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LETTER

Considerations for more actionable consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. Reply to Mallone R [letter]

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Abbreviations
CGM Continuous glucose monitoring
IAb Islet autoantibody

To the Editor: We thank Professor Mallone [1] for his comments on our article, 'Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes' [2], and appreciate the opportunity to respond. Regarding Professor Mallone's first comment on the confirmation of a positive islet autoantibody (IAb) screening in a second sample [1], we concur that confirmation by testing a second sample using the same assay and the same laboratory may currently be the only practical approach in some settings. However, we must emphasise that the international Islet Autoantibody Standardization Program (IASP), which performs assay comparisons using a relatively small number of samples (50 samples from individuals with diagnosed stage 3 type 1 diabetes and 100 samples from individuals with no type 1 diabetes) [3], does not certify assays for population-level screening for early-stage type 1 diabetes. In the USA, the College of American Pathologists (CAP) and the federal Food and Drug Administration (FDA), through the Clinical Laboratory Improvement Amendments (CLIA) mandate [4], may eventually issue such certifications. Meanwhile, there is an urgent need to assess the sensitivity and predictive value of the available assays when used for confirmatory testing in populations with low islet autoimmunity prevalence. The consensus statement [2] is intended to indicate the most rigorous approach to ensure the high positive predictive value of assays used in confirmatory testing and limit the number of people falsely diagnosed with early-stage type 1 diabetes and enrolled in unnecessary monitoring. Throughout the consensus guidance we also acknowledge the need to accommodate unique settings with diverse resources [2].

Concerning the need to precede metabolic monitoring with an OGTT and HbA_{1c} evaluation, we agree that this would be ideal, but in many care settings it would not be realistic; thus, we opted to provide alternative measures for glucose monitoring [2]. Professor Mallone's point that the inclusion of stimulated C-peptide data to an OGTT result may not add critical staging information in routine care settings is also valid [1]. We agree that the most critical need is assessing glucose to determine staging, which should be undertaken as quickly as possible after detection of one or more autoantibodies. However, where possible and practical,

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OGTT-derived C-peptide measurement can be used to assess deterioration of beta cell function and to predict risk for developing stage 3 type 1 diabetes [5], including informing Diabetes Prevention Trial-Type Risk (DPTRS) and Index60 scores. Each of these scores is highly valuable in this context, especially if a therapeutic intervention is possible. However, we have acknowledged in the guidance that access to higher capability laboratory testing for routine care is variable in different settings, and therefore have not mandated C-peptide testing [2].

The third point, suggesting consideration of 1 h rather than 2 h postprandial OGTT to avoid missing the transition from stage 1 to stage 2 type 1 diabetes [1], is interesting, as it speaks to better possible detection of early dysglycaemia. However, more evidence is warranted on the use of the 1 h OGTT in staging at this point in type 1 diabetes. As there are many methods to track metabolic changes during this period, we reiterate that the task of the group was to come to consensus on metrics with clear utility, often based on expert opinion and graded as E [2]. However, Professor Mallone's suggestion could be considered when this guidance is updated, as additional evidence may be available. HbA_{1c} measurement could also be considered in this context, although to be sensitive sequential testing is required to detect increments rather than considering only single time points.

We agree that adults with stage 2 or stage 3 type 1 diabetes may have only a single IAb, for the reasons that Professor Mallone puts forward in his fourth comment [1]. We also agree that there is much to be learned about the natural history of adult stage 1 and stage 2 type 1 diabetes. The current guidance reflects the collegial discussions of experts, and also takes pains to identify gaps in the evidence [2]. Professor Mallone describes strategies to gain further insights [1], which could certainly be considered in future iterations.

Professor Mallone's final comment regarding the potential use of continuous glucose monitoring (CGM) for staging purposes is well made [1]. However, the expert group was careful not to overinterpret the value of current CGM data in stage 1 and stage 2 type 1 diabetes, and noted the significant unmet need for additional evidence [2]. CGM assessments in individuals with presymptomatic type 1 diabetes are increasing, although masked CGM is not always possible in real-world clinical practice. It is our hope that future guidance updates will be able to assess more thoroughly the value of CGM devices in IAb-positive children and adults.

Authors' relationships and activities MP has received honoraria for participation on advisory boards for AstraZeneca, Eli Lilly, MannKind, Medtronic Diabetes, Pfizer, Sanofi, Dompé, LifeScan, Novo Nordisk, Insulet, Provention Bio, Merck, Ascensia, Bayer, Embecta and Tandem, and as a speaker for Eli Lilly, Medtronic Diabetes, Novo Nordisk, Pfizer, Sanofi and Ascensia. MP owns stocks in DreaMed Diabetes and NG Solutions and his institution has received research grant support from Eli Lilly, Medtronic Diabetes, Novo Nordisk, Pfizer, Sanofi, DreaMed Diabetes, NG Solutions, Dompé, Lumos, GWave, OPKO, Provention Bio, AstraZeneca and Omega Galil, and consulting fees from Qulab Medical and Provention Bio. TB has served on advisory boards of Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, Medtronic, Abbott and Indigo Diabetes. TB has received honoraria for participating on the speakers bureau of Eli Lilly, Novo Nordisk, Medtronic, Abbott, Sanofi, Dexcom, Aventis, Astra Zeneca and Roche. TB's institution has received research grant support from Abbott, Medtronic, Novo Nordisk, Sanofi, Novartis, Sandoz, Zealand Pharma, the Slovenian Research and Innovation Agency, the National Institutes of Health and the European Union. REJB is a member of the Provention Bio advisory board and has received a speaker's honorarium from EASD Rising Stars sponsored by Sanofi and a Superior Novo Nordisk PHD Fellowship. EB has received speaker's honoraria from Sanofi. HMC has received research grant support from Sanofi, IQVIA, Breakthrough T1D (formerly known as JDRF), Chief Scientist Office, Diabetes UK and the UK Medical Research Council. HMC has received honorarium from Novo Nordisk and owns shares in Roche Pharmaceuticals and Bayer AG. TD has received lecture/other fees and honoraria from Abbott, Astra Zeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Medtronic, Novo Nordisk, Provention Bio, Roche, Sanofi and Vertex. KD has received honoraria for participation on advisory boards for Medtronic and Novo Nordisk and speaker fees from Abbott, Eli Lilly, Novo Nordisk, Medtronic and Pfizer. OE is a member of the Sanofi and Medtronic Diabetes advisory boards. OE has received research support from Medtronic Diabetes, MannKind Pharmaceutical, Dexcom, Eli Lilly Diabetes, Abbott, Vertex Pharmaceutical and Janssen Pharmaceutical. OE has received consulting and speaker fees from Medtronic Diabetes, Sanofi and Vertex. All financial support from industry for OE has been through his organisation, T1D Exchange. RIGH has received honoraria for speaking from EASD, Eli Lilly, ENCORE, Liberum, Novo Nordisk, Rovi and Boehringer Ingelheim. RIGH has received conference funding from Novo Nordisk and Eli Lilly. OK has received honorarium and lecture fees from the Sanofi advisory board. DMM has received research support from the NIH, Breakthrough T1D (formerly known as JDRF), NSF and Helmsley Charitable Trust and his institution has had research support from Medtronic, Dexcom, Insulet, Bigfoot Biomedical, Tandem and Roche. RWL has received a consultancy fee from Cigna Insurance. AL has received honorarium from Diamyd Medical AB. MJR has received employment/consultancy fees or grants from Sanofi, Provention Bio and Janssen R&D. KMS has received consultancy fees, grants or honorarium from Provention Bio and Sanofi. KMS has been an advisory board member and consultant for Sanofi, received research funding from Protect. EKS has received lecture fees from Medscape, ADA, Health Matters CME and Med Learning Group LLC and employment/consultancy fees from Sanofi and DRI Healthcare. JSS has been a scientific advisory board member for 4Immune, Abvance, ActoBiotics, Avotres, Biomea Fusion, Kriya Therapeutics, Levicure and Quell Therapeutics. JSS has been a data safety board member for Imcyse and Provention Bio and is a board of directors member for Applied Therapeutics and SAB Therapeutics. JSS has been an advisor or consultant for Dexcom, Eli Lilly, Immunomolecular Therapeutics, Novo Nordisk, Remedy Plan Inc, SAB Therapeutics, Sanofi and Shoreline Therapeutics. JSS has shares in or is an option holder for 4Immune, Abvance, Applied Therapeutics, Avotres, Dexcom, Immunomolecular Therapeutics, Levicure, Remedy Plan Inc and SAB Therapeutics. LAD has received research support for their institution from Dompé, Lilly, MannKind, Medtronic, Provention/Sanofi and Zealand and consulting fees from Vertex and Abata. LAD has a patent pending for use of difuoromethylornithine (DFMO). All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

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