic, Dexcom, Novo Nordisk. Received Honoraria/research expenses from Lilly, Medtronic, YpsoMed, Sanofi, Pfizer. DJdS received research support from Insulet. DJdS is a consultant for Dexcom, Insulet. JHdV declares that no conflict interest exists. KD is a member of EU EXPAMED Panel for Medical products. Received speaker honoraria from: Pfizer, Novo Nordisk and Eli Lilly. FJDrd Equity, licensed IP and is a member of the Scientific Advisory Board of Mode AGC. LE received consulting fee from Tandem Diabetes Care and Ypsomed. NF-S declares that no conflict interest exists. GPF received research support from Medtronic, Dexcom, Abbott, Tandem, Insulet, Beta Bionics and Lilly. Consultant, speaker, advisory board for Medtronic, Dexcom, Abbott, Tandem, Insulet, Beta Bionics and Lilly. GG received speaker/Advisory fees from Medtronic and Dexcom. SKG has received Advisory Boards Consulting fee (through University of Colorado Denver) from Medtronic, Zealand and Eli Lilly. Research grants (through University of Colorado Denver) from Eli Lilly, Novo Nordisk, Medtronic, T1D Exchange, NIDDK, JDRF, Dexcom. No stocks in any device

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

or pharmaceutical company. DCG participates in clinical research or has served as a consultant for: Abbott Diabetes Care, Dexcom, and Medtronic. DCS' employer, the non-profit HealthPartners Institute, contracts for his services, and hereceive no personal income from the above activities. LAG-F is the head of HFS-Global LLC which licenses use of Fear of Hypoglycemia Surveys under a partnership with the University of Virginia. AH received research support/consulting fees from Eli Lilly, Medtronic, AgaMatrix, Tandem, Adocia, and Dexcom, and has pending patents in the artificial pancreas area. SH is a member of Medtronic advisory board, a director of Ask Diabetes Ltd providing training and research support in health care settings and received training honoraria from Medtronic, Dexcom and Sanofi and consulting fees for CamDiab. LH is a consultant for a number of companies, one of the owners of Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany. SHe is a speaker for Novo Nordisk, Advisory Boards for Eli Lilly, Novo Nordisk, Zealand, Zucara. Received research support from Dexcom. IBH received Research grants from Medtronic Diabetes, Insulet, Beta Bionics; Consulting fee from Abbott Diabetes Care, Roche, Bigfoot, GWave. KKH received consultant fees from Insulet, Cecelia Health, Lifescan Diabetes Institute. DI Speaker/consultant: Dexcom, Insulet, Abbott, Medtronic, Novo Nordisk. DCK Consultant to: Dexcom, Eli Lilly, Eoflow, Fractyl, Integrity, Lifecare, Roche Diagnostics, Thirdwayv. OK received research support and speaker honoraria from Amgen, B. Braun, Diamyd Medical, Medtronic, Novo Nordisk, Sanofi and is a shareholder of Dreamed Diabetes Ltd. AK declares that no conflict interest exists.
LL Consultant for Roche, Dexcom, Insulet, Boehringer Ingelheim, Janssen, ConvaTec, Medtronic, Dompe, Provention, Eli Lilly. JL declares that no conflict interest exists. RAL Consultant for Abbott Diabetes Care, BioLinq, Capillary Biomedical, Deep Valley Labs, Morgan Stanley,

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Provention Bio and Tidepool. LLe is on the Advisory Board for Abbott Diabetes Care, Dexcom, Insulet, Medtronic, Novo Nordisk, Sanofi Diabetes Care. DMM Consulted for Abbott, Aditxt, the Helmsley Charitable Trust, Sanofi, Novo Nordisk, Eli Lilly, Medtronic, Insulet, and Dompe. HRM Speaker: Dexcom, Roche and Novo Nordisk; Advisory Board: Medtronic. Research support: Dexcom, Abbott Diabetes Care, Medtronic. KN Advisory Board for Medtronic, Abbott Diabetes Care, Novo Nordisk and research support via institution from Dexcom, Medtronic, Novo Nordisk, Zealand Pharma. DO'N Advisory boards and received research support and honoraria from Medtronic, Merck, Novo Nordisk, Sanofi, and Abbott. SO Advisory boards for Dexcom, Cecelia Health, DiabetesWise.org TO Advisory boards for Dexcom, Cecelia Health, DiabetesWise.org. ER Advisory board for Abbott, Air Liquide SI, Dexcom Inc., Insulet, Sanofi, Roche, Novo Nordisk, and Eli-Lilly, and research support from Dexcom Inc. and Tandem. MCR Advisory Board: Zucara Therapeutics, Supersapiens, Eli-Lilly, Insulet, Indigo. Speaker: Sanofi, NovoNordisk, Eli -Lilly, Insulet. DR Consultant for Eli Lilly & Co., Better Therapeutics. SJR Consulting: Beta Bionics, Novo Nordisk, Eli Lilly, Flexion Therapeutics, Senseonics. Received research support: Beta Bionics, Novo Nordisk, Zealand. Patents and patents pending assigned to MGH and licensed to: Beta Bionics. Honoraria and travel support: Novo Nordisk, Roche, Senseonics. Scientific advisory board: Unomedical, Companion Medical. DAS Advisory Board: Abbott, Medtronic. SNV Advisory board: Sanofi, Medscape. Speaker: Dexcom, Insulet. Grants: Dexcom, Insulet, Eli-Lilly, Novo Nordisk, Sanofi. JLS Consultant to Cecelia Health, Lexicon, Lilly, Insulet, Medtronic, and Sanofi. Advisory board member for Bigfoot Biomedical, Cecelia Health, Insulet, Medtronic, the T1D Fund, and Vertex. Research support from Dexcom, Insulet, and Medtronic. GDS Advisory Board: Merck. Grants: Abbott. RPW

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Advisory board: Dompe, speaker: Tandem Diabetes Care, Research support: Dexcom, Eli Lilly & Co, Tandem Diabetes Care. CW Consultant: CamDiab. SAW Consultant for Zealand Pharma. Speaker for Abbott, Dexcom, Insulet, Medtronic, Tandem. Research support (to Institution) from Abbott. EW Personal fees from Abbott Diabetes Care, Dexcom, Eli Lilly, Insulet, Medtronic, Novo Nordisk, Sanofi Aventis. TB served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Medtronic, Indigo, DreaMed Diabetes. TB received honoraria for participating on the speaker's bureau of Eli Lilly, Novo Nordisk, Medtronic, Abbott, Sanofi, Aventis, Astra Zeneca, and Roche. TBa owns stocks of DreamMed Diabetes. TB's Institution received research grant support from Abbott, Medtronic, Novo Nordisk, GluSense, Sanofi, Novartis, Sandoz, and Zealand Pharma.

CORRESPONDING AUTHOR: Moshe Phillip, MD; The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah Tikva 4920235, Israel; Email: mosheph@tauex.tau.ac.il; Tel: +972-3-9253731; Fax: +972-3-9253836
ORCID ID: 0000-0002-6616-5612
CORRESPONDING AUTHOR: Revital Nimri, MD; The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah Tikva 49202, Israel ; E-mail: revitalnimri@gmail.com, Ravitaln@clalit.org.il ; Tel: +972-3-9253859; Fax: +972-3-9253836
ORCID ID: 0000-0003-3571-4938

ACCEPTED MANUSCRIPT

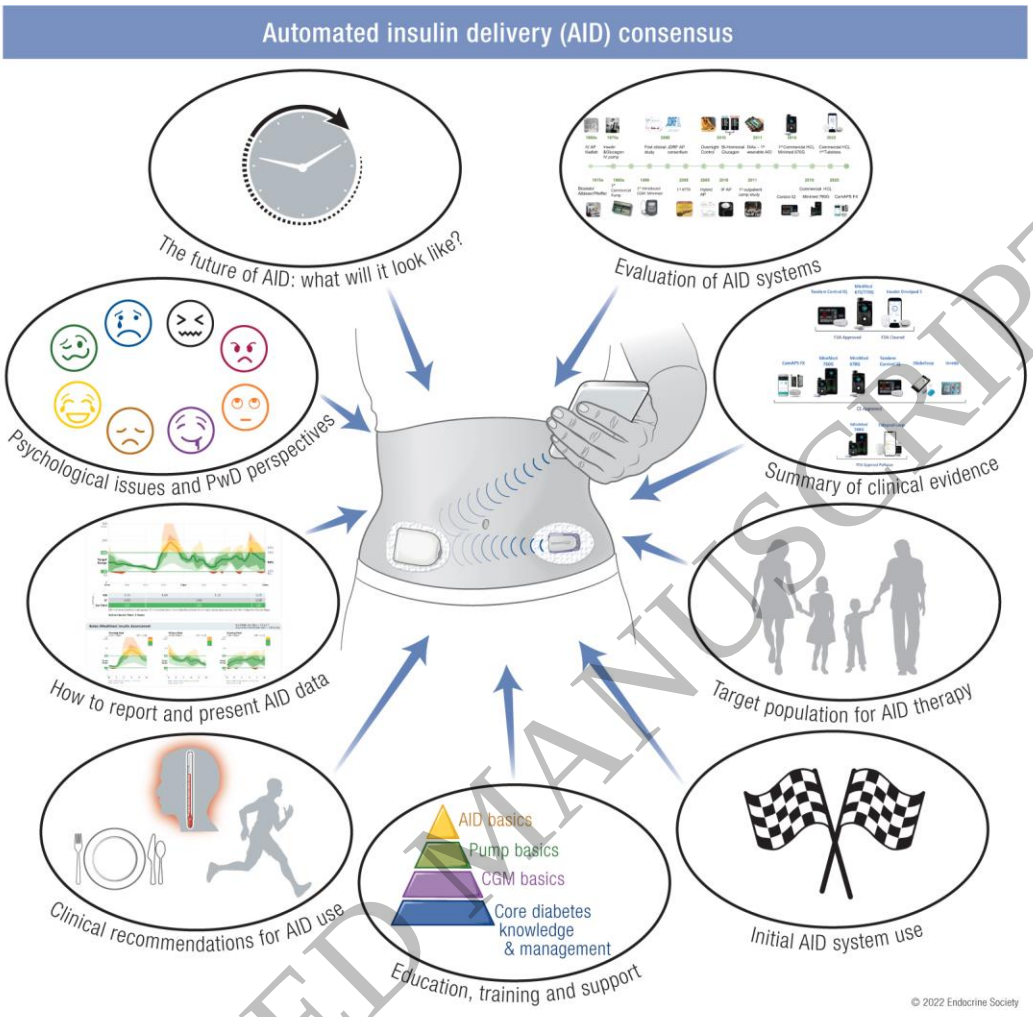
Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Abstract

The significant and growing global prevalence of diabetes continues to challenge people with diabetes (PwD), healthcare providers and payers. While maintaining near-normal glucose levels has been shown to prevent or delay the progression of the long-term complications of diabetes, a significant proportion of PwD are not attaining their glycemic goals. During the past six years, we have seen tremendous advances in automated insulin delivery (AID) technologies. Numerous randomized controlled trials and real-world studies have shown that the use of AID systems is safe and effective in helping PwD achieve their long-term glycemic goals while reducing hypoglycemia risk. Thus, AID systems have recently become an integral part of diabetes management. However, recommendations for using AID systems in clinical settings have been lacking. Such guided recommendations are critical for AID success and acceptance. All clinicians working with PwD need to become familiar with the available systems in order to eliminate disparities in diabetes quality of care. This report provides much-needed guidance for clinicians who are interested in utilizing AIDs and presents a comprehensive listing of the evidence payers should consider when determining eligibility criteria for AID insurance coverage.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022



Graphical Abstract

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Introduction

Diabetes is a chronic, demanding condition that poses a constant burden both on people with diabetes and on healthcare systems. Only a minority of persons with type 1 diabetes (T1D) meet widely accepted glycemic goals (1), demonstrating that there is an unmet need for better methods to achieve these goals. During the past six years, we have seen tremendous advances in automated insulin delivery (AID) technologies. Studies with various AID systems unequivocally demonstrate improvement in glycemic outcomes in people with T1D across all age groups, in all genders and regardless of diabetes duration, prior insulin delivery modality, or baseline HbA1c (2-6). Studies have also suggested cost-effectiveness of these systems (7-10). Yet despite the success of AIDs in improving glycemic control, guidance for integrating AID systems into clinical practice is limited. Moreover, as with all new technologies, negotiating insurance coverage for AID has been protracted.

In 2021, the Advanced Technologies & Treatments for Diabetes (ATTD) Congress organized an international panel of clinicians, researchers and patient advocacy with expertise in AID to develop clinical guidelines for initiating AID for individuals with T1D. The panel was divided into nine working groups to address the various aspects of AID therapy, including: evolution of AID; clinical evidence; determining the target population for AID use; initiation of AID; education and training; utilization of AID; AID data reporting; psychological issues/user perspective; and the future of AID. Recommendations from each working group were presented to the full panel and voted upon. This article summarizes the consensus recommendations from the panel.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

The purpose of this report is two-fold: 1) to provide needed guidance to clinicians who are interested in utilizing AID; and 2) to serve as a comprehensive review of evidence for payers to consider, when determining eligibility criteria for AID insurance coverage.

1. Evolution of AID Systems

Refinements in continuous glucose monitoring (CGM) technologies and dosing algorithms have led to the development of AID systems for the purpose of enhancing glucose management and minimizing burden around insulin delivery. AID systems utilize a sophisticated controller algorithm that continuously adjusts insulin delivery in response to real-time sensor glucose levels, residual insulin action and other inputs, such as meal intake and exercise announcement. The algorithm accommodates variability of insulin requirements between and within individual users. However, despite significant advances in controller algorithms in providing closed-loop insulin delivery between meals, users must still manually announce carbohydrate intake to achieve adequate postprandial insulin coverage. This is needed because current hybrid systems are not physiologic in that they rely on a delayed subcutaneous glucose signal (4-10 min sensor lag time) (11) and delayed subcutaneous insulin delivery into the circulation (peak insulin levels appear 45-60 minutes after injection) (12). Therefore, one of the major limitations for fully automated systems is the pharmacokinetics and pharmacodynamics profiles of commercially available insulins.

Currently, all commercially available AID systems are single hormone (insulin only) systems. Dual hormone AID systems, which incorporate other hormones (glucagon, pramlintide) to more closely mimic pancreatic physiology, are under development (13),(14).

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

The addition of glucagon to AID system may confers additional protection from hypoglycemia. Pramlintide, an analogue of amylin which is co-secreted with insulin from beta-cells, reduces post-prandial glucose excursions by slowing gastric emptying and suppressing glucagon secretion.

AID algorithms

Several types of control algorithms have been developed, including model predictive control (MPC), proportional integral derivative (PID) and fuzzy logic (FL) controllers (15). MPC algorithms use patient-specific model parameters to calculate insulin delivery by minimizing the difference between model-predicted glucose concentrations and target glucose over a pre-specified prediction time horizon. Thus, the algorithm adjusts the insulin treatment in order to bring the predicted glucose levels into the target range. PID controllers are reactive, adjusting insulin delivery by assessing glucose excursions from three perspectives: the proportional component calculates the deviation of measured glucose level from the target glucose; the integral component calculates the area under the curve between measured and target glucose, and the third derivative component takes into account the rate of change of measured glucose, and all together dictate the amount of insulin delivered. Some PID controllers have been modified to also include feedback of a model-predicted insulin profile. Fuzzy logic control algorithm is a clinical approach to the modulation of insulin delivery based on a set of rules that imitate the line of reasoning of diabetes practitioners, which in turn are based on common medical knowledge, experience of diabetes practitioners and known recommendations.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Hybrid and fully AID systems

Current commercially available AID systems require users to manually enter prandial insulin boluses and signal exercise while automatically modulating insulin delivery. Fully AID systems, which obviate the need for carbohydrate counting and manually initiated prandial boluses, are under development at present, but the benefits in reduced user burden come at the expense of glycemic control (16). Use of truly faster insulin analogs within the AID system or glucose-lowering adjuvant therapies may make this approach more feasible in the future (see chapter 9). **Table 1** presents a description of commercially available AID systems. **Table 2** presents some of the AID systems that are currently in development or under regulatory review.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

1 ***Table 1. Commercially available AID systems***

	Medtronic 670G/770G	**Medtronic 780G**	**CamAPS FX**	**Diabeloop**	**Control IQ**	**Omnipod 5**
Algorithm and approach	PID algorithm with insulin feedback with adaptive insulin limits Located on pump	PID algorithm with insulin feedback with adaptive insulin limits and model based auto-corrections Located on pump	Treat to target adaptive MPC algorithm (interoperable) App on unlocked smartphone	Treat to target adaptive MPC algorithm App on smartphone /Handheld device	Treat to range adaptive MPC algorithm (interoperable) Located on pump	Treat to target adaptive MPC algorithm (interoperable) Located within pod (controlled from the Omnipod 5 controller or a phone App)
Target glucose	Fixed target:120 mg/dL (6.7 mmol/L) Optional activity target 150mg/dL (8.3 mmol/L)	Target: 100 mg/dL (5.6 mmol/L) (default); Customizable: 110 mg/dL (6.1 mmol/L) or 120 mg/dL (6.7 mmol/L) Optional activity target 150mg/dL (8.3 mmol/L)	Target: 104 mg/dL (5.8 mmol/L) (default); customizable between 80 mg/dL and 200 mg/dL (4.4 mmol/L and 11.0 mmol/L) Optional activity mode	Target: 110 mg/dL (6.1 mmol/L) (default); customizable between 100 mg/dL (5.5mmol/L) to 130 mg/dL (7.2 mmol/L) Zen-mode: (20-40 mg/dL-0.5-2.2 mmol/L) higher than current target Activity mode (customizable)	Fixed target range: 112.5 -160 mg/dL (6.2–8.9 mmol/L) Intensified overnight target range of 112.5-120 mg/dL (6.2–6.7 mmol/L) Optional activity range 140-160 mg/dL (7.8-8.9 mmol/L)	Target: customizable between 110 mg/dL and 150 mg/dL (6.1 mmol/L and 8.3 mmol/L) in 10 mg/dL increments Optional activity target 150 mg/dL (8.3 mmol/L)
Basal insulin delivery	Algorithm driven basal insulin delivery adjusted every 5-10 minutes based on real-time CGM data.					
Automated correction boluses	None. Manual correction boluses targeting 150 mg/dL (8.3 mmol/L) based on control algorithm parameters not programmed sensitivity factors	Automated correction boluses targeting 120 mg/dL (6.7 mmol/L) once automatic basal reaches maximum. Correction boluses based on control algorithm parameters not programmed sensitivity factors	Automated correction boluses via more aggressive basal rate adjustments Optional use of 'Boost' mode (user ability to temporary increase insulin delivery) Manual correction boluses optional based on programmed sensitivity factors	Automated correction boluses	Automated correction boluses (60% of the calculated correction dose) if glucose predicted to exceed 180 mg/dL (10.0 mmol/L) targeting glucose of 110 mg/dL (6.1 mmol/L) Manual correction boluses optional	Automated correction boluses via more aggressive basal rate adjustments Manual correction boluses optional
Safety parameters	Maximum hourly basal insulin delivery, but not maximum total hourly delivery Maximum 4h basal insulin delivery Minimum insulin delivery for 2.5h Maximum bolus amount	Maximum hourly basal insulin delivery, but not maximum total hourly delivery Maximum 7h basal insulin delivery Maximum basal delivery in 24h Maximum bolus amount Minimum insulin delivery for 3-6h	Maximum insulin delivery in 24h Maximum bolus amount Minimum insulin delivery for 1.5h	Variable aggressiveness A bolus for a given meal can be modulate by ± 10% increment Alert for rescue carbohydrates	Maximum insulin delivery in 2h Maximum insulin delivery in 24h Maximum bolus amount	Maximum individual insulin delivery at any given time Maximum bolus amount

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Settings that can be modified by user/HCP	Insulin to carbohydrate ratio Active insulin time Temp glucose target	Insulin to carbohydrate ratio Active insulin time Target glucose for algorithm Temp glucose target	Target system glucose Insulin to carbohydrate ratio Boost or Ease off – more or less aggressive algorithm	Target system glucose Total daily dose Algorithm treatment reactivity (aggressiveness) Insulin to carbohydrate ratio	Basal insulin rates Insulin to carbohydrate ratio Insulin sensitivity factor Temp glucose target Sleep mode	Insulin to carbohydrate ratio Insulin sensitivity factor (user boluses) Active insulin time (user boluses) Target glucose for algorithm Activity glucose target with attenuated insulin delivery
Algorithm learning	Based on TDD and an estimate of fasting glucose and the plasma insulin concentration at the time of fasting	Based on TDD and an estimate of fasting glucose and the plasma insulin concentration at the time of fasting	Adapts to day-to-day, prandial and diurnal patterns; independent of programmed basal and sensitivity pump settings		Based on TDD	Based on TDD, updated with each Pod change (every 3 days)
Compatible insulin pump	670G/770G	780G	Designed as interoperable controller; currently available with Dana RS, Dana I, mylife YpsoPump	Kaleido patch pump Roche Accu-Chek	Designated by FDA as interoperable controller; currently available in Tandem t:slim X2	Designated by FDA as interoperable controller; Omnipod 5 ACE
Compatible CGM system	Guardian 3 Duration 7 days Requires calibrations (min 4-6x/d)	Guardian 3 Duration 7 days Requires calibrations (min 2x/d) CE mark: Guardian 4, duration 7 days, factory calibrated, optional calibration	Dexcom G6 Duration 10 days Factory calibrated, optional calibration	Dexcom G6 Duration 10 days Factory calibrated, optional calibration	Dexcom G6 Duration 10 days Factory calibrated, optional calibration	Interoperable iCGM currently available: Dexcom G6 Duration 10 days Factory calibrated, optional calibration
Data management system	Carelink; manual downloading of pump required for 670G, automated download with 770G	Carelink; automated app compatibility	Diasend; automated download	Diasend; download	t:Connect mobile; automated download	Omnipod Connect; automated download
Compatible insulin	Rapid only	Rapid only	Rapid and ultra-rapid	Rapid only	Rapid only	Rapid only
Approved indications for use	FDA and CE mark 7 years and upwards excluding pregnancy for 670G and 2 years and upwards for 770G (FDA only)	CE mark 7 to 80 years excluding pregnancy	CE mark 1 year and upward including pregnancy	CE mark 12-18 y (DBL4T) >18 y (DBLG1) excluding pregnancy	FDA and CE mark 6 years and upwards excluding pregnancy	FDA cleared 6 years and upwards excluding pregnancy

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Other benefits	Extensive clinical experience (>200,000 users) Robust training and support Remote monitoring capabilities (770G)	Evidence base from clinical trials Increased usability compared to 670G Remote monitoring capability	Evidence base from clinical trials Mobile app for remote insulin bolusing Online app updates Remote monitoring capability Online training for HCPs and users	Remote monitoring capability- YourLoops web-based platform	Extensive clinical experience (>270,000 users) FDA cleared the t:connect mobile app for remote insulin bolusing Online firmware upgrade Online training for HCPs and users	Evidence base from clinical trials Online firmware upgrade Online training for HCPs and users
PID – Proportional Integral Derivate, MPC- Model Predictive Control, TDD – Total Daily Dose, HCP – Health Care Provider						

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Table 2. AID systems under development or regulatory review

	Tidepool Loop	**iLet (insulin only)**	**Inreda (**Insulin and glucagon**)**
Algorithm and approach	MPC algorithm iPhone app	MPC algorithm Located on pump	Insulin PID algorithm Located on pump
Compatible insulin pump	Omnipod patch pump Minimed Medtronic	iLet pump	Inreda pump
Compatible CGM system	Dexcom G6 Medtronic Guardian Connect	Dexcom G6	Medtronic
Regulatory status	FDA Regulatory submission made	Not submitted	CE mark
MPC- Model Predictive Control, PID- Proportional Integral Derivative			

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Interoperability and Intraoperability

The ability of components of an AID system (CGM, insulin pump and algorithm) to communicate accurately and interact effectively with each other is critical for achieving optimal glycemic control. This can come in the form of intra- or interoperability. Intraoperability describes the exchange of data and interaction within the same system provided by the same manufacturer. Interoperability facilitates the exchange of data and interaction of different AID system components, offering users increased choice and flexibility for a personalized AID system. However, this depends on commercial agreements between device manufacturers.

2. Summary of Clinical Evidence

Clinical evidence supporting the efficacy and safety of AID systems has grown over the last five years with the introduction of multiple commercially available, and soon to become available, AID systems. As of March 2022, the U.S. Food & Drug Administration (FDA) has approved the Medtronic 670G/770G (4; 17; 18), the Control-IQ (2; 19; 20) and recently cleared the first tubeless AID system, the Insulet Omnipod 5 (21). CE-approval has been granted to Medtronic 780G (5; 22; 23); CamAPS FX (6); Diabeloop (24; 25); Inreda (26); Control-IQ and Medtronic 670G. Some systems are currently under FDA review, including the Medtronic 780G (5; 22; 23) and Tidepool Loop (27).

Randomized Controlled Trials

Randomized controlled trials (RCTs) and single-arm studies with interventions of 3 months or longer, including children as young as two-years-old and adults as old as 75-years-old with T1D have been conducted (**Table 3, Table 4**). Some RCTs provide separate analyses for

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

adolescents and adults allowing evaluation in specific age groups. Study designs vary from single-arm trials without a concurrent comparator to parallel-group studies and crossover randomized trials. The lack of a control group in single-arm studies limits the ability to determine how much of this achievement is attributed to AID use, as opposed to a study effect. Furthermore, some of the populations studied differ in baseline Time-in-Range (refer to TIR of 70-180mg/dL). Lower baseline TIR was found to be associated with a greater improvement in TIR on AID (28). These differences in study design impair the ability to do cross-study comparisons.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Table 3. Randomized Controlled Trials for Commercially Available AID Systems

AID System (Author & Publication year)	Study Design (Type, duration, comparison group)	Study Population (Number of participants & Age, Mean baseline HbA1c)		Glycemic Outcomes*					
				ΔMean Sensor Glucose	ΔTIR 70-180 mg/dL	ΔTBR<70 mg/dL	ΔTBR<54 mg/dL	ΔTAR>250 mg/dL (or 300 or 180 mg/dL)	ΔHBA1c
Children/Adolescents									
AHCL vs 670G Bergenstal et al, 2021(23)	Crossover trial, two 13w periods, comparison of AHCL v. 670G¶ and to baseline**	N=113, 14-29 yo, T1D, baseline mean: HbA1c 7.9%, TIR 57%		-7 mg/dL¶ -7 mg/dL-670G -14 mg/dL-AHCL	+4%¶ +6% -670G +10% -AHCL	0%¶ -0.1%-670G -0.2% -AHCL	-0.04%¶ +0.04%-670G 0%-AHCL	-1%¶ -3% - 670G -4%- AHCL	-0.2%¶ -0.3%- 670G -0.5%-AHCL
AHCL Collyns et al, 2021(5)	Crossover trial, two 4-w periods, comparison of AHCL v. PLGS	N=33, 7-21 yo, (N=14, 14-21yo, N=19, 7-13yo), T1D, baseline mean HbA1c, TIR :NA		-13 mg/dL :14-21yo -9 mg/dL :7-13yo	+14% :14-21yo +12% :7-13yo	-0.4% :14-21yo -0.7% :7-13yo	-0.1% :14-21yo -0.2%- :7-13yo	-14% :14-21yo -11% :7-13yo (T>300 mg/dL)	NA
Control IQ Isganaitis et al, 2020(3)	6m randomized trial, comparing CIQ with SAP	N=63, 14-24 yo, T1D, baseline mean HbA1c 8.1%, TIR 52%		-18 mg/dL	+13%	-0.7%	-0.09%	-8%	-0.30%
Control IQ Breton et al, 2020(20)	16w randomized trial, comparing CIQ with SAP	N=101, 6-13 yo, T1D, baseline mean HbA1c 7.7%, TIR 53%		-13 mg/dL	+11%	-0.40%	-0.07%	-6%	-0.40%
CamAPS FX Fuchs et al, 2021(29)	4m randomized trial, comparing CamAPS FX with SAP	N=74, 1-7yrs old, T1D, baseline mean HbA1c 7.3%, TIR:NA		-13 mg/dL	+9%	+0.07%	+0.02%	-1% (T>300 mg/dL)	-0.4%
Adults									
670G McAuley et al 2020(4)	6m randomized trial comparing 670G with MDI/CSII	N = 120, ≥ 25 yo, T1D, baseline mean HbA1c 7.4%, TIR 55%		-13 mg/dL	+15%	-2.0% Median	-0.6% Median	-2.9% Median	-0.4%
Control-IQ Brown et al, 2019(2)	6m randomized trial, comparing CIQ with SAP	N=168, 14-71 yo, T1D, baseline mean HbA1c 7.4%, TIR 61%	All the group	-13 mg/dL	+11%	-0.9%	-0.1%	-5.3%	-0.33%
			N=105, 25-71yo		+10%	-2.2%			
CamAPS, FX Tauschmann et al, 2018(6)	3m randomized trial, comparing CamAPS FX algorithm with SAP	N=86, ≥ 6 yo, T1D, baseline mean HbA1c 8.3% #, TIR: NA	All the group	-15 mg/dL	+11%	-0.8%	-0.1% (<50mg/dL)	-1.4% (T>300mg/dL)	-0.36%
			N=44, ≥ 22yo		+10%	-0.5% (<63mg/dL)			-0.3%
CamAPS FX Boughton et al, 2022(30)	4m randomized trial, comparing CamAPS FX with SAP	N=37, 60yo and older, T1D, baseline mean HbA1c 7.4%, TIR:70%		-13 mg/dL	+9%	-0.1%	-0.0%	-0.7% (T>300 mg/dL)	-0.2%
Diabeloop. Benhamou et al, 2019(24)	Crossover trial, two 12w periods, comparing Diabeloop with SAP	N=68, ≥ 18 yo, T1D, baseline mean HbA1c 7.6%, TIR: NA		-9 mg/dL	+9%	-2.4%	-0.5% (<50mg/dL)	-4.3%	-0.15%

*Reported glycemic metrics are mean differences between groups for randomized trial **Glycemic metrics estimated from reported means in each group # Differences reported from rank tests ¶ Comparison between two AIDs. MDI-multiple daily injections, CSII – continuous subcutaneous insulin delivery, SAP – sensor augmented pump, yo – years old , TIR – Time In Range (70-180 mg/dL [3.9-10 mmol/L]), TBR- Time Below Range (<70 mg/dL [<3.9 mmol/l], <54 mg/dL [<3.0 mmol/l), TAR-Time above Range (>180 mg/dL [>10.0 mmol/l], >250 mg/dL [13.9 mmol/l)

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

1

Table 4. Single-Arm Studies for Commercially Available AID Systems

AID System (Author & Publication year)	Study Design (Type, duration, comparison group)	Study Population (Number of participants &Age, Mean baseline HbA1c)	Glycemic Outcomes*					
			ΔMean Sensor Glucose	ΔTIR 70-180 mg/dL	ΔTBR<70 mg/dL	ΔTBR<54 mg/dL	ΔTAR>250 mg/dL (or 300 or 180 mg/dL)	ΔHBA1c
Children/Adolescents								
670G Bergenstal et al, 2016(17) Garg et al, 2017(31)	3m single-arm study	N=30, 14-21 yo, T1D, baseline mean HbA1c 7.7%, TIR 60%	-5 mg/dL	+7%	-1.5%	-0.2%	-1% (T>300 mg/dL)	-0.6%
780G Carlson et al, 2022(22)	3m single-arm study	N=39, 14-21 yo, T1D, Baseline mean HbA1c 7.5%, TIR 62%	-6 mg/dL	+6%	-1%	-0.3%	-1.6%	-0.5%
670G Forlenza et al,2019(18)	3m single-arm study	N=105, 7-13 yo, T1D, baseline mean HbA1c 7.9%, TIR 56%	-7 mg/dL	+9%	-1.7%	-0.5%	-3%	-0.4%
670G Forlenza et al, 2022(32)	3m single-arm study	N=46, 2-7 yo, T1D, baseline mean HbA1c 8.0%, TIR 56%	-12 mg/dL	+8%	-0.1%	0%	-4%	-0.5%
Omnipod 5[¥] Brown et al, 2021(21)	3m single-arm study	N=112, 6-13 yo, T1D, baseline mean HbA1c 7.7%, TIR 53%	-23 mg/dL	+16%	-0.4%	-0.1%	-9%	-0.7%
Omnipod 5[¥] Sherr et al, 2021(33)	3m single-arm study	N=80, 2-6 yo, T1D, baseline mean HbA1c 7.4%, TIR 57%	-14 mg/dL	+11%	-0.3%	+0.1%	-6%	-0.6%
Adults								
670G Bergenstal et al, 2016(17)	3m single-arm study	N=94, 22-75 yo, T1D, baseline mean HbA1c 7.3%, TIR 69%	+2 mg/dL	+5%	-3%	-0.5% (<50mg/dL)	-0.5% (T>300 mg/dL)	-0.5%
780G Carlson et al, 2022(22)	3m single-arm study	N=118, 22-75 yo, T1D, baseline mean HbA1c 7.5%, TIR 71%	-4 mg/dL	+4%	-0.9%	-0.3%	-1%	-0.5%
Omnipod 5 Brown et al, 2021(21)	3m single-arm study	N=129, 14-70 yo, T1D, baseline mean HbA1c 7.2%, TIR 65%	-8 mg/dL	+9%	-1.6%	-0.4%	-4%	-0.4%

*Reported glycemic metrics are mean change from baseline to follow up for single-arm studies (comparison of study period with baseline)

[¥] Omnipod 5 is expected to be commercially available during 2022

TIR – Time In Range (70-180 mg/dL [3.9-10 mmol/L]), TBR- Time Below Range (<70 mg/dL [<3.9 mmol.l], <54 mg/dL [<3.0 mmol/l), TAR-Time above Range (>180 mg/dL [>10.0 mmol/l], >250 mg/dL [13.9 mmol/l)

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

In general, all the AID systems have uniformly demonstrated an increase in TIR and a reduction in mean glucose, time in hyperglycemia, and HbA1c. Overall improvement in glycemic control was similar across all age groups and was evident during both day- and night-time. Yet even with AID use, TIR improves more overnight than during the day. TIR increased by 9-16% for most systems while HbA1c levels decreased by 0.3-0.5%, with either no change or a reduction in time in hypoglycemia. The greatest improvement in glycemic control is seen in those who have the lowest baseline TIR or highest HbA1c (28; 34). The effect on hypoglycemia has varied, also depending on the comparison group features and the amount of hypoglycemia present at baseline. In some studies, use of AID has been shown to reduce hypoglycemia even when compared to sensor augmented pump (SAP) therapy with predictive low glucose suspend (PLGS) (5; 35). Of note, AID use resulted in reduced rates of both hypoglycemia and hyperglycemia, thus increasing TIR. This contradicts the paradigm that improving glycemic control necessarily leads to an increase in hypoglycemia (36).

Real-World Studies

Real-world data are now also available, shedding light on true AID acceptance and performance. It is reassuring to find that outcomes are similar to those of the pivotal studies in the means of TIR and TBR, with a modest reduction in HbA1c of 0.3-0.4% (35; 37-40). **(Table 5).** Current data also supports improved quality of life and users' reported outcomes (41; 42). However, several publications on real-world use of the Medtronic 670G revealed that approximately one-third of youth starting on the 670G system discontinue use within one year (43; 44). Recent studies showed increased use of auto-mode on Medtronic's Advanced Hybrid AID compared to 670G (86% vs 75%, respectively (23) and the real-world data of the use of Tandem's Control-IQ which reported 94% use of auto-mode (35).

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Table 5. Key Real-World Studies

Closed-Loop System (Author & Publication year)	Study Design (Type, duration, comparison group)	Study Population (Number of participants & Age, Mean baseline HbA1c)	Number of participants by age category	Glycemic Outcomes (start to end of study)					
				ΔMean Sensor Glucose	ΔTIR 70-180 mg/dL	ΔTBR<70 mg/dL	ΔTBR<54 mg/dL	ΔTAR>250 mg/dL	ΔHBA1c
670G Stone MP et al, 2018(37)	3m retrospective, CareLink system data comparing baseline	N=3141, >7 yo, T1D, no baseline HbA1c	N=2066, 22-60Y N=649, ≥60Y	-7mg/dL -6mg/dL	+8% +6%	-0.7% -0.4%	-0.1%	-2.7%	
			N=105, 7-13Y N=244, 14-21Y	-17mg/dL -10mg/dL	+11% +8%	+0.5% -0.3%			
670G Akturk et al, 2019(38)	6m retrospective single center study comparing study period with baseline SAP use	N=127, 21-68 yo, T1D, baseline mean HbA1c 7.6%		-12 mg/dL	+11%	-1%	-0.2%	-0.5%	-0.4%
780G Da Silva et al, 2022(40)	2m retrospective, CareLink system data comparing baseline	N=812, T1D, baseline mean estimated HbA1c 7.2%	No Data	-15.7 mg/dL	+12%	-0.3%	-0.1%	-4.2%	-0.4%
Control-IQ Breton & Kovatchev 2021(35)	12m retrospective, real world observational study, comparing study period with baseline (PLGS)**	N=9010, 6-91 yo, T1D or T2D, baseline mean estimated HbA1c 7.3% (N=7813 T1D)	N=5616, 19-63Y N=1773, >63Y	-13 mg/dL -12 mg/dL	+10% +9%	-0.8% 0 %	+0.1% 0 %	-3% -2%	-0.3% GMI for all group
			N=716, 6-13Y N=905, 14-18Y	-15.5 mg/dL -13 mg/dL	+12% +12%	+0.1% +0.1%	+0.1% +0.1%	-5% -6%	
Control-IQ Messer et al 2021(45)	6 m prospective, real world single center comparing study period with baseline	N=191, children and adolescents with T1D, baseline mean HbA1c 7.6%		-12.5 mg/dL	+9.4%	-0.4%	0%	-4.3%	-0.3% GMI
Loop Open Source Lum et al, 2021(46)	6m prospective, real world observational study comparison of study period with baseline**	N=558, 1-71 yo, T1D, baseline mean HbA1c 6.8%		-10 mg/dL	+7%	-0.2%	-0.05%	-2%	-0.3%

GMI - Glycemic Management Index

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Altogether, the data gathered provide solid evidence for the safety and efficacy of AID system use for a broad age range of PwD. Rates of acute complications such as severe hypoglycemia (SH) and diabetic ketoacidosis (DKA) were low. Of note, almost all pivotal trials exclude (or have very few) participants with a recent history of DKA or SH, thereby substantially lowering the risk of such complications. Real-world observational trials show lower rates of DKA/SH than those published in the US T1D Exchange Registry (1). Several studies also suggested improved quality of life, reduced diabetes burden, reduced fear of hypoglycemia and a return to restful sleep for PwD and family (42; 47-53), while few studies failed to find improvements in patient-reported outcomes (41; 54) (see chapter 8).

Knowledge Gaps

Cost effectiveness studies of AID systems are scarce. However, an analysis of the MiniMed 670G AID system versus CSII, showed that the higher acquisition costs of the AID system were offset by clinical benefits, reduced complication costs and quality of life improvements, which represented an overall cost-effective treatment option for people with T1D (8). Similar results were reported for MiniMed 670G AID system versus MDI and intermittent scanned CGM (isCGM)(10). Additional data on other systems will be valuable.

Another knowledge gap is the use of AID systems in special populations. Data are accumulating on AID use in young children (<6 years) with T1D (55-57). Several feasibility studies describe AID use in other populations such as pregnant women with T1D (58; 59) and people with T2D (60; 61). To support AID implementation in these populations, larger and

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

longer randomized control studies are needed. In addition, both RCTs and real-world studies lack racial and ethnic diversity, thereby limiting universal AID adoption (62).

3. Target Populations for AID Therapy

Selecting the people who will benefit most from AID system use is essential to optimize both efficacy and safety of treatment. **Table 6** presents graded evidence-based recommendations for individuals who should be considered for AID system use (ADA evidence-grading system) (63).

Table 6. Summary of Recommendations: Target Populations

● Strongly consider recommending AID systems to all people with T1D to improve glycemic control ○ School aged children (7-14 years) (2; 3; 5; 20; 44; 64-68) **A** ○ Adolescents/ Adults (3; 6; 69) **A** ● Consider recommending to: ○ Older Adults (above 65 years) (2; 30; 69; 70) **B** ○ Preschool children (<7 years) (32; 33; 56; 57; 71-74) **B** ○ People with moderate/severe hypoglycemia and hypoglycemia unawareness (75-78) **C** ○ Pregnancy complicated with T1D (58; 60; 79-82) **C** ○ People with comorbidities: chronic renal failure and gastroparesis (83-85) **C**
● Consider recommending appropriate AID systems to people with other types of diabetes treated with intensive insulin therapy (multiple daily injections or pump therapy): ○ People with type 2 diabetes (60; 61) **C** ○ People after pancreatectomy **E** ○ People with cystic fibrosis related diabetes (86; 87) **C**
● Use of AID under supervision should be allowed in hospital settings if not contraindicated by clinical status or treatment needs **E**

AID should be considered for all people with T1D, especially those experiencing suboptimal glycemia, problematic hypoglycemia and/or significant glycemic variability. AID use can be particularly useful in persons at moderate to high risk for frequent and/or severe hypoglycemia (75; 88) and hypoglycemia unawareness (76; 77). Furthermore, small initial

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

studies reported an improvement in hypoglycemia awareness with the use of AID systems (77; 78).

Additionally, lifestyle and quality of life issues should be considered when determining treatment options. As previously mentioned, evidence from numerous RCTs and real-world studies support the safety and efficacy of use of AID systems in young, school-aged pediatric populations and in adolescent/adult populations ((2; 3; 5; 17; 18; 20; 23; 31; 35; 44; 56; 57; 64-68; 71-74; 89; 90). Although some studies included children from the age of one year, and adult populations above 65 years of age (2; 4; 23; 30; 35; 37; 46; 69; 70; 89; 91), additional research is required to truly estimate the impact of AID in these age groups.

AID use can be beneficial in pregnant women (58; 60; 79-82), but the glucose targets needed during pregnancy are lower than most commercially available AID systems currently offer. The benefits of AID have also been demonstrated in insulin-naïve users with T2D in outpatient (60) and inpatient, noncritical care settings (61; 92), and in people on hemodialysis (83; 85) or with gastroparesis (84). However, additional studies are needed to confirm safety and efficacy for these populations.

Each candidate for AID use should be evaluated by their healthcare provider, to determine their ability to manage intensive insulin therapy. Factors to consider include proficiency in mealtime insulin dosing, motivation, willingness to participate in formal device training, manual dexterity/visual status, and financial/insurance status.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

4. Initiating AID System Use

Table 7 presents general recommendations for initiating AID use in PwD.

Table 7. Summary of Recommendations: Initiating AID Use

● Make AID systems available to all people with T1D (2; 3; 7; 8)
● Initiation of AID can be done with in-clinic or digital/virtual training; further research is warranted on how to design, implement, and evaluate individual training programs, including required follow-up and long-term glycemic outcomes.
● Ensure that the PwD and their care partners can demonstrate proficiency in intensive insulin therapy knowledge and skills before initiating AID
● Individualize training in AID based on each PwD's current therapy: ○ MDI + blood glucose monitoring ○ MDI + CGM ○ CSII + blood glucose monitoring ○ CSII + CGM (as nonintegrated and integrated components) ○ AID system ● Personalize training and follow-up based on the PwD/family, health care settings, etc.
● Consider starting people with T1D who are "*technology naïve*" on either an insulin pump or CGM before transitioning to AID. In some cases, the insulin pump and CGM can be initiated simultaneously.
● Advise people with T1D who are transitioning from prior insulin pump therapy to AID to use current pump settings if glycemic control is acceptable; however, pump parameters (basal rate, bolus settings) may need reassessment ● Address insulin-to-carbohydrate ratios (ICRs), correction doses, basal rates, accounting for ratio of basal/TDD as well carbohydrate intake (e.g., low carb diets) ● Individualize the approach to AID depending on the AID system, considering target glucose, active insulin time, etc.
● Provide fundamental guidance regarding hypoglycemia and hyperglycemia treatment with AID, exercise management, switching to open loop or MDI (for "pump vacation"), sick day management, etc. (*See clinical recommendation section)
● Particular attention should be paid to use of adjunctive therapies (e.g., SGLTs), and whether continuing such therapy is safe or feasible
● The diabetes care team should discuss limitations and benefits for AID use: ○ Set realistic expectations for AID system user requirements: handling mealtime boluses/timing; handling CGM and pump use; handling exercise with pre-, during, and post-exercise adjustment as needed; manual insulin delivery during CGM warm-up, loss of connectivity, etc. ○ Review published data on the expected benefit on glycemic outcomes, improvement in overnight glucose control, restful sleep
● Considerations should be made when initiating AID for people with long diabetes duration (especially those with eating disorders) and/or sub-optimal control: ○ Potential transient worsening of retinopathy with need for ophthalmologic care prior to initiation of AID along with close follow-up with ophthalmology ○ Potential temporary neuropathic pain, insulin edema, increase in microalbuminuria and other microvascular complications.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

The optimal time to initiate AID

Early initiation of diabetes technologies in recently diagnosed PwD has been shown to improve and sustain long-term glycemic control, and thereby perhaps reduce the risk of diabetes related complications (93-95). Moreover, tight glycemic control from disease onset in people with T1D may help to preserve beta-cell function (96). There are no definitive data to support the benefit of early initiation of AID systems on long-term metabolic control or beta cell preservation (97). Studies are underway to examine the safety and efficacy of early AID adoption in adults and children newly diagnosed with T1D (98; 99). Likely benefits of early initiation include long-term glycemic control, long-term device acceptance, durable use and a particular benefit for preschool age (100).

Setting Up the AID System

AID settings should be selected according to individualized glycemic targets, based on recently acquired CGM metrics (101). In poorly controlled individuals, using the highest system glucose target possible for the first few weeks is suggested. When determining the settings, the healthcare provider should use conservative estimates to ensure prevention of hypoglycemia. The information needed for initiating the AID system and the parameters that affect automated insulin delivery differ widely across different AID systems. Clinical judgement should be used where programmed regimens do not result in optimal glycemic outcomes. Requirements for initiating AID for specific systems are provided in **Table 8.**

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

1 ***Table 8. Recommendation for preparation and initiation of AID system***

	Medtronic 670G/ 770G/ 780G	**Tandem Control IQ**	**CamAPS FX**	**Insulet OP5**
Preparation before starting AID	● Set-up realistic expectation, assess user willingness to learn and adapt to new technologies ● In individuals who are CGM naïve, initiation of CGM 1-2 weeks prior to commencing AID may be helpful ● In individuals using MDI, initiation of pump (along with CGM) and education on infusion set issues, early recognition and treatment of ketosis diabetic ketoacidosis, 1-2 weeks prior to commencing AID may be helpful ● Training videos may be helpful to understand AID system and its requirements			
Information needed to start AID	TDD from 3-7 days of using the Medtronic AID pump	Body weight and TDD, basal profile, CHO:I ratios, CF's.	Body weight and TDD	Basal profile, CHO:I ratios, CF's, AIT.
Recommended initial settings	● Basal rate does not play role in auto mode but is needed for manual mode and it should be reduced by 10% if it constitutes more than 50% of TDD ● ICR should be strengthened by 10% ● AIT between 2-4 hours (shorter AIT is better)	● Optimize the basal rate (general guide is 50% of TDD) ● Set up sleep activity which narrows glucose targets to 112.5-120 mg/dL (6.3 -6.7 mmol/L), best to extend beyond usual breakfast bolus time	● Optimize the basal rate (general guide is 50% of TDD should be basal) ● Extended bolus feature must be on when using Dana pumps ● Maximum bolus should be set at 50% of TDD ● Daily maximum should be 3 times the TDD for Dana pumps	● Basal rate does not play role in auto mode but is needed for manual mode and it should be reduced by 10% if it constitutes more than 50% of TDD.
Glucose Targets	● 670G/770G is 120 mg/dL (6.7 mmol/L), nonadjustable ● 780G can be 100 mg/dL (5.6 mmol/L) or 120 mg/dL (6.7 mmol/L); may use 120 mg/dL (6.7 mmol/L) initially in a person with high A1c or in children and older adults.	● A control to range algorithm with daytime range of 112.5 to 160 mg/dL (6.3-8.9 mmol/L), and sleep target range of 112.5 to 120 mg/dL (6.3-6.7 mmol/L).	● Set individualized glucose targets between 80-200 mg/dL (4.4-11.1 mmol/L).	● Individualized glucose targets between 110-150 mg/dL (6.1-8.3 mmol/L), can be programmed throughout a day (up to 8 segments).
AID Adaptivity	● TDD updated daily with fading memory over 6 days. Adjusts CF, basal rates.	● TDD uses 6-day average to adjust algorithm aggressiveness.	● Continually adapts independent of pump settings	● Occurs with each pod change. First pod is constrained, after first pod, then full adaptivity. Estimates TDD by multiplying programmed basal insulin by 2

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Autocorrection	● None with 670G/770G ● Every 5 minutes with 780G	● Can occur 1 hour after a previous bolus: 60% of calculated to a target of 110 mg/dL (6.1 mmol/L)	● None (algorithm tuned not to need bolus autocorrection)	
Modifiable factors to optimize AID	● ICR and AIT	● Basal rate, correction factor, and ICR, Sleep duration and timing ● Exercise- targets glucose at 140-160 mg/dL (7.8-8.9 mmol/L).	● None – algorithm independent of pump settings	● ICR, and correction factor, glucose targets ● AIT is only for user-initiated bolus (with corrections and food boluses). Pump's AIT is not used for auto mode insulin delivery
Exercise	● Temp target to 150 mg/dL (8.3 mmol/L), programmable duration	● Target glucose is 140-160 mg/dL (7.8-8.9 mmol/L), stops basal at 80 mg/dL (4.4 mmol/L). Currently must be manually stopped (no duration setting)	● "Ease-off" – target glucose increased by 40 mg/dL (2.2 mmol/L), and insulin sensitivity increased programmable for 10 min to 24 hours (can also be preplanned)	● "HypoProtect" target is 150 mg/dL (8.3 mmol/L. All basal/bolus/corrections are 50%. Duration is programmable for 1-72 hours
Reverse Correction if below target	● With 780G uses "safe bolus"	● No	● Yes	● Yes, but can be toggled off
Extended Bolus	● No	● Yes, current max time is 2 hours	● No	● No
Use of CGM trend in bolus calculation	● No	● No	● No	● Yes

1 TDD, total daily insulin dose; ICR, insulin to carb ratio; AHCL, advanced hybrid AID; CGM, continuous glucose monitor; AIT, active insulin time

2

3

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

5. Education, Training and Support

A rigorous, comprehensive, consistent, and structured education curriculum for AID must be of high priority for all AID systems and must be individualized for each PwD. The following recommendations present the essential elements that should be considered in providing education and training to individuals who are initiating AID. **Table 9** presents recommendations for patient training and education.

Table 9. Summary of Recommendations for Training and Education

• Advise users to consistently wear the CGM, respond to system alerts, and perform actions as needed to stay in AID mode as much as possible for optimal glycemic control.
• Proactively address user expectations (102-104): AID systems may take several weeks to perform optimally, and PwD need time to acclimate to the system. Psychological considerations such as learning to develop trust in the automated system as well as having realistic expectations for glycemic control should be proactively addressed prior to AID start and on an ongoing basis.
• Reinforce the importance of maintaining self-management skills including blood glucose checking, ketone checking, administering a syringe or insulin pen injection, regular review of default basal insulin delivery settings, calculating a correction dose of insulin in case of system malfunction, identifying diabetes emergencies and carrying supplies to handle them (102; 104).
• Remind users how to recognize signs of infusion set failure: in cases of sustained hyperglycemia above 250 mg/dL, and/or after a bolus insulin correction, the glucose level does not drop by at least 50 mg/dL within one hour of treatment (105). (*See clinical recommendation section for more information on pump malfunction)
• Emphasize the importance of understanding the benefits of pre-meal bolusing and AID response to postprandial hyperglycemia. Encourage users to bolus accurately for all meals and snacks (104; 106). Educate users, in case a meal bolus was missed, to give half of the meal bolus amount or not to bolus at all, depending on when they remembered the missed bolus (*See clinical recommendation section for more information on bolusing)
• Advise users to consider treating hypoglycemia with less carbohydrates than usual, and respond to system cues such as CGM arrows, CGM trend, and insulin on board (104). Remind users that the AID system may have reduced/suspended insulin prior to hypoglycemia.
• Assist users in setting CGM alerts to be actionable and not a nuisance. (*See clinical recommendation section for more information on alert fatigue)
• Educate users about the risk of trying to “trick the system”. Using techniques such as entering fictitious carbohydrates, overriding bolus calculators, taking extra insulin outside of the system, etc. can lead to increased glucose lability and decreased system performance.
• Counsel PwD how to handle their AID system in special situations (illness, exercise, pregnancy). Users may consider transitioning to open loop in circumstances where more manual control is desired (e.g., ketones, steroid bursts, sports competition, pregnancy, altered mental status, etc.). When disconnecting their AID system for more than 15-30 minutes, advise users to suspend insulin delivery so AID does not try to automate insulin while disconnected.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Training for AID Systems

It is important to emphasize that transition to AID systems should be individualized. In general, persons who are CGM naïve will benefit from several days of CGM use before commencing AID. This period can be used for education on alarms, trend arrows, and data interpretation for optimization of insulin therapy, which may allow for better starting parameters for AID transition. CGM user engagement requires insertion of sensors, replacing sensors when failures occur, and knowledge on how to troubleshoot sensor failures. This education is vital to avoid burnout, frustration, and to optimize successful device use. Those who are naïve to CSII therapy should follow existing protocols for switching from MDI to CSII therapy, considering 1-2 weeks of SAP therapy before commencing AID. Education for CSII-related eventualities such as alternating pump insertion sites, replacing infusion sets, how to troubleshoot pump occlusions are advised. Pump users should consider using SAP mode for several days if switching from a different pump brand, allowing for adaptation both to the user interface and to the bolus calculator that may require insulin dose adjustments. It is recommended that PwD and care partners demonstrate understanding of the AID system features, how to use them and how to troubleshoot. Initial training can be successful when delivered face-to-face, by videoconference (107-110) and with supporting roles for e-learning, video, simulation apps, and combined approaches. Where applicable, industry should continue their essential role in certifying trainers to provide initial device training.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Emphasize choice and personal reasons

PwD should have the opportunity to assess the full benefit and burden of available AID systems to decide if and which device is most suitable for them. Educational support, personal resources, age/licensing/availability/insurance, and personal preferences need to be considered, and unbiased sources should be heavily utilized by PwD (e.g., clinical educators, non-commercial entities such as JDRF, ADA, ADCES, Diabeteswise.org or BDCPantherDiabetes.org).

Prioritize comprehensive education

PwD must be trained and assessed for proficiency on general diabetes management, carbohydrate counting, insulin pump use, and CGM use in order to use an AID system safely. We recommend the creation and use of a universal pre-AID checklist or framework to comprehensively review essential education. AID training is not just technical and cannot be separated from the overall management of diabetes. It is actually adding the tip of the pyramid of education. The base is the core diabetes knowledge and management education, CGM basics, insulin pump basics and on the top is the AID basics education. **Table 10** presents a comprehensive pre-AID education checklist.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Table 10. Pre-AID comprehensive education checklist

Core Diabetes Knowledge	
	Insulin action time
	Blood glucose and blood ketone testing
	Importance of proper nutrition
	Importance of physical activity
	Treating hypoglycaemia
	Carbohydrate counting
	Checking in with psychological concerns around diabetes and diabetes care
Insulin pump basics	
	Set changes and site rotation
	Connecting and disconnecting infusion set or tubing (if applicable)
	Bolus insulin vs. basal insulin
	Data interpretation
	Physical activity and sport, holiday, alcohol, menstrual cycle, etc. management
	Infusion set failures, manual injections, checking ketones, emergency management
Continuous glucose monitoring basics	
	Sensor changes and site rotation
	Connecting, pairing, programming components
	Calibrating (if applicable)
	Using CGM information (trend line, trend arrows, alerts, data sharing, downloads)
AID (prior to device training)	
	Understanding the different CL system options to weigh the burden and benefit of each one to the PwD
	Importance of maintaining knowledge of diabetes management principles described above
	Expectations of CL
	How CL differs from open loop insulin therapy
	Importance of early follow-up with clinical team after starting CL

It is helpful for PwD to know how to check progress they are making when using an AID system, both through reports on their mobile devices, on their personal cloud-based accounts or eventually their electronic health record AID summary reports. Further, PwD need to

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

anticipate new challenges and learning opportunities with AID systems and expect the need for clinical follow-up early after AID initiation.

Implement universal early follow-up

PwD are at increased risk for discontinuing devices in the first 3-6 months of use (43; 66; 69), therefore early clinical follow-up is essential, but often not defined or consistent with routine diabetes follow-up (111; 112). Diabetes teams should consider creating "Initial Device Optimization" follow-up plans for new AID device users to: a) assess system use; b) reinforce appropriate expectations; c) optimize insulin dosing and behavior; d) provide troubleshooting; and e) gain trust in the system. These topics should be universally covered, but the content and timing can be personalized to the needs of the user, ideally within the first 2-4 weeks after device initiation. This could be accomplished through phone calls with data review, videoconference, or in-person visits with their diabetes team. Additional use and creation of e-learning, and training videos may be useful. Although there are no data related to worsening or occurrence of neuropathy with AID initiation, there may be a need for retinal checks and/or retinal stabilization before and after initiation of AID in people with suboptimal glycemic control.

Clinical roles

There is no universal role differentiation between diabetes providers, diabetes educators, and other members of the healthcare team with AID systems, as every practice environment is different. All clinicians should be aware of how AID systems work (104) and could benefit from brief training videos, webinars, demonstration devices, step-by-step tools,

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

and device simulation apps (102; 113). Additionally, practices or regions should consider the role of "Diabetes Technology Specialists" to provide more specific troubleshooting and device optimization strategies to support other clinicians and PwD. Consider the development of a standard curriculum, clarifying the scope of this role, and possible certification programs to formalize this role.

Routine clinical assessment

Diabetes clinicians must be able to provide competent clinical assessment of AID use for routine care (28; 102). **Table 11** presents a proposed standard approach for clinical practice, which includes four key components. Clinical AID tools should be developed to standardize these principles across AID systems and models of care.

Table 11. Proposed approach to the assessment of AID use

1. System descriptions	Clinicians can be provided with a brief summary of device information, using **CARES** framework (provides information on how each system **C**alculates insulin delivery, which parameters can be **A**djusted, when users should **R**evert to traditional insulin pump settings, critical **E**ducation points, and key aspects of the sensor and **S**haring capabilities of the system) (104; 114) or other.
2. How to ASSESS glycemic information	Clinicians can explain how they interpret CGM data, including TIR, TAR, TBR, mean glucose, Glycemic Management Index (GMI) and glycemic variability (101; 115).
3. How to OPTIMIZE AID settings	Clinicians can explain which settings/parameters can be changed, best practices for insulin dose titration as applicable to the system, comparing AID basal to open loop basal.
4. How to GUIDE behavioral recommendations	Clinicians can explain bolus behavior, use of special modes, frequency of infusion set changes (28).

6. Clinical Recommendations for AID Use

AID systems are labelled for efficacy and safety based upon manufacturer-specified instructions. PwD should be advised that actions such as entering fictitious carbohydrates,

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

performing postprandial meal boluses, manual insulin bolus corrections or overriding recommended doses unless educated to do so (e.g., during prolonged exercise after a meal) can lead to glucose instability, increased hypoglycemic risk and destabilized systems.

We should reconsider the traditional concepts of "basal" insulin and "bolus" insulin, which become less useful with AID, as both types of insulin delivery are used to mitigate hypoglycemia and hyperglycemia and contend with carbohydrate consumption. Instead of basal-bolus we suggest using the terms of *user-initiated* and *algorithm modulated insulin delivery*. Importantly, all current commercial AID systems still require user-initiated bolusing for carbohydrate intake. Pump settings (such as insulin action time, basal rates, etc.) are handled differently in the various AID systems, dissimilarities which preclude our ability to provide general recommendations. Refer to **Table 8** for system specifications. The following are general recommendations for use of AID systems (should be tailored individually). (**Table 12**). Recommendations for AID adjustments for physical activity are presented in **Table 13.**

Table 12. Summary of Recommendations for Use of AID System

● *User initiated bolus for meal: carbohydrate ratio (ICR) settings are important:* ○ For hybrid AID systems which use ICR for meal bolus, the ICR should be evaluated routinely after initiation by assessing post-meal glucose excursions and aiming for <60 mg/dL (< 3.3 mmol/L) increase compared to pre-meal, similar to the recommendations for open loop systems. ○ Some systems benefit from more aggressive ICR (e.g. numerically lower ICR) by 10 to 20% (116; 117) as compared to open loop settings to help minimize post meal glucose excursions.
● *User initiated bolus timing for meals:* ○ Timing user-initiated insulin boluses prior to carbohydrate intake is especially important, as AID will automatically increase algorithm modulated insulin delivery after an initial rise of glucose levels, so a bolus delivered either during or after carbohydrate consumption could lead to insulin stacking and hypoglycemia. ○ Generally, user initiated meal boluses should be given in advance of a meal (usually 10-20 minutes) unless there is incipient hypoglycemia, gastroparesis, or high protein/fat meal. Faster insulins may shorten the timing of the bolus. Adjunct therapy and meal composition may also influence timing. ○ In situations where a meal bolus is missed or delayed, consider giving half the bolus 30-60 minutes after the start of the meal, or if more than 60-minutes have elapsed from start of the meal a user-initiated correction bolus can be given, based on the glycemic rise (e.g., the system recommended correction bolus only). ○ While some systems have the ability to give an extended bolus, the clinical utility may be limited in most AID

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

systems. This is due to the fundamental algorithm modulated insulin delivery (AMID) that is the hallmark of these systems, which will inevitably increase algorithmic insulin delivery for persistently elevated glucose that can be seen after certain meals, like those with high fat content.
  - Low carbohydrate intake may be used to improve glycemic control for adults using AID ((118)).

- *Exercise management:*
  - Setting a higher glucose target, ideally well before starting the activity (up to 1 to 2 hours in advance), particularly for prolonged aerobic exercise. This temporary target can be cancelled at the end of exercise or be maintained post exercise if post-exercise hypoglycemia is a concern
  - Minimizing activity at times of peak bolus insulin action appears to increase AID efficacy around exercise. To facilitate this, a pre-meal bolus dose can be reduced by approximately 25 to 75% if prolonged exercise is anticipated within 3 hours of a meal.
  - If the pump is disconnected during exercise, insulin delivery should be suspended so that the algorithm does not account for algorithm modulated insulin delivery that is not delivered to the person with diabetes.

- *Carbohydrates before exercise:*
  - Advise users against consuming carbohydrates 15-60 minutes prior to exercise, unless glucose is trending towards hypoglycemia because AID systems will respond by automatically increasing insulin delivery which might increase the risk for hypoglycemia during the activity. However, this recommendation should be individualized, and carbohydrates can be suggested in the following circumstances:
  - Advise 15g carbohydrate if glucose is <120 mg/dL (6.7 mmol/L), 10 min pre-exercise, especially for moderate intensity exercise.
  - Simple carbohydrates can be taken at exercise onset, or just prior to exercise as long as the temporary target is set. Carbohydrate feeding during a prolonged exercise activity, without entering the carbohydrate intake into the AID, may be needed to help maintain glycemia and help with endurance performance. If the AID function is suspended during the activity (i.e., if the pump is set to "open loop" or "standard" mode), carbohydrates can be taken freely before and/or during exercise to increase or maintain a desired glucose target.
  - Summary table for exercise management is provided in the Appendix **Table 3**.

- *Treatment of hypoglycemia event (>15 minutes at <70 mg/dL, hypoglycemia alert event):* ((119))
  - Start hypoglycemia event treatment with 5-10g carbs with an exception for hypoglycemia with exercise, or in case of significant over-estimation of carbs / meal bolus.
  - Wait for 15 minutes before re-treating hypoglycemia to avoid oscillating glucose levels.

- *Treatment of hyperglycemia event and ketones:*
  - In case of sustained hyperglycemia, it is recommended to measure blood glucose (by glucometer), monitor ketones and perform a set change.
  - As with all insulin pumps, DKA remains a concern due to potential infusion set failure. A user-initiated correction bolus might be needed.
  - A correction may be more effective using an insulin pen/syringe, as in case of set failure and multiple correction attempts, IOB may be falsely elevated thus preventing an additional bolus.
  - If giving a corrective insulin injection, advise users that the AID should be turned off for 2 to 4 hours that insulin-on-board (IOB) is accurate.

- *Sick days treatment:*
  - Advise users to consider stopping AID and move to open loop sick day management plans (e.g., monitor ketones and increase open loop insulin), especially in case of elevated ketones and glucose levels within normal range.
  - Before small procedures (such as gastroscopy) AID can be used with a temporary glucose target or hypoglycemia protect mode.

- *Types of insulin:*
  - A rapid-acting insulin is recommended for AID systems. Using ultra-rapid analogs may be considered for a greater clinical advantage in PwD who tend to miss meal boluses or prefer to bolus immediately before a meal (if approved for use in the system).

- *Tuning open loop settings:*
  - Adjustments to open loop settings should be performed for times when PwD may need to use, or choose to

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

use, open loop therapy. ○ If a PwD is going off AID for extended periods, consider using more conservative ICR settings as a method to avoid hypoglycemia, since ICR are often intensified for optimal AID performance. ○ Multiple daily injection regimens should be available when switching from AID to MDI in case of pump failure or pump break.
● *Avoiding alarm fatigue*: ○ Advise users that minimizing alarms to those that require immediate attention can help avoid alarm fatigue. ○ Clinicians need to assist users to develop plans to respond to alerts (for example, advising that fewer carbohydrates will be needed to treat hypoglycemia while on an AID system). ○ One suggestion is to start with hypoglycemia only alerts (at a lower threshold of 65-70 mg/dL [3.6-3.9mmol/L]), and add hyperglycemia alerts if tolerated (starting higher, 250-300 mg/dL [13.8-16.7mmol/L]).
● *Glycemic targets with AID:* ○ Although many PwD are able to achieve currently recommended targets for time in range, separate targets for AID are currently not recommended. However, these may be subject to change as the technology evolves and should be customized according to the individual PwD.

1

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Table 13. Adjustments for physical activity in AID

Type of Exercise	Before Exercise	During Exercise	After Exercise	Overnight
Aerobic	Reduce basal rate with 'exercise targe' 1-2 hours prior	Reduce basal rate with 'exercise targe' or suspend insulin delivery*	Reduce basal rate with 'exercise targe' 0-6 hours after	'Exercise target' overnight (up to 6 hours) as necessary And/Or Uncovered bedtime snack
Aerobic & Anaerobic	Reduce bolus amount by 0-25% in 1-3 hours prior (maybe up to 75% is prolonged exercise is anticipated)	In case glucose level is below 120 mg/dL, consume 10-20gr carbohydrates at start or 10 min prior^	Reduce bolus up to 50% at post-exercise meal	
		Carbohydrates as needed		
Anaerobic	May not need insulin adjustments	May not need insulin adjustments	Reduce bolus or cancel exercise target	

* Confirm insulin pump suspension

^ Avoid consuming carbohydrates 15-60 minutes prior to exercise (can be given as needed during exercise)

Prepared by Laurel H Messer

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

7. How to Report and Present AID Data

Internationally agreed standardization of CGM metrics, targets and a report to visualize them were published and endorsed by a wide range of diabetes associations and endocrine societies (101; 119-121). The use of AID systems is based on CGM data, and its success may be measured in improved CGM outcomes such as TIR. As the use of AID grows, it is therefore important that clinical teams receive AID data reports with consistent and familiar data displays (122). Data should be provided in a way that assists with appropriate modification of insulin delivery settings.

An academic panel of experts in AID system development, research or clinical use collaborated to generate a template for an AID system data report. The standardized two-page "Automated Insulin Delivery Report" (AID Report) (**Figure 1**) template was arranged to make sure that the clinically most important glucose and insulin metrics are shown at the very top of the first page (upper panel). The middle panel of the first page contains the Ambulatory Glucose Profile (AGP) chart that has become the standardized way to represent aggregated CGM data, usually over 14 days. The bottom panel of the first page contains the bolus (mealtime) insulin assessment with average meals per day and average carbs entered per day indicated at the top of the section banner. Each mealtime displays a glucose profile created when one or more insulin boluses is delivered within the specified mealtimes.

The second page of the report shows detailed daily glucose profiles (**Figure 2**). Most clinicians want to see records over a useful period of time, commonly 14 days, there will likely be further pages of daily views, as requested. Note, only one daily profile is shown for illustrative purposes.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

AID systems differ in the way glucose is controlled and insulin is delivered. Therefore, modification of the report might be needed according to the specific system features. The report aims to present the relevant data and metrics that can assist the health care provider in decision making and in adjustment of the system parameters that can be modified.

8. Psychological Issues and PwD Perspectives on AID Systems

An increasing number of trials with AID systems incorporate psychosocial variables among their outcome measures. Improvements in patient reported outcomes have not been consistent (48-51; 123; 124), yet all studies showed there was no deterioration, if not an improvement, in quality of life (QoL). Some have reported a significant reduction in fear of hypoglycemia (50; 124) and others have found a reduction in diabetes distress and increased quality of sleep (53). Many PwD as well as their care partners including parents, spouses, adult children of a PwD and other caregivers, feel that AID has been “life-changing” and restores a greater sense of well-being, and that they have great hope for the next steps toward full automation of insulin delivery (125).

A major issue in sustainable AID use is supporting user acceptance, helping the users to integrate AID use into their daily lives, and to address the numerous challenges accompanying long-term AID use. In addition, user expectations should be acknowledged by different health care providers. Because many of these challenges are psychological and behavioral in nature, further research is needed to develop strategies that effectively address these issues. **Table 14** presents recommendations, gaps and opportunities.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Table 14. Summary of Recommendations, Gaps and Opportunities: Addressing Psychological and Behavioral Issues

Recommendations
● AID clinical trials should include participants from diverse populations to ensure equitable access; to improve sustainable engagement in poor areas; to reduce healthcare disparities and make this technology more broadly accessible to underserved areas.
● Trials should pivot away from the typical participants of past studies who tend to be quite "tech-savvy" and have already adopted use of devices such as CGM and insulin pumps. Studies of the processes involved in AID adaptation and adoption in these groups will likely reveal an even more urgent need for PwD education and support, as well as programs to address psychosocial barriers to technology use.
● Engaging primary care is essential for bringing AID technology as a viable option to the full quorum of PwDs to ensure they can consider its use. This will require not only industry support, but also increased education.
● Specific support should be available to all clinicians caring for people with diabetes, including the necessary resources to make AID systems viable options in as many clinical settings as possible. This support should also focus on improving workflow and reducing HCP burden.
● AID systems must be used to focus on reducing time spent on diabetes self-management, increasing well-being. The avoidance of medicalizing psychosocial outcomes must be emphasized.
Opportunities/Gaps
● AID systems can be used to detect daily glucose fluctuations related to psychological stress. Algorithms can be improved accordingly, as user experience is taken into account during algorithm development (126).
● Future research should consider the role of AID in PwD with eating disorders and other vulnerable groups.
● Further work exploring AID associated improvement for children and families is necessary. Improvement should be quantified and contextualized in terms of potential reduction of risk of intended self-injury and suicidal acts.
● Studies evaluating long-term health benefits of AID related to improved glycemia are needed (such as reduction in diabetes related complications, neurocognitive outcomes, etc).

It is well-established that there are considerable disparities in healthcare delivery, access to structured diabetes education, uptake of diabetes technologies and achievement of diabetes-related treatment targets across gender, geographic area, racial/ethnic groups and level of social deprivation (127; 128). Although the use of new technology has been proven to be beneficial in clinical trials, participation in such trials has so far lacked the necessary diversity across ethnicity, socio-economic status, and health literacy. One explanation for this may be

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

that research has largely been conducted through academic medical centers, posing a barrier to participants who are unable to travel to these centers in part due to social determinants of health. However, other factors may also play a role such as providers' bias in recruiting study participants, and clinical sites whose population either does not include or includes few members of racial/ethnic minority groups. The importance of including minorities in clinical studies, beyond the generalizability of outcomes, is the contribution to device development along with improved propagation and marketing policies to increase AID use among underrepresented groups (62).

In 2020 and 2022, the FDA published guidelines on how to enhance population diversity in clinical trials. These include specifying enrollment targets according to race/ethnicity, choosing clinical sites in geographic areas that will enable representation of minority populations, and including a diverse study team of health care providers to help in recruitment (129). Recently, leading journals are required to provide detailed racial/ethnic distributions in clinical trials and hopefully, this would lead to more representation of minorities in trials in the future (130; 131). Still, there is a need to create regulation and reporting procedures that will promote inclusion and diversity in clinical trials. In addition to multidisciplinary stakeholder engagement in disparities research (132).

Inequalities in technology access have not been overcome, and the reasons for this beyond the socioeconomic status are poorly understood (133; 134). Unfortunately, many healthcare systems make access to diabetes technologies in general, and AID systems in particular, very difficult to obtain and maintain. Advocacy efforts are required to make diabetes technology and AID systems available to all people with diabetes who would benefit

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

from their use. Failure to achieve equity and access to AID systems may translate into a two-tiered system of diabetes care based on who can, and cannot, access diabetes technology.

Moving forward: to support access to AID systems, all clinicians working with PwD will have to become familiar with the available systems. Appropriate education should be developed that is high in quality, efficient, and accessible. Coordination and cooperation across professional organizations should be encouraged to maximize impact and reach. Shared professional resources should be encouraged. Greater coordination, cooperation, and partnership will be the key to providing adequate support and equip clinicians with the required skills so they may confidently offer their patients the best diabetes technologies available, including AID systems. It is clear that this technology has brought positive life-changing experiences for many users.

9. The Future of AID: What Will It Look Like?

There are several directions for the future development of the next generation of AID systems:

AID component interoperability

In December 2019, the FDA authorized the first interoperable AID controller (135). According to the FDA press release: "*This authorization paves the way for Integrated CGMs (iCGMs) and alternate controller-enabled insulin pumps (ACE pumps) to be used with an interoperable automated glycemic controller as a complete automated insulin dosing system*." Other algorithms will follow and, together with iCGM and ACE pumps, will create an ecosystem

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

of AID components that can be mixed and matched. Regulatory agencies across the world are reviewing this issue and we are confident that positive steps will be taken. Nevertheless, challenges will remain; thus, academic and corporate groups should continue working on a global interoperability standard.

Better Insulin Time-action Profiles

The delay associated with insulin absorption from the subcutaneous insulin depot into the bloodstream is still a bottleneck. Thus, virtually all commercial AID systems are "hybrid," necessitating meal and exercise announcements to achieve glycemic targets. Insulin analogs that are absorbed faster are becoming increasingly available (136), and it is assumed that faster insulin will contribute to better glucose control. However, several studies of insulin delivery via insulin pump or AID found that this assumption is not necessarily accurate in terms of TIR; ultra-rapid insulin provides a modest advantage over rapid insulin analogs, at best, or no advantage (137; 138). Future studies will show whether proper adaptation of the AID control algorithms to ultra-rapid insulin will result in clinically significant changes.

Alternative routes of insulin delivery are being explored to improve post prandial glycemic control, and initial results are promising: Intraperitoneal (IP) insulin delivery (139; 140), or premeal inhaled insulin (Afrezza) when added to an AID system (141).

Fully-automated AID systems

The progress in this direction is directly related to better insulin time-action profiles, alternative routes of insulin delivery, novel control algorithms and adjunctive agents (e.g., glucagon, amylin, GLP-1 and SGLT-2). Additional inputs, such as motion sensing, meal detection,

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

and disturbance anticipation can be employed to control post-meal hyperglycemia and exercise-related hypoglycemia. Funding agencies are actively supporting research on sensors that could provide additional signals, e.g., active insulin, lactate, or ketones, though the utility of these additional signals will still be subject to the pharmacokinetics of subcutaneous insulin delivery.

Multi-hormone closed-loop systems, which include AID plus glucagon (13), pramlintide (14) or adjuvant medications such as GLP-1 receptor agonists (142) and SGLT-2 inhibitors (143; 144) to further improve post-prandial hyperglycemia, are under investigation. Of note, the data suggest that the control algorithm in these systems may need to be adaptive to the physiological changes caused by some of these medications, thereby increasing technological complexity and regulatory barriers for multi-hormonal systems.

AID usability

The size, shape, battery life, physical specifications, and additional customizations of the AID hardware and software will remain critical to system acceptance by the users (145). The stability and safety of data communications, both locally between system components and the user's smartphone, and between the AID system and the Cloud, is critical as well. Convenience and longevity of the infusion sets or tubeless insulin delivery devices must continue to improve – currently, the infusion set is the weakest link in most AID systems. User burden may be reduced with implanted sensors and combined insulin delivery glucose sensing platforms. And last but not least, AID affordability and reimbursement by health care systems will remain the gateway to system adoption.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

The future technology vision

Cloud databases will play an increasingly important role to support data sharing, virtual clinic visits, and remote access and will allow the deployment of data science tools, such as pattern recognition, neural networks, deep learning, and artificial intelligence. *In silico* pre-clinical trials have been, and will continue to be, used for rapid and cost-effective testing of new ideas (146). Merging large databases with *in silico* models will create a comprehensive virtual environment for experimenting with new system components, prior to their deployment in clinical trials. A most promising application of Cloud databases and data science tools is the use of adaptation technologies that can "learn" and personalize the response of an AID system to the individual. Preliminary work showing the potential of adaptation is already published (147), and long-term vision for AID personalized medicine strategy has been presented (148). AID key discreet data and the presented consensus report need to be directly integrated into the electronic health record (EHR). This integration is most important for ease of access by clinicians, ease of communication with PwD and for population health management (case management). Smart insulin pens connected with CGM will enable a kind of AID for people who prefer to use MDI therapy.

Summary

Given the associated improvements in glycemic control and quality of life measures, clinicians should strongly consider use of AID systems in their PwD who would benefit from this technological option. We recommend that payers support usage of AID systems and other

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

emerging technologies that reduce diabetes burden and improve patient reported outcomes. Furthermore, studies have suggested long term cost saving for health care system using these systems. Therefore, we strongly recommend that all payers (government and private) should reimburse/cover AID systems along with initial and ongoing AID education and training to support the management of people with T1D. Failure to reimburse diabetes technologies such as AID systems will deprive many individuals with T1D who would benefit from this valuable technology and may result in increased disparities in diabetes outcomes, racial and social inequities (149; 150).

Acknowledgements

The consensus group participants wish to thank the ATTD congress for organizing and coordinating the meeting and Rachel Naveh (The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel) for assistance in organizing the meeting. The authors also wish to thank Christopher G Parkin, MS, CGParkin Communications, Inc., for his assistance in preparing this manuscript.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

REFERENCES

1. Foster NC, Beck RW, Miller KM, et al. State of Type 1 Diabetes management and outcomes from the T1D Exchange in 2016–2018. Diabetes Technol Ther 2019;21(2):66-72.

2. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. N Engl J Med 2019 Oct 31;381(18):1707-1717.

3. Isganaitis E, Raghinaru D, Ambler-Osborn L, et al. Closed-Loop Insulin Therapy Improves Glycemic Control in Adolescents and Young Adults: Outcomes from the International Diabetes Closed-Loop Trial. Diabetes Technol Ther 2021;23(5);342-349.

4. McAuley SA, Lee MH, Paldus B, et al. Six Months of Hybrid Closed-Loop Versus Manual Insulin Delivery With Fingerprick Blood Glucose Monitoring in Adults With Type 1 Diabetes: A Randomized, Controlled Trial. Diabetes Care 2020;43:3024-3033.

5. Collyns OJ, Meier RA, Betts ZL, et al. Improved Glycemic Outcomes With Medtronic MiniMed Advanced Hybrid Closed-Loop Delivery: Results From a Randomized Crossover Trial Comparing Automated Insulin Delivery With Predictive Low Glucose Suspend in People With Type 1 Diabetes. Diabetes Care. Apr 2021;44(4):969-975.

6. Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. Lancet 2018;392:1321-1329.

7. Pease A, Zomer E, Liew D, Earnest A, Soldatos G, Ademi Z, Zoungas S. Cost-Effectiveness Analysis of a Hybrid Closed-Loop System Versus Multiple Daily Injections and Capillary Glucose Testing for Adults with Type 1 Diabetes. Diabetes Technol Ther. 2020 Nov;22(11):812-821.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

8. Jendle J, Pöhlmann J, de Portu S, Smith-Palmer J, Roze S. Cost-Effectiveness Analysis of the MiniMed 670G Hybrid Closed-Loop System Versus Continuous Subcutaneous Insulin Infusion for Treatment of Type 1 Diabetes. Diabetes Technol Ther. 2019 Mar;21(3):110-118.

9. Bott OJ, Hoffmann I, Bergmann J, et al. HIS modelling and simulation based cost-benefit analysis of a telemedical system for closed-loop diabetes therapy. Int J Med Inform. 2007 Dec;76(Suppl 3):S447-55.

10. Serné EH, Roze S, Buompensiere MI, Valentine WJ, De Portu S, de Valk HW. Cost-Effectiveness of Hybrid Closed Loop Insulin Pumps Versus Multiple Daily Injections Plus Intermittently Scanned Glucose Monitoring in People With Type 1 Diabetes in The Netherlands. Adv Ther 2022; ;39(4):1844-1856.

11. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. Diabetes. 2003;52:2790–2794.

12. Slattery D, Amiel SA, Choudhary P. Optimal prandial timing of bolus insulin in diabetes management: a review. Diabet Med. 2018 Mar;35(3):306-316.

13. Castellanos LE, Balliro CA, Sherwood JS, Jafri R, Hillard MA, Greaux E, Selagamsetty R, Zheng H, El-Khatib FH, Damiano ER, Russell SJ. Performance of the Insulin-Only iLet Bionic Pancreas and the Bihormonal iLet Using Dasiglucagon in Adults With Type 1 Diabetes in a Home-Use Setting. Diabetes Care. 2021; 44(6):e118-e120.

14. Haidar A, Tsoukas MA, Bernier-Twardy S, Yale JF, Rutkowski J, Bossy A, et al. A novel dual-hormone insulin-and-pramlintide artificial pancreas for type 1 diabetes: a randomized controlled crossover trial. Diabetes Care. 2020;43(3):597-606.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

15. El Youssef J, Castle J, Ward WK. A review of closed-loop algorithms for glycemic control in the treatment of type 1 diabetes. Algorithms 2009;2:518-32.

16. Forlenza GP, Cameron FM, Ly TT, Lam D, Howsmon DP, Baysal N, et al. Fully closed-loop multiple model probabilistic predictive controller artificial pancreas performance in adolescents and adults in a supervised hotel setting. Diabetes Technol Ther 2018;20(5):335-43.

17. Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. Jama 2016;316:1407-1408.

18. Forlenza GP, Pinhas-Hamiel O, Liljenquist DR, Shulman DI, Bailey TS, Bode BW, et al. Safety evaluation of the minimed 670g system in children 7-13 years of age with type 1 diabetes. Diabetes Technol Ther 2019;21(1):11-19.

19. Brown SA, Beck RW, Raghinaru D, et al. Glycemic Outcomes of Use of CLC Versus PLGS in Type 1 Diabetes: A Randomized Controlled Trial. Diabetes Care 2020 ;43(8):1822-1828.

20. Breton MD, Kanapka LG, Beck RW, et al. A Randomized Trial of Closed-Loop Control in Children with Type 1 Diabetes. N Engl J Med 2020;383:836-845.

21. Brown S.A., Forlenza G.P., Bode B.W., et al. Multicenter Trial of a Tubeless, On-Body Automated Insulin Delivery System With Customizable Glycemic Targets in Pediatric and Adult Participants With Type 1 Diabetes. Diabetes Care 2021; 44, 1630-1640 .

22. Carlson A.L., Sherr J.L., Shulman D.I, et al. Safety and glycemic outcomes during the MiniMed™ Advanced Hybrid Closed-Loop system pivotal trial in adolescents and adults with type 1 diabetes. Diabetes Technol. Ther 2022;24(3):178-189.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

23. Bergenstal RM, Nimri R, Beck RW, Criego A, Laffel L, Schatz D, et al. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. Lancet. 2021;397(10270):208-19.

24. Benhamou P-Y, Franc S, Reznik Y, et al. Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial. The Lancet Digital Health 2019;1:e17-e25.

25. Kariyawasam D, Morin C, Casteels K, Le Tallec C, Sfez A, Godot C, Huneker E, Garrec N, Benhamou PY, Polak M, Charpentier G, Franc S, Beltrand J. Hybrid closed-loop insulin delivery versus sensor-augmented pump therapy in children aged 6-12 years: a randomised, controlled, cross-over, non-inferiority trial. Lancet Digit Health 2022;4:e158-e168

26. Blauw H, A Joannet Onvlee AJ, Klaassen M, van Bon AC, DeVries JH. Fully Closed Loop Glucose Control With a Bihormonal Artificial Pancreas in Adults With Type 1 Diabetes: An Outpatient, Randomized, Crossover TriaDiabetes Care 2021;44(3):836-838.

27. Burnside M, Lewis D, Crocket H, et al. CREATE (Community deRivEd AutomaTEd insulin delivery) trial. Randomised parallel arm open label clinical trial comparing automated insulin delivery using a mobile controller (AnyDANA-loop) with an open-source algorithm with sensor augmented pump therapy in type 1 diabetes. J Diabetes Metab Disord 2020 May 30;19(2):1-15.

28. Schoelwer MJ, Kanapka LG, et al. Predictors of Time-in-Range (70-180 mg/dL) Achieved Using a Closed-Loop Control System. Diabetes Technol Ther 2021 Jul;23(7):475-481.

29. Fuchs J., Allen J.M., Boughton C.K., et al. Cambridge hybrid closed-loop in very young children with type 1 diabetes: a multi-national 4-month randomized trial EASD annual meeting, Virtual 2021.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

30. Boughton CK, Hartnell S, Thabit H, Mubita WM, Draxlbauer K, Poettler T, Wilinska ME, Hood KK, Mader JK, Narendran P, Leelarathna L, Evans ML, Roman H. Hybrid closed-loop glucose control with sensor augmented pump therapy in older adults with type 1 diabetes: an open-label multicentre, multinational, randomised, crossover study. Lancet Healthy Longevity, 2022, p. e135–142

31. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose Outcomes With the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults With Type 1 Diabetes. Diabetes Technol Ther 2017;19(3):155-163.

32. Forlenza GP, Ekhlaspour L, DiMeglio LA, Fox LA, Rodriguez H, Shulman DI, Kaiserman KB, Liljenquist DR, Shin J, Lee SW, Buckingham BA. Glycemic outcomes of children 2-6 years of age with type 1 diabetes during the pediatric MiniMed™ 670G system trial. Pediatr Diabetes 2022; 23(3):324-329.

33. JL S, BW B, GP F, LM L, M S, BA B, AB C, DJ D, SA M, DW H, TT L. Glycemic control with the Omnipod 5 Automated Insulin Delivery System in very young children with type 1 diabetes. International Society for Pediatric and Adolescent Diabetes (ISPAD) 47th Annual Conference; Virtual, 2021

34. Ekhlaspour L, Town M, Raghinaru D, Lum JW, Brown SA, Buckingham BA. Glycemic Outcomes in Baseline Hemoglobin A1C Subgroups in the International Diabetes Closed-Loop Trial. Diabetes Technol Ther 2022; Online ahead of print.

35. Breton MDS, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. Diabetes Technol Ther 2021 ;23(9):601-608.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

36. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. N Engl J Med 1993;329, 977-986.

37. Stone MP, Agrawal P, Chen X, et al. Retrospective Analysis of 3-Month Real-World Glucose Data After the MiniMed 670G System Commercial Launch. Diabetes Technol Ther. 10 2018;20(10):689-692.

38. Akturk HK, Giordano D, Champakanath A, et al. Long-term Real-Life Glycaemic Outcomes With a Hybrid Closed-Loop System Compared With Sensor-Augmented Pump Therapy in Patients With Type 1 Diabetes. Diabetes Obes Metab 2020;22(4):583-589.

39. Beato-Víbora PI, Gallego-Gamero F, Ambrojo-López A, Gil-Poch E, Martín-Romo I, Arroyo-Díez FJ. Rapid Improvement in Time in Range After the Implementation of an Advanced Hybrid Closed-Loop System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther 2021 ;23(9):609-615.

40. Da Silva J., Lepore G., Battelino T., et al. Real-world Performance of the MiniMed 780G System: First Report of Outcomes from 4'120 Users. Diabetes Technol.Ther. 2022;24(2):113-119.

41. Cobry EC, Hamburger E, Jaser SS. Impact of the Hybrid Closed-Loop System on Sleep and Quality of Life in Youth with Type 1 Diabetes and Their Parents. Diabetes Technol Ther 2020;22(11):794-800.

42. Abraham MB, de Bock M, Smith GJ, Dart J, Fairchild JM, King BR, Ambler GR, Cameron FJ, McAuley SA, Keech AC, Jenkins A, Davis EA, O'Neal DN, Jones TW, group AJDRFC-LR. Effect of a Hybrid Closed-Loop System on Glycemic and Psychosocial Outcomes in Children and

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Adolescents With Type 1 Diabetes: A Randomized Clinical Trial. JAMA Pediatr 2021;175:1227-1235

43. Messer LH, Berget C, Vigers T, Pyle L, Geno C, Wadwa RP, Driscoll KA, Forlenza GP. Real world hybrid closed-loop discontinuation: Predictors and perceptions of youth discontinuing the 670G system in the first 6 months. Pediatr Diabetes 2020;21:319-327.

44. Berget C, Messer LH, Vigers T, et al. Six months of hybrid closed loop in the real-world: An evaluation of children and young adults using the 670G system Pediatr Diabetes. 2020; 21(2): 310–318.

45. Messer LH, Berget C, Pyle L, Vigers T, Cobry E, Driscoll KA, Forlenza GP. Real-World Use of a New Hybrid Closed Loop Improves Glycemic Control in Youth with Type 1 Diabetes. Diabetes Technol Ther 2021;23:837-843.

46. Lum JW, Bailey RJ, Barnes-Lomen V, et al. A Real-World Prospective Study of the Safety and Effectiveness of the Loop Open Source Automated Insulin Delivery System. Diabetes Technol Ther 2021;23(5):367-375.

47. Bergenstal RM, Gal RL, Connor CG, et al. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. Ann Intern Med. 2017;167(2):95-102.

48. Ziegler C, Liberman A, Nimri R et al. Reduced worries of hypoglycaemia, high satisfaction, and increased perceived ease of use after experiencing four nights of MD-logic artificial pancreas at home (DREAM4). Journal Diabetes Res 2015; 2015: 590308.

49. Cobry EC, Kanapka LG, Cengiz E, et al. Health-Related Quality of Life and Treatment Satisfaction in Parents and Children with Type 1 Diabetes Using Closed-Loop Control. Diabetes Technol Ther 2021;23(6):401-409.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

50. Bisio A, Brown SA, McFadden R, et al. Sleep and Diabetes-Specific Psycho-Behavioral Outcomes of a New Automated Insulin Delivery System in Young Children with Type 1 Diabetes and Their Parents. Pediatr Diabetes. 2021 ;22(3):495-502.

51. Wheeler BJ, Collyns OJ, Meier RA, et al. Improved technology satisfaction and sleep quality with Medtronic MiniMed Advanced Hybrid Closed-Loop delivery compared to predictive low glucose suspend in people with Type 1 Diabetes in a randomized crossover trial. Acta Diabetol. 2021;27.

52. Kudva Y.C., Laffel L.M., Brown S.A., et al. Patient-Reported Outcomes in a Randomized Trial of Closed-Loop Control: The Pivotal International Diabetes Closed-Loop Trial. Diabetes Technol.Ther 2021;23, 673-683.

53. Cobry EC, Bisio A, Wadwa RP, Breton MD. Improvements in Parental Sleep, Fear of Hypoglycemia, and Diabetes Distress With Use of an Advanced Hybrid Closed Loop System. Diabetes Care 2022; 1;45(5):1292-1295.

54. Barnard KD, Wysocki T, Ully V et al. Closing the loop in adults, children and adolescents with sub-ptimally controlled type 1 diabetes under free living conditions: a psychosocial substudy. J Diabetes Sci Technol 2017;11:1080–1088.

55. Tauschmann M, Allen JM, Nagl K, et al. Home Use of Day-and-Night Hybrid Closed-Loop Insulin Delivery in Very Young Children: A Multicenter, 3-Week, Randomized Trial. Diabetes Care 2019;42:594-600.

56. Ekhlaspour L, Schoelwer MJ, Forlenza GP, et al. Safety and Performance of the Tandem t:slim X2 with Control-IQ Automated Insulin Delivery System in Toddlers and Preschoolers. Diabetes Technol Ther. 2021;23(5):384-391.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

57. Salehi P, Roberts AJ, Kim GJ. Efficacy and Safety of Real-Life Usage of MiniMed 670G Automode in Children with Type 1 Diabetes Less than 7 Years Old. Diabetes Technol Ther. 2019 ;21(8):448-451.

58. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. N Engl J Med. 2016 Aug 18;375(7):644-54.

59. Stewart ZA, Wilinska ME, Hartnell S, et al. Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial. Diabetes Care 2018;41(7):1391-1399.

60. Kumareswaran K, Thabit H, Leelarathna, et al. Feasibility of closed-loop insulin delivery in type 2 diabetes: a randomized controlled study. Diabetes Care 2014;37(5):1198-203.

61. Thabit H, Hartnell S, Allen JM, et al. Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. Lancet Diabetes Endocrinol 2017;5:117-124.

62. Akturk HK, Agarwal S, Hoffecker L, Shah VN. Inequity in Racial-Ethnic Representation in Randomized Controlled Trials of Diabetes Technologies in Type 1 Diabetes: Critical Need for New Standards. Diabetes Care. 2021 May 20;44(6):e121-3.

63. American Diabetes Association. ADA evidence-grading system for “Standards of Medical Care in Diabetes” Diabetes Care 2021 Jan;44(Suppl 1):S221-S222.

64. Dovc K, Battelino T. Closed-loop insulin delivery systems in children and adolescents with type 1 diabetes. Expert Opin Drug Deliv. 2020;17(2):157-166.

65. Sherr JL, Buckingham BA, Forlenza GP, et al. Safety and Performance of the Omnipod Hybrid Closed-Loop System in Adults, Adolescents, and Children with Type 1 Diabetes Over 5 Days Under Free-Living Conditions. Diabetes Technol Ther. 2020 ;22(3):174-184.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

66. Lal RA, Basina M, Maahs DM, et al. One Year Clinical Experience of the First Commercial Hybrid Closed-Loop System. Diabetes Care. 2019 Dec;42(12):2190-2196.

67. Braune K, O'Donnell S, Cleal B, et al. Real-World Use of Do-It-Yourself Artificial Pancreas Systems in Children and Adolescents With Type 1 Diabetes: Online Survey and Analysis of Self-Reported Clinical Outcomes. JMIR Mhealth Uhealth. 2019 Jul 30;7(7):e14087.

68. Varimo T, Pulkkinen MA, Hakonen E, et al. First year on commercial hybrid closed-loop system - experience on 111 children and adolescents with type 1 diabetes. Pediatr Diabetes. 2021 ;22(6):909-915.

69. Berget C, Akturk HK, Messer LH, et al. Real world performance of hybrid closed loop in youth, young adults, adults and older adults with type 1 diabetes: Identifying a clinical target for hybrid closed loop use. Diabetes Obes Metab 2021 ;23(9):2048-2057.

70. McAuley SA, Trawley S, Vogrin S, Ward GM, Fourlanos S, Grills CA, Lee MH, Alipoor AM, O'Neal DN, O'Regan NA, Sundararajan V, Colman PG, MacIsaac RJ. Closed-Loop Insulin Delivery Versus Sensor-Augmented Pump Therapy in Older Adults With Type 1 Diabetes (ORACL): A Randomized, Crossover Trial. Diabetes Care 2022;45:381-390

71. Fuchs J, Hovorka R. Benefits and Challenges of Current Closed-Loop Technologies in Children and Young People With Type 1 Diabetes. Front Pediatr. 2021 Apr 30;9:679484.

72. Fuchs J, Allen JM, Boughton CK, et al. Assessing the efficacy, safety and utility of closed-loop insulin delivery compared with sensor-augmented pump therapy in very young children with type 1 diabetes (KidsAP02 study): an open-label, multicentre, multinational, randomised cross-over study protocol. BMJ Open. 2021;11(2):e042790.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

73. Petruzelkova L, Jiranova P, Soupal J, et al. Pre-school and school-aged children benefit from the switch from a sensor-augmented pump to an AndroidAPS hybrid closed loop: A retrospective analysis. Pediatr Diabetes. 2021;22(4):594-604.

74. Dovc K, Boughton C, Tauschmann M, et al. Young Children Have Higher Variability of Insulin Requirements: Observations During Hybrid Closed-Loop Insulin Delivery. Diabetes Care 2019;42(7):1344-1347.

75. Anderson SM, Buckingham BA, Breton MD, et al. Hybrid Closed-Loop Control Is Safe and Effective for People With Type 1 Diabetes Who Are at Moderate to High Risk for Hypoglycemia. Diabetes Technol Ther . 2019;21(6):356-363.

76. Abitbol A, Rabasa-Lhoret R, Messier V, et al. Overnight Glucose Control with Dual- and Single-Hormone Artificial Pancreas in Type 1 Diabetes with Hypoglycemia Unawareness: A Randomized Controlled Trial. Diabetes Technol Ther 2018 Mar;20(3):189-196.

77. Malone SK, Peleckis AJ, Grunin L, et al. Characterizing Glycemic Control and Sleep in Adults with Long-Standing Type 1 Diabetes and Hypoglycemia Unawareness Initiating Hybrid Closed Loop Insulin Delivery. J Diabetes Res 2021 Feb 12;2021:6611064.

78. Burckhardt MA, Abraham MB, Dart J, Smith GJ, Paramalingam N, O'Dea J, de Bock M, Davis EA, Jones TW. Impact of Hybrid Closed Loop Therapy on Hypoglycemia Awareness in Individuals with Type 1 Diabetes and Impaired Hypoglycemia Awareness. Diabetes Technol Ther 2021;23:482-490.

79. Polsky S, Akturk HK. Case series of a hybrid closed-loop system used in pregnancies in clinical practice. Diabetes Metab Res Rev. 2020 Mar;36(3):e3248.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

80. Farrington C, Stewart Z, Hovorka R, Murphy H. Women's Experiences of Day-and-Night Closed-Loop Insulin Delivery During Type 1 Diabetes Pregnancy. J Diabetes Sci Technol. 2018 Nov;12(6):1125-1131.

81. Farrington C, Stewart ZA, Barnard K, Hovorka R, Murphy HR. Experiences of closed-loop insulin delivery among pregnant women with Type 1 diabetes. Diabet Med. 2017 Oct;34(10):1461-1469.

82. Stewart ZA, Yamamoto JM, Wilinska ME, et al. Adaptability of Closed Loop During Labor, Delivery, and Postpartum: A Secondary Analysis of Data from Two Randomized Crossover Trials in Type 1 Diabetes Pregnancy. Diabetes Technol Ther. 2018 Jul;20(7):501-505.

83. Bally L, Gubler P, Thabit H, et al. Fully closed-loop insulin delivery improves glucose control of inpatients with type 2 diabetes receiving hemodialysis.Kidney Int 2019 Sep;96(3):593-596.

84. Kaur H, Schneider N, Pyle L, et al. Efficacy of Hybrid Closed-Loop System in Adults with Type 1 Diabetes and Gastroparesis. Diabetes Technol Ther 2019 Dec;21(12):736-739.

85. Boughton CK, Tripyla A, Hartnell S, Daly A, Herzig D, Wilinska ME, Czerlau C, Fry A, Bally L, Hovorka R. Fully automated closed-loop glucose control compared with standard insulin therapy in adults with type 2 diabetes requiring dialysis: an open-label, randomized crossover trial. Nat Med 2021;27:1471-1476.

86. Sherwood JS, Jafri RZ, Balliro CA, et al. Automated glycemic control with the bionic pancreas in cystic fibrosis-related diabetes: A pilot study. J Cyst Fibros. 01 2020;19(1):159-161.

87. Scully KJ, Palani G, Zheng H, Moheet A, Putman MS. The effect of Control IQ™ hybrid closed loop technology on glycemic control in adolescents and adults with cystic fibrosis related diabetes. Diabetes Technol Ther 2022;24(6):446-452.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

88. Kovatchev BP, Kollar L, Anderson SM, et al. Evening and overnight closed-loop control versus 24/7 continuous closed-loop control for type 1 diabetes: a randomised crossover trial. Lancet Digit Health 2020 Feb;2(2):e64-e73.

89. Carlson AL, Bode BW, Brazg, et al. 97-LB: Safety and Glycemic Outcomes of the MiniMed Advanced Hybrid Closed-Loop (AHCL) System in Subjects with T1D American Diabetes Association 80th Scientific Sessions. June 12-16, 2020; Virtual.

90. Thabit H, Tauschmann M, Allen JM, et al. Home Use of an Artificial Beta Cell in Type 1 Diabetes. N Engl J Med 2015;373(22):2129-2140.

91. Bisio A, Gonder-Frederick L, McFadden R, et al. The Impact of a Recently Approved Automated Insulin Delivery System on Glycemic, Sleep, and Psychosocial Outcomes in Older Adults With Type 1 Diabetes: A Pilot Study. J Diabetes Sci Technol 2022 ;16(3):663-669.

92. Bally L, Thabit H, Hartnellet S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. N Engl J Med 2018;379:547-556.

93. Mulinacci G, Alonso GT, Snell-Bergeon JK, Shah VN. Glycemic Outcomes with Early Initiation of Continuous Glucose Monitoring System in Recently Diagnosed Patients with Type 1 Diabetes. Diabetes Technol Ther. 2019 Jan;21(1):6-10.

94. Kamrath C, Tittel SR, Kapellen TM, et al. Early versus delayed insulin pump therapy in children with newly diagnosed type 1 diabetes: results from the multicentre, prospective diabetes follow-up DPV registry. Lancet Child Adolesc Health. 2021 Jan;5(1):17-25.

95. Champakanath A, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Continuous Glucose Monitoring Initiation Within First Year of Type 1 Diabetes Diagnosis Is Associated With Improved Glycemic Outcomes: 7-Year Follow-Up Study. Diabetes Care 2022;45:750-753.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

96. Shah SC, Malone JI, Simpson NE. A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med. Mar 1989;320(9):550-4.

97. Buckingham B., Beck R.W., Ruedy K.J., et al. Effectiveness of early intensive therapy on β-cell preservation in type 1 diabetes. Diabetes Care 2013; 36, 4030-4035.

98. University of Cambridge. Closed Loop From Onset in Type 1 Diabetes (CLOuD). https://clinicaltrials.gov/ct2/show/NCT02871089. Accessed September 22, 2021.

99. Jaeb Center for Health Research. Hybrid Closed Loop. Hybrid Closed Loop Therapy and Verapamil for Beta Cell Preservation in New Onset Type 1 Diabetes (CLVer). https://clinicaltrials.gov/ct2/show/NCT04233034. Accessed September 22, 2021.

100. Patton SR, Noser AE, Youngkin EM, Majidi S, Clements MA. Early Initiation of Diabetes Devices Relates to Improved Glycemic Control in Children with Recent-Onset Type 1 Diabetes Mellitus. Diabetes Technol Ther 2019;21(7):379-384.

101. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range.Diabetes Care. 2019;42(8):1593-1603.

102. Kimbell B, Rankin D, Ashcroft NL, et a. What Training, Support, and Resourcing Do Health Professionals Need to Support People Using a Closed-Loop System? A Qualitative Interview Study with Health Professionals Involved in the Closed Loop from Onset in Type 1 Diabetes (CLOuD) Trial. Diabetes Technol Ther 2020;22:468-475.

103. Messer LH. Why Expectations Will Determine the Future of Artificial Pancreas. Diabetes Technol Ther 2018;20:S265-S268.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

104. Boughton CK, Hartnell S, Allen JM, Fuchs J, Hovorka R. Training and Support for Hybrid Closed-Loop Therapy. J Diabetes Sci Technol 2022 Jan;16(1):218-223.

105. Cescon M, DeSalvo DJ, Ly TT, Maahs DM, Messer LH, Buckingham BA, Doyle FJ, Dassau E. Early Detection of Infusion Set Failure During Insulin Pump Therapy in Type 1 Diabetes. J Diabetes Sci Technol 2016;10:1268-1276.

106. Boughton CK, Hartnell S, Allen JM, Hovorka R. The importance of prandial insulin bolus timing with hybrid closed-loop systems. Diabet Med 2019;36:1716-1717.

107. Pinsker JE, Harsimran Singh H, Molly McElwee Malloy MM, et al. A Virtual Training Program for the Tandem t:slim X2 Insulin Pump: Implementation and Outcomes. Diabetes Technol Ther 2021 Jun;23(6):467-470.

108. Vigersky RA, Velado K, Zhong A, Agrawal P, Cordero TL. The Effectiveness of Virtual Training on the MiniMed™ 670G System in People with Type 1 Diabetes During the COVID-19 Pandemic. Diabetes Technol Ther 2021;23:104-109.

109. Gómez AM, Henao D, Parra D, et al. Virtual training on the hybrid close loop system in people with type 1 diabetes (T1D) during the COVID-19 pandemic. Diabetes Metab Syndr. 2021; 15(1): 243–247.

110. Petrovski G, Campbell J, Almajali D, Al Khalaf F, Hussain K. Successful Initiation of Hybrid Closed-Loop System Using Virtual Pump Training Program in a Teenager With Type 1 Diabetes Previously Treated with Multiple Daily Injections. J Diabetes Sci Technol 2021 Nov;15(6):1394-1398.

111. Berget C, Thomas SE, Messer LH, et al. A Clinical Training Program for Hybrid Closed Loop Therapy in a Pediatric Diabetes Clinic. J Diabetes Sci Technol 2020;14:290-296.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

112. Messer LH, Berget C, Ernst A, et al. Initiating Hybrid Closed Loop: A Program Evaluation of an Educator-Led Control-IQ Follow-up at a Large Pediatric Clinic. Pediatr Diabetes 2021 Jun;22(4):586-593.

113. Levine BJ, Close KL, Dalton D, et al. Enhancing resources for healthcare professionals caring for people on intensive insulin therapy: Summary from a national workshop. Diabetes Res Clin Pract 2020;164:108169.

114. Messer LH, Berget C, Forlenza GP. A Clinical Guide to Advanced Diabetes Devices and Closed-Loop Systems Using the CARES Paradigm. Diabetes Technol Ther 2019;21:462-469.

115. Ekhlaspour L, Tabatabai I, Buckingham B. A Review of Continuous Glucose Monitoring Data Interpretation in the Age of Automated Insulin Delivery. J Diabetes Sci Technol 2019;13:645-663.

116. Messer LH, Forlenza GP, Sherr JL, et al. Optimizing Hybrid Closed-Loop Therapy in Adolescents and Emerging Adults Using the MiniMed 670G System. Diabetes Care 2018;41(4):789-796.

117. O'Malley G, Messer LH, Levy C, et al. Clinical Management and Pump Parameter Adjustment of the Control-IQ Closed-loop Control System: Results from a 6-month Multicenter Randomized Clinical Trial. Diabetes Technol Ther 2021 Apr;23(4):245-252.

118. Lehmann V, Zueger T, Zeder A, et al. Lower Daily Carbohydrate Intake Is Associated With Improved Glycemic Control in Adults With Type 1 Diabetes Using a Hybrid Closed-Loop System. Diabetes Care. 2020 Dec;43(12):3102-3105.

119. Danne T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-1640.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

120. Holt R.I.G., DeVries J.H., Hess-Fischl A., et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021; 44, 2589-2625 .

121. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022 Jan; 45 (Supplement 1): S83-S96.

122. Shah VN, Garg SK. Standardized Hybrid Closed-Loop System Reporting. Diabetes Technol Ther 2021 May;23(5):323-331.

123. Weissberg-Benchell J, Hessler D, Polonsky WH, Fisher L. Psychosocial Impact of the Bionic Pancreas During Summer Camp. J Diabetes Sci Technol. 2016 Jun 28;10(4):840-4.

124. Weissberg-Benchell J, Hessler D, Fisher L, Russell SJ, Polonsky WH. Impact of an Automated Bihormonal Delivery System on Psychosocial Outcomes in Adults with Type 1 Diabetes. Diabetes Technol Ther 2017;19(12):723-729.

125. Lawton J, Blackburn M, Rankin D, et al. Participants' Experiences of, and Views About, Daytime Use of a Day-and-Night Hybrid Closed-Loop System in Real Life Settings: Longitudinal Qualitative Study. Diabetes Technol Ther. 2019 Mar;21(3):119-127.

126. Gonder-Frederick LA, Grabman JH, Kovatchev B, et al. Is Psychological Stress a Factor for Incorporation Into Future Closed-Loop Systems?.J Diabetes Sci Technol. 2016;10(3):640-646.

127. Oser SM, Oser TK. Diabetes Technologies: We Are All in this Together. Clinical Diabetes 2020 April;38(2):188-9.

128. Barnard-Kelly K.D. & Chernavsky D. Social Inequalities and Diabetes: A Commentary. Diabetes Therapy 2020; 11, 803-811.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

129. U.S. Food and Drug Administration. Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry, April 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations. Accessed 14 June 2022.

130. Editors, Rubin E. Striving for Diversity in Research Studies. N Engl J Med. 2021 Oct 7;385(15):1429-1430. doi: 10.1056/NEJMe2114651. Epub 2021 Sep 13. PMID: 34516052.

131. Flanagin A, Frey T, Christiansen SL, AMA Manual of Style Committee. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. JAMA. 2021; 17;326(7):621-627.

132. Agarwal S, Crespo-Ramos G, Leung SL, et al. Solutions to Address Inequity in Diabetes Technology Use in Type 1 Diabetes: Results from Multidisciplinary Stakeholder Co-creation Workshops. Diabetes Technol Ther. 2022 Jun;24(6):381-389.

133. Agarwal S, Kanapka LG, Raymond JK, et al. Racial-Ethnic Inequity in Young Adults With Type 1 Diabetes. J Clin Endocrinol Metab 2020;105(8):e2960-e2969.

134. Addala A, Auzanneau M, Miller K, et al. A Decade of Disparities in Diabetes Technology Use and HbA1c in Pediatric Type 1 Diabetes: A Transatlantic Comparison. Diabetes Care. 2021 Jan;44(1):133-140.

135. U.S. Food & Drug Administration. FDA authorizes first interoperable, automated insulin dosing controller designed to allow more choices for patients looking to customize their individual diabetes management device system. https://www.fda.gov/news-events/press-

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

announcements/fda-authorizes-first-interoperable-automated-insulin-dosing-controller-designed-allow-more-choices. Accessed May 4, 2021.

136. Svehlikova E, Mursic I, Augustin T, et al. Pharmacokinetics and Pharmacodynamics of Three Different Formulations of Insulin Aspart: A Randomized, Double-Blind, Crossover Study in Men With Type 1 Diabetes. Diabetes Care 2021 Feb 1;44(2):448-55.

137. Dovc K, Piona C, Yeşiltepe Mutlu G, et al. Faster Compared With Standard Insulin Aspart During Day-and-Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial. Diabetes Care. 2020 Jan;43(1):29-36.

138. Boughton CK, Hartnell S, Thabit H, et al. Hybrid closed-loop glucose control with faster insulin aspart compared with standard insulin aspart in adults with type 1 diabetes: A double-blind, multicentre, multinational, randomized, crossover study. Diabetes Obes Metab. 2021 Jun;23(6):1389-1396.

139. Dassau E, Renard E, Place J, et al. Intraperitoneal insulin delivery provides superior glycaemic regulation to subcutaneous insulin delivery in model predictive control-based fully-automated artificial pancreas in patients with type 1 diabetes: a pilot study. Diabetes Obes Metab. 2017; 19:1698-1705.

140. Lo Presti J, Galderisi A, Doyle FJ, Zisser HC, Dassau E, Renard E, Toffanin C, Cobelli C. Intraperitoneal Insulin Delivery: Evidence of a Physiological Route for Artificial Pancreas From Compartmental Modeling. J Diabetes Sci Technol 2022:19322968221076559. Online ahead of print.

141. Galderisi A, Cohen N, Calhoun P, et al. Effect of Afrezza on Glucose Dynamics During HCL Treatment. Diabetes Care 2020;43(9)2146-2152.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

142. Sherr JL, Patel NS, Michaud CI, Palau-Collazo MM, Van Name MA, Tamborlane WV, Cengiz E, Carria LR, Tichy EM, Weinzimer SA. Mitigating Meal-Related Glycemic Excursions in an Insulin-Sparing Manner During Closed-Loop Insulin Delivery: The Beneficial Effects of Adjunctive Pramlintide and Liraglutide. Diabetes Care 2016;39:1127-1134.

143. Biester T, Muller I, von dem Berge T, Atlas E, Nimri R, Phillip M, Battelino T, Bratina N, Dovc K, Scheerer MF, Kordonouri O, Danne T. Add-on therapy with dapagliflozin under full closed loop control improves time in range in adolescents and young adults with type 1 diabetes: The DAPADream study. Diabetes Obes Metab 2021;23:599-608.

144. Haidar A, Yale JF, Lovblom LE, Cardinez N, Orszag A, Falappa CM, Gouchie-Provencher N, Tsoukas MA, El Fathi A, Rene J, Eldelekli D, Lanctôt SO, Scarr D, Perkins BA. Reducing the need for carbohydrate counting in type 1 diabetes using closed-loop automated insulin delivery (artificial pancreas) and empagliflozin: A randomized, controlled, non-inferiority, crossover pilot trial. Diabetes Obes Metab 2021;23:1272-1281.

145. Commissariat PV, Roethke LC, Finnegan JL, et al. Youth and parent preferences for an ideal AP system: It is all about reducing burden. Pediatr Diabetes. 2021 Nov;22(7):1063-1070.

146. Viceconti M, Cobelli C, Haddad T, Himes A, Kovatchev BP, Palmer M. In silico assessment of biomedical products: The conundrum of rare but not so rare events in two case studies. Proc Inst Mech Eng H 2017;231: 455–466.

147. Messori M, Kropff J, Del Favero S, et al. for the AP@home consortium. Individually Adaptive Artificial Pancreas in Subjects with Type 1 Diabetes: A One-Month Proof-of-Concept Trial in Free-Living Conditions. Diabetes Technol Ther 2017, 19: 560-571.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

148. Shi D, Dassau E, Doyle III FJ, Multivariate Learning Framework for Long-Term Adaptation in the Artificial Pancreas. Bioeng Transl Med 2018; 4: 61-74.

149. Lipman TH, Hawkes CP. Racial and Socioeconomic Disparities in Pediatric Type 1 Diabetes: Time for a Paradigm Shift in Approach. Diabetes Care. 2021 Jan;44(1):14-16.

150. Walker AF, Hood KK, Gurka MJ, et al. Barriers to Technology Use and Endocrinology Care for Underserved Communities With Type 1 Diabetes. Diabetes Care 2021 Jul;44(7):1480-1490.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Figure Legend:

Figure 1: Automated Insulin Delivery Report: Page 1

Upper Panel

1. The upper left section contains the clinically important time in ranges bar and internationally recognized goals to allow the clinician to quickly ascertain the overall level of glucose management.
2. The essential device use information including percentage of time AID and CGM was active along with infusion set and sensor change information is at the top of the first page to alert the clinician of ant data sufficiency or safety concerns.
3. The middle upper panel contains essential glucose metrics including average glucose, glucose management indicator (GMI), and glucose variability calculated as percentage coefficient of variation.
4. The final component of the upper panel is a table containing detailed insulin metrics divided by how the insulin is delivered, either automatically by the AID system (called automated insulin) or user-initiated insulin delivery. Automated insulin metrics include the average amount of insulin delivered per day and the calculated average units per hour. In addition, the daily average automated correction bolus delivered along with the calculated percentage of total daily dose (TDD) is listed. Detailed insulin metrics describing the average user-initiated amounts of bolus insulin given for food, correction insulin given with the food bolus and correction only insulin is listed. In addition, the average amount of user overrides insulin delivered per day and average overrides per day are listed.

Middle Panel Below the AGP are the AID system settings including the insulin-to-carbohydrate (ICR) (1unit insulin/ g CHO), correction factor (CF) (or ISF, Insulin Sensitivity Factor) (1 unit insulin/mg/dl or 1 unit insulin/mmol/L), algorithm glucose set point and active insulin time (that may or may not be adjusted depending on the AID system).

Lower Panel The mealtime glucose metrics begin 1 hour before the meal to show the user's average glucose level prior to the meal and ends four hours after the start of the meal. The start of the meal is the time when the user-initiated bolus is delivered. The number of days with meal boluses recorded is listed to help identify mealtimes where user-initiated bolus insulin may have been omitted. The average amount of carbs per mealtime is also listed. Of note, automated correction boluses may have also been delivered (in AID systems that have this feature) during the post-meal period and may be reflected in the late post-meal period.

Figure 2. Automated Insulin Delivery Report: Page 2

1.The top part of the daily profile displays the CGM tracing and is color coded to match the time in ranges bar (e.g. green when in target range of 70-180 mg/dL, red when less than 70 mg/dL ang gold when above 180 mg/dL). The user-entered carbohydrate is shown above the CGM tracing in grey circles and total amount of carbohydrates is shown on the bar right. Just below the glucose tracing is the amount of user-initiated bolus insulin in dark purple with the common "insulin sail" to show that active bolus insulin is available.

2. The lower section of the daily profile contains the automated basal insulin tracing in light purple with the left y-axis showing the rate in units/hour and the automated correction boluses delivered with the right y-axis showing units per hour. The total amount of correction boluses delivered in each one-hour period of the day is shown by the thin blue line with the number of corrections in that hour shown in parenthesis below the total insulin amount. Total insulin amount for each day is shown on the right of each daily profile using icons to designate how the insulin was delivered along with the TDD.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

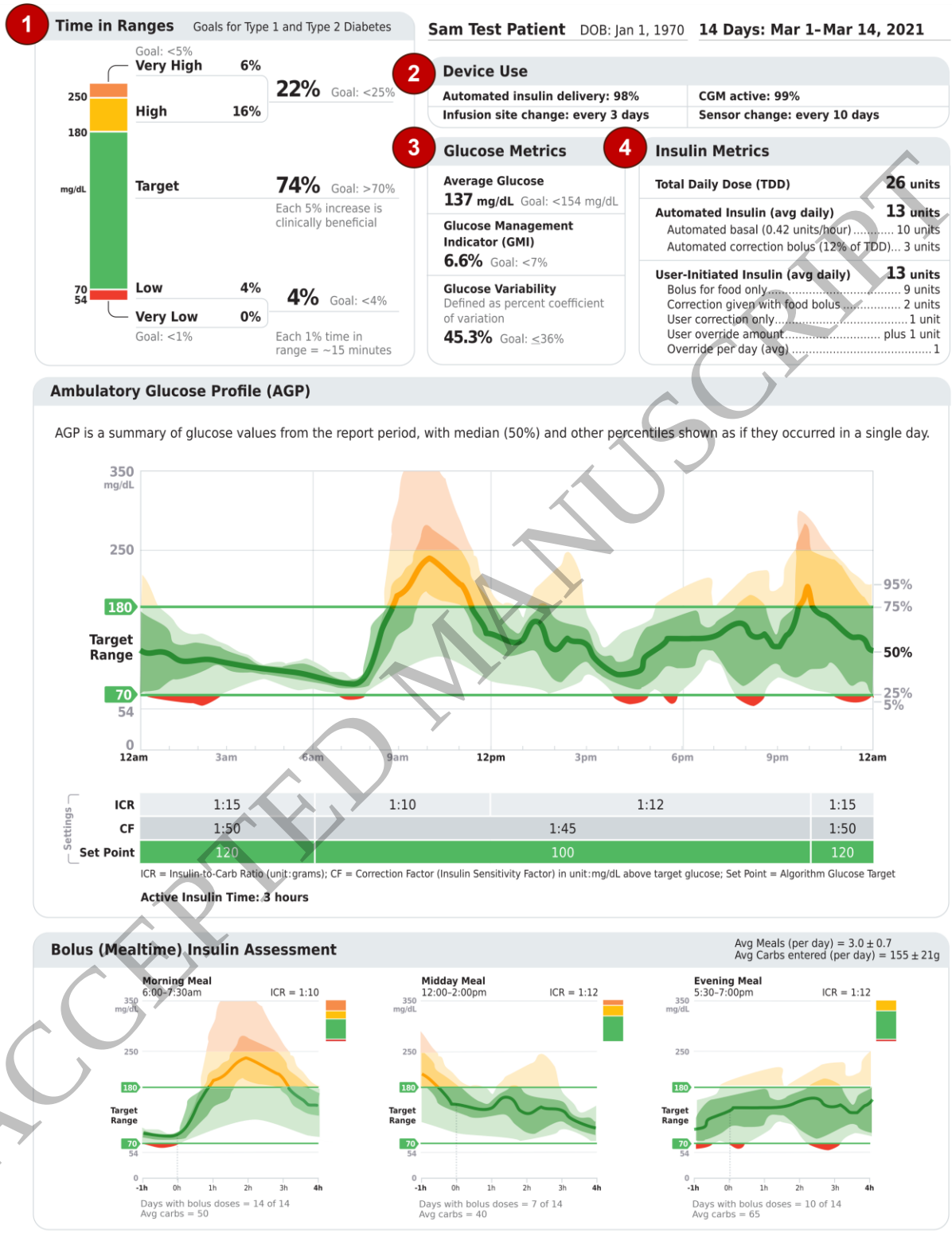


Figure 1
165x205 mm (.10 x DPI)

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

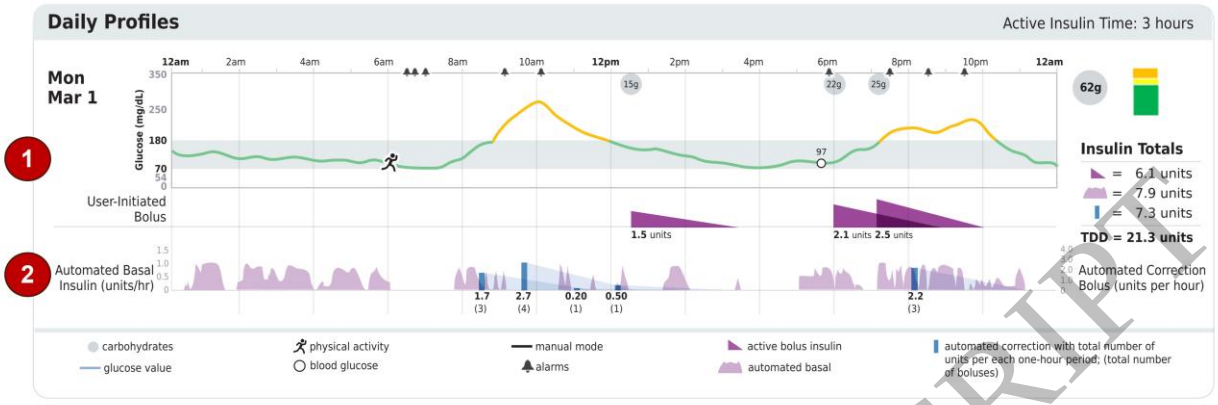


Figure 2
165x58 mm (.10 x DPI)

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

Consensus Recommendations for the Use of Automated Insulin Delivery (AID) Technologies in Clinical Practice

ESSENTIAL POINTS

- AID therapy increases time in target glucose range with either no increase or a reduction in hypoglycemia compared to other diabetes therapies, AID therapy should therefore be considered for all populations with type 1 diabetes as it increases the likelihood of reaching recommended glycemic targets.

- Healthcare providers need to be aware of the different AID systems available, their benefits and limitations to be able to advise and support people with diabetes to increase the likelihood that the clinical benefits of AID are realized.

- Commercially available AID systems still require basic diabetes management skills, including carbohydrate counting, for optimal glycemic control, opportunities to review and refresh these skills, where needed, should be sought.

- Specific AID training and support for users and healthcare providers are important to maximize clinical benefits of AID therapy.

- AID therapy is associated with significant improvements in quality of life and reduced burden of diabetes management for people with diabetes and their families.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022

- Clinical outcomes with AID therapy depend on high AID usage therefore consideration should be given to the usability of available AID systems, ooptimal AID systems require low user input to achieve excellent glycemic outcomes.

- There are well documented and multifactorial racial and ethnic disparities in prescribing AID system technologies. Healthcare provider preconceptions and unconscious biases about individual, family and psychological attributes required to use AID technology effectively should be recognized and mitigated to ensure fair and equitable access to AID systems.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/edrv/advance-article/doi/10.1210/endrev/bnac022/6692818 by guest on 07 October 2022