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# Examination of the Igls Criteria for Defining Functional Outcomes of β-Cell Replacement Therapy: IPITA symposium report

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## Abstract

**Context:** The Igls criteria were developed to provide a consensus definition for outcomes of β-cell replacement therapy in the treatment of diabetes during a January 2017 workshop sponsored by the International Pancreas & Islet Transplant Association (IPITA) and the European Pancreas & Islet Transplant Association (EPITA). In July 2019, a symposium at the 17th IPITA World Congress was held to examine the Igls criteria after two years in clinical practice, including validation against continuous glucose monitoring (CGM)-derived glucose targets, and to propose future refinements that would allow for comparison of outcomes with artificial pancreas system approaches.

**Evidence acquisition:** Utilization of the criteria in various clinical and research settings were illustrated by population as well as individual outcome data of four islet and/or pancreas transplant centers. Validation against CGM metrics was conducted in 55 islet transplant recipients followed-up to 10 years from a fifth center.

**Evidence synthesis:** The Igls criteria provided meaningful clinical assessment on an individual patient and treatment group level, allowing for comparison both within and between different β-cell replacement modalities. Important limitations include the need to account for changes in insulin requirements and C-peptide levels relative to baseline. In islet transplant recipients, CGM glucose time-in-range improved with each category of increasing β-cell graft function.

**Conclusions:** Future Igls 2.0 criteria should consider absolute rather than relative levels of insulin use and C-peptide as qualifiers with treatment success based on glucose assessment using CGM-metrics on par with assessment of HbA1c and severe hypoglycemia events.

Key words: pancreas transplantation; islet transplantation; type 1 diabetes; β-cell replacement; continuous glucose monitoring

## Introduction

The aim of β-cell replacement therapy is to achieve near-normal glycemic control in the absence of clinically significant hypoglycemia for patients with diabetes and β-cell failure experiencing severe hypoglycemia, hypoglycemia unawareness, and/or marked glycemic lability, and for patients with diabetes already committed to immunosuppression in support of another organ transplant. Current options for β-cell replacement include whole pancreas[1] or isolated islet transplantation,[2] both of which can restore endogenous insulin secretion and improve glycemic control and stability, ameliorate clinically significant hypoglycemia, and reduce diabetes-related complications.[3] As an alternative to restoration of endogenous insulin secretion, the artificial pancreas (AP) uses continuous glucose monitoring (CGM) to automate exogenous insulin delivery.[4] Despite varying uses and options for β-cell replacement therapy, there had been a lack of clear and standardized definitions for graft function and clinical success, as well as poor alignment of glycemic control metrics used to evaluate AP systems impeding comparison of outcomes with cellular and technological approaches to therapy.[5] To that end, in January 2017 the International Pancreas and Islet Transplant Association (IPITA) and the European Pancreas and Islet Transplant Association (EPITA) held a two-day workshop in Igls, Austria, to develop a standardized definition for functional and clinical outcomes of β-cell replacement therapy, now known as the Igls criteria.[6,7]

The Igls criteria define β-cell graft function as optimal, good, marginal, or failure, based on glycated hemoglobin ($HbA_{1c}$); severe hypoglycemia events (SHEs); insulin requirements; and C-peptide levels (Table 1). A SHE is defined as an event associated with loss-of-consciousness or requiring third-party assistance for recovery.[8] Optimal graft function requires near-normal glycemic control defined by $HbA_{1c}$ ≤6.5% (48 mmol/mol), absence of SHE, insulin independence (including absence of other antihyperglycemic therapy), and a C-

peptide increase over pretransplant measurement. Good β-cell graft function requires on-target glycemic control defined by $HbA_{1c}$ <7.0% (53 mmol/mol), absence of SHE, a reduction in insulin requirements of more than 50% compared to pretransplant (or use of non-insulin antihyperglycemic therapy), and a C-peptide increase over pretransplant measurement. Marginal graft function is defined by either $HbA_{1c}$ ≥7.0% (53 mmol/mol), occurrence of any SHE, or a reduction in insulin requirements of less than 50% in the presence of a C-peptide increase from pretransplant. When C-peptide measures less than 0.5 ng/ml (0.17 nmol/l), or lower than the patient's baseline prior to transplantation, the graft is considered to have functionally failed.[6,7] Optimal and good function are considered clinically successful outcomes, whereas marginal and failure are not.

In July 2019, a daylong symposium was held as part of the 17th IPITA World Congress in Lyon, France, to examine implementation of the Igls criteria after two years of use in clinical practice. The aims included evaluating the utility and limitations of the current criteria in assessing β-cell graft function, identifying possible areas for improvement, and proposing further refinements to the original criteria. Five experienced transplant centers illustrated of the usefulness of the Igls criteria in various clinical and research settings, and the symposium included discussion of limitations and recommendations for paving the way toward future implementation of the Igls criteria to compare outcomes of β-cell replacement therapies with AP system approaches to diabetes management.

## Methods

### Utilization of the Igls criteria

To illustrate the various uses of the Igls criteria, patient data from four different transplant centers were used. Usefulness in a clinical setting on a population level was demonstrated by data from Center A. All consecutive data on patients that had completed at least 1 year of follow-up after either an islet or solitary pancreas transplant in this center were

included. In addition, all patients were included who received a simultaneous pancreas-kidney (SPK) transplant in the year 2014 to provide at least 4 years of follow-up. Igls criteria were assessed at 6 months, 1-, 2-, and 4-years post-transplantation and are presented as a percentage of the population for each of the 3 β-cell replacement therapy groups (i.e. islet transplantation, solitary pancreas transplantation, and SPK transplantation).

Usefulness of the criteria in a clinical setting on an individual level was illustrated by Centers B and C using data from islet and solitary pancreas transplant recipients who had completed at least 2 years of follow-up. For Center B, patients were followed-up at 6 months, 1- and 2-years post-transplantation, longitudinally describing individual patients' graft function according to the Igls criteria using all functional categories. For Center C, individual patients' graft function was longitudinally delineated using the dichotomous Igls criteria definition of treatment success (optimal or good β-cell graft function) and treatment failure (marginal or failed β-cell graft function).

Usefulness of the criteria in a research setting was illustrated by data of Center D, describing consecutive islet transplant recipients included in a research study of a novel immunosuppressive approach that avoided calcineurin inhibitors as previously reported,[9] followed now over a 10-year period.

**Comparison with CGM metrics**

To address whether CGM metrics should be included as part of functional criteria that would better align glycemic control metrics with the AP field, validation of the Igls criteria against standard CGM metrics of glycemic control was provided using data from another transplant center, experienced in CGM in islet transplant recipients.

All CGM data collected during annual post-transplant follow-up in a cohort of patients with type 1 diabetes (T1D) before and after islet transplantation in Center E were

analyzed.[10] CGM metrics were assessed using a blinded system (Medtronic MiniMed, Northridge, CA) for 3 to 5 consecutive days during usual daily life activities and diet as previously described.[11] The percentages of glucose time-in-range (TIR) 70-180 mg/dl (3.9-10 mmol/l) and time-below-range (TBR) <70 mg/dl (3.9 mmol/l) were categorized according to the Igls criteria as optimal, good, marginal, and failure based on 146, 36, 90, and 30 patient assessments, respectively, and evaluated using one-way ANOVA.

## Results

The Igls criteria provide the ability to present and compare data on multiple clinically important levels. On a population level, the Igls criteria are useful to cross-sectionally present and compare functional outcomes of different β-cell replacement modalities (Fig. 1). Using the Igls criteria, functional outcomes of 36 islet transplant recipients (30 islet-after-kidney (IAK)[12], 4 islet-alone transplants (ITA), 2 islet-after-lung (IALu)[13]), 29 solitary pancreas transplant recipients (26 pancreas-after-kidney (PAK), 3 pancreas transplant alone (PTA), and 23 SPK recipients from Center A were evaluated at 6 months, 1-, 2- and 4-years post-transplantation. Good and marginal β-cell graft function is experienced most often with islet transplantation, and optimal and failure with solitary pancreas transplantation, such that treatment success (optimal or good) is experienced by ~60% of recipients over the first two-years, with more durable function in the pancreas than islet group at 4 years. The highest rate of treatment success is seen with SPK.

The Igls criteria can also be used for individual longitudinal description of β-cell graft function over time. Graft function in individual patients following islet transplantation (1 IAK[14], 2 ITA, 3 simultaneous islet-kidney, 1 simultaneous islet-liver-lung-kidney[15]), 1 solitary pancreas transplantation (PTA) and 8 SPK was assessed at 6 months, 1- and 2-years post-transplantation by Center B (Fig. 2A). Islet transplant recipients more often experienced

good and marginal functional outcomes with high fluctuation between functional categories, whereas pancreas transplant recipients showed either optimal function or graft failure. Describing β-cell graft function using the binary Igls criteria outcome measure of treatment success (optimal or good) versus treatment failure (marginal or failed) in 7 individuals following ITA and 7 following PTA from Center C (Fig. 2B) shows that achieving treatment success is less fluctuant and follows similar patterns in ITA compared to PTA recipients.

Apart from clinical settings, the Igls criteria can also be used in a research setting to describe and compare β-cell graft function. Graft function according to the Igls criteria was structurally assessed in ten consecutive ITA recipients from Center D that received islet transplantation under protocols evaluating belatacept and efalizumab (Fig. 3). A switch in graft function from treatment success to treatment failure according to the Igls criteria always predated the clinical decision to perform a supplemental islet infusion[16,17] or subsequent pancreas transplant.[18]

CGM data was collected in a cohort of 55 patients with T1D before and after ITA (n = 39) or IAK (n = 16) in Center E, providing over 302 patient-years based on individual follow-up periods of 1 to 10 years.[10] After islet transplantation, median (IQR) TIR was incrementally improved at 100% (95-100; optimal function), 90% (78-97; good function), 75% (64-89; marginal function) and 58% (44-73; failure) as compared to 54% (44-71) pretransplant (*P* <0.0001, Fig. 4A). Similarly, TBR was 0% (0-1; optimal function), 0% (0-5; good function), 2% (0-7; marginal function) and 7% (3-13; failure), as compared to 9% (3-15) pretransplant (*P* <0.0001, Fig. 4B).

## Discussion

The Igls criteria represent an important step forward in the process of standardizing the assessment of outcomes for β-cell replacement therapy, allowing for individual patient monitoring and the comparison of outcomes by different treatment approaches (i.e. islet and pancreas transplantation). Illustrated by outcome data of experienced transplant centers, the criteria have shown versatility to capture information on different levels in a clinical (at both a treatment group and at an individual patient level) as well as in a research setting.

Existing registries for pancreas (International Pancreas Transplant Registry [IPTR]) and islet (Collaborative Islet Transplant Registry [CITR]) transplantation have used different definitions for functional graft outcomes. IPTR previously defined pancreas graft failure or success by whether insulin was used or not, irrespective of glucose regulation. Recently, this definition has been revised to insulin requirements ≥0.5 units/kg per day,[19] which remains limited as an outcome in the absence of glucose criteria. In addition to insulin requirements, CITR requires reporting of measures for glucose regulation ($HbA_{1c}$, fasting glucose, severe hypoglycemia events) and C-peptide levels, with primary outcomes defined for insulin independence, $HbA_{1c}$ ≤6.5% (48 mmol/mol), absence of SHE, and C-peptide ≥0.3 ng/ml (0.10 nmol/l).[20] Similar metrics are being collected by CITR for a registry of patients undergoing total pancreatectomy with islet autotransplantation.[21] Thus, CITR is positioned to implement assessment by the Igls criteria across both allogeneic and autologous islet transplantation, and IPTR could expand its data reporting requirements for pancreas transplant recipients. By combining measures of glucose regulation and β-cell graft function, the Igls criteria allow for treatment success of whole pancreas, isolated islet, or future stem cell-derived islet transplantation with ongoing insulin use, provided goals for glycemic control and elimination of severe hypoglycemia are met, and clinically significant endogenous insulin secretion (C-peptide) has been restored.

**Limitations of the Igls criteria**

The basis of β-cell graft functional categories on the achievement of $HbA_{1c}$ targets, absence of SHE, reduction in insulin requirements, and restoration of clinically significant C-peptide production is currently limited by the requirement for baseline measures prior to transplantation. In addition, while the thresholds used for defining a successful graft outcome are unavoidably arbitrary, the rationale for glycemic control metrics (i.e. $HbA_{1c}$ and severe hypoglycemia events) is stronger than that for those reflecting graft function to secrete insulin (i.e. insulin use and C-peptide levels).

The requirement for good β-cell graft function of a 50% reduction in insulin use (which should also be <0.5 units/kg per day) is based on expert opinion.[22] Insulin requirements are, however, highly variable and depend on factors which not only vary day-to-day but are also independent of β-cell graft secretory capacity, such as dietary habits, physical activity, insulin sensitivity, kidney function, and the use of non-insulin antihyperglycemic agents. Patient requirements for glucocorticoid therapy, particularly the maintenance of supraphysiologic dosing in combined islet and lung transplants for individuals with β-cell failure due to cystic fibrosis,[13,15] may result in higher insulin requirements due to steroid-induced insulin resistance despite all other criteria being optimal/good. Thus, when insulin requirements are the only component leading to classification of marginal β-cell graft function with glycemic control targets being met, it may be difficult to conclude that the treatment is not clinically successful.

For patients with chronic pancreatitis undergoing total pancreatectomy with islet autotransplantation, the assessment for a reduction of insulin requirements or an increase in C-peptide levels relative to baseline prior to intervention (pre-pancreatectomy) is not possible. Thus, good β-cell graft function that is required to meet criteria for treatment

success depends on the presence of insulin requirements <0.5 units/kg per day and C-peptide levels that are >0.5 ng/ml (0.17 nmol/l) fasting or stimulated. In the absence of a stimulated C-peptide, a recent validation study of the Igls criteria in autologous islet recipients substituted a fasting C-peptide ≥0.2 ng/ml (0.07 nmol/l) that was highly predictive of a stimulated C-peptide >0.5 ng/ml (0.17 nmol/l) when both measures were available for analysis.[23] Measurement of C-peptide provides an estimate of the contribution of engrafted islets to glycemic control, enabling determination of whether improvements in $HbA_{1c}$ are due to changes in insulin dosing or to effective secretory function of the β-cell graft.

**Incorporation of CGM metrics**

At the time of the IPITA/EPITA Opinion Leaders Workshop in 2017, consensus targets for CGM-derived metrics of glycemic control had not been established. Since then, the use of CGM has increasingly expanded in clinical practice. The use of CGM metrics such as TIR may identify changes in glycemia sooner than a change in $HbA_{1c}$, allow simultaneous assessment of hypoglycemia from time-below-range (TBR), and would allow for more direct comparison of β-cell replacement with AP system outcomes.[24,25] In addition, glucose variability has gained increasing importance as both a therapeutic target and an outcome measure in diabetes clinical trials,[26] including of islet transplantation,[27] where improvement in glucose variability may be related to improvements in measures of neuropathy.[28]

The Igls criteria were well-correlated to CGM parameters in the allogeneic islet transplant recipients reported here, with similar findings recently demonstrated in a smaller cohort of autologous islet transplant recipients.[23] These results support an approach that applies CGM metrics to the assessment of β-cell graft function, thus further enabling comparisons of results with AP system technology. As even a marginal β-cell graft function

is enough to increase TIR, these results further support that marginal function could still provide benefit to an individual patient by reducing the risk for experiencing future SHE.[29-31]

The increasing use of CGM has led to the recent publication of an international consensus for TIR targets, which may soon be adopted as a surrogate for $HbA_{1c}$.[25] In the international consensus, two situations were distinguished: for adults with type 1 or type 2 diabetes, TIR should be greater than 70%, TBR less than 4%, and TAR less than 25%. For older or high-risk patients, avoidance of hypoglycemia is prioritized such that the goal is first aimed at limiting TBR to less than 1%, and decreasing the requirement of TIR to greater than 50% with TAR less than 50%.[25] While such a compromise in glycemic control is appropriate when hypoglycemia is a significant risk, the objective of β-cell replacement therapies to eliminate hypoglycemia should allow for the achievement of TIR >70-80% even for high-risk individuals such as those with hypoglycemia unawareness or having already undergone kidney transplantation. These TIR targets are based on validation against $HbA_{1c}$, whereby TIR >50% relates to $HbA_{1c}$ <8.0%, TIR >60% to $HbA_{1c}$ <7.5%, TIR >70% to $HbA_{1c}$ <7.0%, and a TIR >80% to $HbA_{1c}$ ≤6.5%.[32]

In the results from Center E, and as previously reported by the same group,[10,11] those with a failed islet transplant spent only 58% TIR but with 7% TBR, and so clearly struggled with achieving even the less stringent CGM criteria for high-risk patients with T1D. Those with marginal β-cell graft function spent 75% TIR with only 2% TBR, and so are most often achieving adult standards for glycemic control. Those with good or optimal β-cell graft function spent 90 and 100% TIR, respectively, with no TBR, clearly meeting stringent glycemic control targets. Thus, there is close agreement of the Igls criteria for defining β-cell graft function with increasing time spent in the target glucose range and decreasing time spent with exposure to hypoglycemia. This relationship of CGM time spent both within and below the normal glucose range with the CGM-independent metrics used in Igls 1.0 should

enable the adoption of CGM metrics as the most accurate approach to compare both cellular therapies and technological approaches to glycemic control.

For high-risk individuals being considered for and receiving β-cell replacement therapy, it is particularly important to also examine time spent with serious, clinically significant hypoglycemia <54 mg/dl (3.0 mmol/l)[33] and glucose variability that more strongly relate to risk for experiencing SHE.[34] Moreover, since β-cell replacement therapy targets near-normal glycemic control (even for high-risk patients), <4% TBR is acceptable as long as time spent <54 mg/dl (3.0 mmol/l) is negligible (<1%) as this amount of CGM measured hypoglycemia is present in healthy, non-diabetic individuals.[35]

**Looking forward: paving the way for Igls 2.0**

In summary, the Igls criteria are considered a great improvement for standardized classification of graft function and treatment success for current β-cell replacement therapies, including both isolated islet and whole pancreas transplantation. Temporal assessment is important and should be included any time a clinical change in β-cell graft function is suspected, and at the time of any additional β-cell transplant. Limitations include the absence of CGM metrics that preclude direct comparison of outcomes to AP systems. In addition, insulin requirements were found to be very dependent on confounding factors such as diet, exercise, and glucocorticoids rather than β-cell graft function, and the requirement for obtaining a stimulated C-peptide >0.5 ng/ml (>0.17 nmol/l) to document β-cell graft function in cases where the fasting level fell below this threshold was felt too cumbersome. Additionally, the dichotomous outcome definition of treatment success and treatment failure was thought to be insensitive to the clinical benefits associated with a marginal β-cell graft

function. Together with insulin requirements, C-peptide levels also cannot be used for comparison of cellular to technologic treatment approaches to glycemic control.

Future steps forward to improve upon the current criteria should incorporate CGM metrics in order to ensure comparison between β-cell replacement therapies and new developments in AP systems technology. We suggest that a new Igls 2.0 form composite criteria in which clinical outcome based on glucose regulation is separated from β-cell graft function, with the latter considered only for further qualification of β-cell replacement modalities (Table 2). Clinical outcome would encompass glycemic control and hypoglycemia and be sufficient for defining treatment success, and only the assessment of β-cell graft function would further require the addition of C-peptide and insulin use criteria. Reflecting the potential of a marginal β-cell function providing clinical benefit, this subdivision also would ensure the possibility for scoring treatment success, even with marginal β-cell graft function. Glycemic control and hypoglycemia could be assessed with or without CGM. Glucose regulation in patients with CGM could be assessed through %TIR and %TBR, while in those without CGM through $HbA_{1c}$ and the occurrence of SHE.

Since insulin requirements are extremely dependent on individual lifestyle-related factors,[36] and are not useful for comparison to AP systems, it was suggested to remove percent reductions for defining β-cell graft function in a future Igls 2.0 criteria. Furthermore, while a threshold for insulin requirements <0.5 units/kg body weight per day was felt by some to represent a reasonable expectation of a clinically successful β-cell graft with good function (consistent with the IPTR)[19], others felt that only insulin-independence should be required for defining optimal β-cell graft function. By removing the amount of insulin that may be required to optimize glycemic control, these revised criteria for insulin use would

also allow for more direct application of the Igls criteria to patients undergoing total pancreatectomy with islet autotransplantation.

The treatment goal for C-peptide level as a functional measure of β-cell graft insulin secretion should still meet the stimulated threshold >0.5 ng/ml (0.17 nmol/l) established by the Diabetes Control and Complications Trial (DCCT) as associated with reduced risk for experiencing severe hypoglycemia events as well as for the development and progression of microvascular complications.[37] This threshold is also associated with improved glycemic control and avoidance of hypoglycemia following islet transplantation for T1D,[38] where it is usually related with a fasting C-peptide of at least 0.2 ng/ml (0.07 nmol/l).[23] C-peptide below this threshold, but at least 0.3 ng/ml (0.10 nmol/l) stimulated[39] (as reported in CITR)[20] or 0.1 ng/ml (0.03 nmol/l) fasted, could be compatible with a marginal β-cell graft. While lower levels of residual C-peptide detectable by high sensitivity assays have been associated with a reduced risk of hypoglycemia in type 1 diabetes,[39,40] in the phase 3 Clinical Islet Transplantation Consortium trial involving individuals with type 1 diabetes complicated by hypoglycemia unawareness, only those transplant recipients who lost islet graft function defined by a stimulated C-peptide <0.3 ng/ml (0.10 nmol/l) experienced a recurrence of severe hypoglycemia,[41] and so should be considered failed.

It is still not known whether the Igls criteria may predict outcomes in β-cell replacement therapy, nor whether the Igls criteria may guide physicians in clinical decision making, e.g. whether a shift from optimal to good function should prompt closer metabolic monitoring or immunological surveillance. Finally, given the heavy psychological burden of T1D affecting disease management,[42] recent clinical trials of diabetes treatments increasingly include patient-reported outcomes (PROs), which have been recognized as a clinically

meaningful outcomes in T1D.[24] Future updates to the criteria should also take into account PROs, including health-related quality of life, diabetes distress, fear of hypoglycemia, and patient satisfaction with their current treatment.[43] It is important to note that the herewith-proposed Igls 2.0 criteria are only preliminary. We propose that experts and practitioners in the field re-convene for another workshop in order to generate consensus of the incorporation of CGM-metrics as proposed here, as well as considering the addition of PROs that could be applied to comparative effectiveness evaluation of both β-cell replacement and AP system approaches to diabetes treatment.

## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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**Table 1. Igls definition of functional and clinical outcomes for β-cell replacement therapy (ref. 6 & 7 [joint publication])**

| β-cell graft functional status | $HbA_{1c}$, % (mmol/mol)[a] | Severe hypoglycemia, events per yr | Insulin requirements, $U \cdot kg^{-1} \cdot d^{-1}$ | C-peptide | Treatment success |
|---|---|---|---|---|---|
| Optimal | ≤6.5 (48) | None | None | >Baseline[b] | Yes |
| Good | <7.0 (53) | None | <50% baseline[c] | >Baseline[b] | Yes |
| Marginal | Baseline | <Baseline[d] | ≥50% baseline | >Baseline[b] | No[e] |
| Failure | Baseline | Baseline[f] | Baseline | Baseline[g] | No |

Baseline, pre-transplant assessment (not applicable to total pancreatectomy with islet autotransplantation patients).
[a]Mean glucose should be used to provide an estimate of the $HbA_{1c}$, termed the glucose management indicator (GMI), in the setting of disordered red blood cell life span.
[b]Should also be >0.5 ng/ml (>0.17 nmol/l) fasting or stimulated.
[c]Should also be <0.5 $U \cdot kg^{-1} \cdot d^{-1}$; might include the use of non-insulin antihyperglycemic agents.
[d]Should severe hypoglycemia occur following treatment, then continued benefit may require assessment of hypoglycemia awareness, exposure to serious hypoglycemia (<54 mg/dl [3.0 mmol/l]), and/or glycemic variability/lability with demonstration of improvement from baseline.
[e]Clinically, benefits of maintaining and monitoring β-cell graft function may outweigh risks of maintaining immunosuppression.
[f]If severe hypoglycemia was not present before β-cell replacement therapy, then a return to baseline measures of glycemic control used as the indication for treatment (ref. 6 & 7) may be consistent with β-cell graft failure.
[g]May not be reliable in uremic patients and/or in those patients with evidence of C-peptide production prior to β-cell replacement therapy.

**Table 2. Proposed Igls criteria 2.0**

| Treatment outcome | Glycemic control | | Hypoglycemia | | Treatment success |
|---|---|---|---|---|---|
| | **$HbA_{1c}$, % (mmol/mol)[a]** | **CGM, % time-in-range** | **Severe hypoglycemia, events per yr** | **CGM, % time <54 mg/dl (3.0 mmol/l)** | |
| Optimal | ≤6.5 (48) | ≥80 | None | 0 | Yes |
| Good | <7.0 (53) | ≥70 | None | <1 | Yes |
| Marginal | ≤Baseline | >Baseline | <Baseline[d] | <Baseline | No[e] |
| Failure | ~Baseline | ~Baseline | ~Baseline[f] | ~Baseline | No |

| **β-cell graft function[g]** | **C-peptide, ng/ml (nmol/l)[h]** | **Insulin use or non-insulin antihyperglycemic therapy** |
|---|---|---|
| Optimal | Any | None |
| Good | >0.5 (0.17) stimulated<br>≥0.2 (0.07) fasting | Any |
| Marginal | 0.3-0.5 (0.10-0.17) stimulated<br>0.1-<0.2 (0.04-<0.07) fasting | Any |
| Failure | <0.3 (0.10) stimulated<br><0.1 (0.04) fasting | Any |

Baseline, pre-transplant assessment (not applicable to total pancreatectomy with islet autotransplantation patients).
[a]Mean glucose should be used to provide an estimate of the $HbA_{1c}$, termed the glucose management indicator (GMI), in the setting of disordered red blood cell life span.
[b]Should also be >0.5 ng/ml (>0.17 nmol/l) fasting or stimulated.
[c]Should also be <0.5 $U \cdot kg^{-1} \cdot d^{-1}$; might include the use of non-insulin antihyperglycemic agents.
[d]Should severe hypoglycemia occur following treatment, then continued benefit may require assessment of hypoglycemia awareness, exposure to serious hypoglycemia (<54 mg/dl [3.0 mmol/l]), and/or glycemic variability/lability with demonstration of improvement from baseline.
[e]Clinically, benefits of maintaining and monitoring β-cell graft function may outweigh risks of maintaining immunosuppression.
[f]If severe hypoglycemia was not present before β-cell replacement therapy, then a return to baseline measures of glycemic control used as the indication for treatment (ref. 6 & 7) may be consistent with β-cell graft failure.
[g]Categorization of β-cell graft function must first meet treatment outcome based on measures of glucose regulation.
[h]May not be reliable in uremic patients and/or in those patients with evidence of C-peptide production prior to β-cell replacement therapy.

**Figure 1. Igls criteria in a clinical setting on a population level**
Illustration of the Igls criteria utility for cross-sectional comparison between β-cell replacement modalities, illustrated by consecutive data from Center A at 0.5, 1-, 2-, and 4-years post-transplantation. Igls criteria functional categories are presented as a percentage of each population for ITx (islet transplantation; n = 36), PTx (solitary pancreas transplantation; n = 29), and SPK (simultaneous pancreas-kidney transplantation; n = 23), respectively. Describing the natural course post-transplantation according to current clinical practice, this includes 17 islet transplant recipients that received a subsequent islet infusion by the 2-year assessment, and one pancreas transplant recipient with a failed graft at 1 and 2 years receiving a subsequent whole pancreas transplant with optimal graft function at 4 years.

**Figure 2. Igls criteria in a clinical setting on an individual level**
Illustration of the Igls criteria utility for individual longitudinal description of β-cell graft function over time for individual patients after ITA (islet transplant alone), IAK (islet after kidney), SIK (simultaneous islet-kidney), SILLK (simultaneous islet-liver-lung-kidney), PTA (pancreas transplant alone) and SPK (simultaneous pancreas-kidney).

A. Illustrated by data of patients from Center B followed-up at 0.5, 1 and 2 years post-transplantation, using all functional categories of the Igls criteria.

B. Illustrated by data of patients from Center C, using the binary Igls criteria outcomes of treatment success (optimal or good β-cell graft function) versus treatment failure (marginal or failed β-cell graft function).

**Figure 3. Igls criteria in a research setting**
Illustration of the Igls criteria utility for individual longitudinal description of β-cell graft function over time in a research setting, illustrated by ten structurally and consecutively followed patients that received islet transplantation under protocols investigating BELA (belatacept) or EFA (efalizumab) from Center D. Both islet and pancreas transplants were applied in these patients. The binary Igls criteria outcomes of treatment success (optimal or good β-cell graft function) versus treatment failure (marginal or failed β-cell graft function) were used. IS: immunosuppression.

**Figure 4. Igls criteria and continuous glucose monitoring metrics of glycemic control**
Continuous glucose monitoring (CGM) metrics of glycemic control categorized according to the Igls criteria for scoring β-cell graft function as optimal, good, marginal or failure, using data of a cohort of islet transplant recipients (n = 55) followed-up to ten years from Center E. CGM parameters incrementally improved with each consecutive category of Igls classification following islet transplantation ($p < 0.0001$ for both, one-way ANOVA test for linear trend). Values are represented as median (IQR).

A. Glucose time-in-range (TIR, %) 70 – 180 mg/dl (3.9 – 10 mmol/l) for each of the functional categories of the Igls criteria

B. Glucose time-below-range (TBR, %) <70 mg/dl (<3.9 mmol/l) for each of the functional categories of the Igls criteria

Figure 1

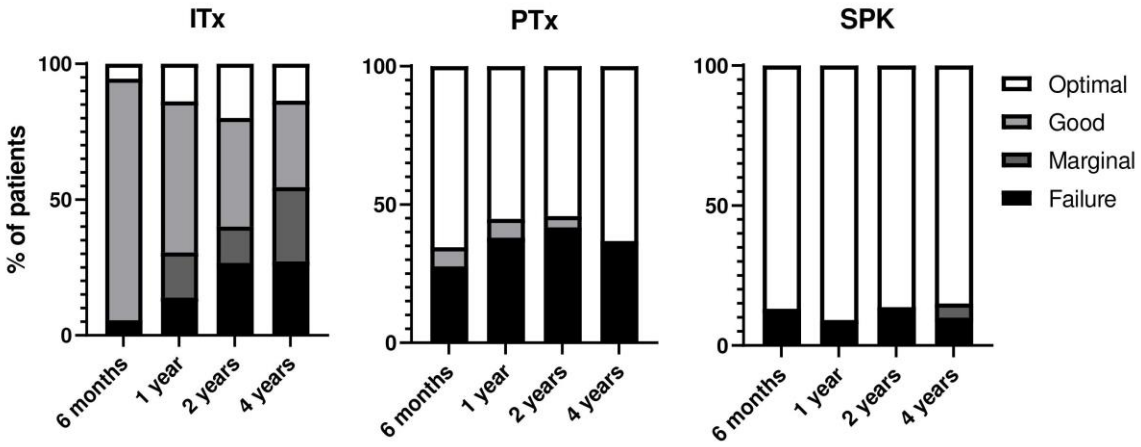

Figure 2A

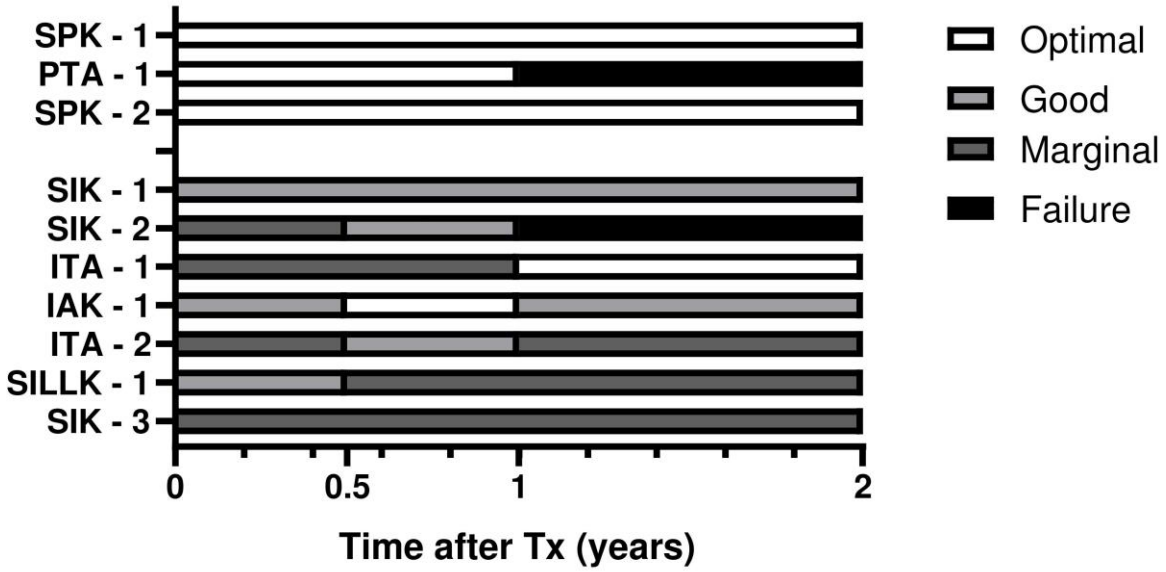

Figure 2B

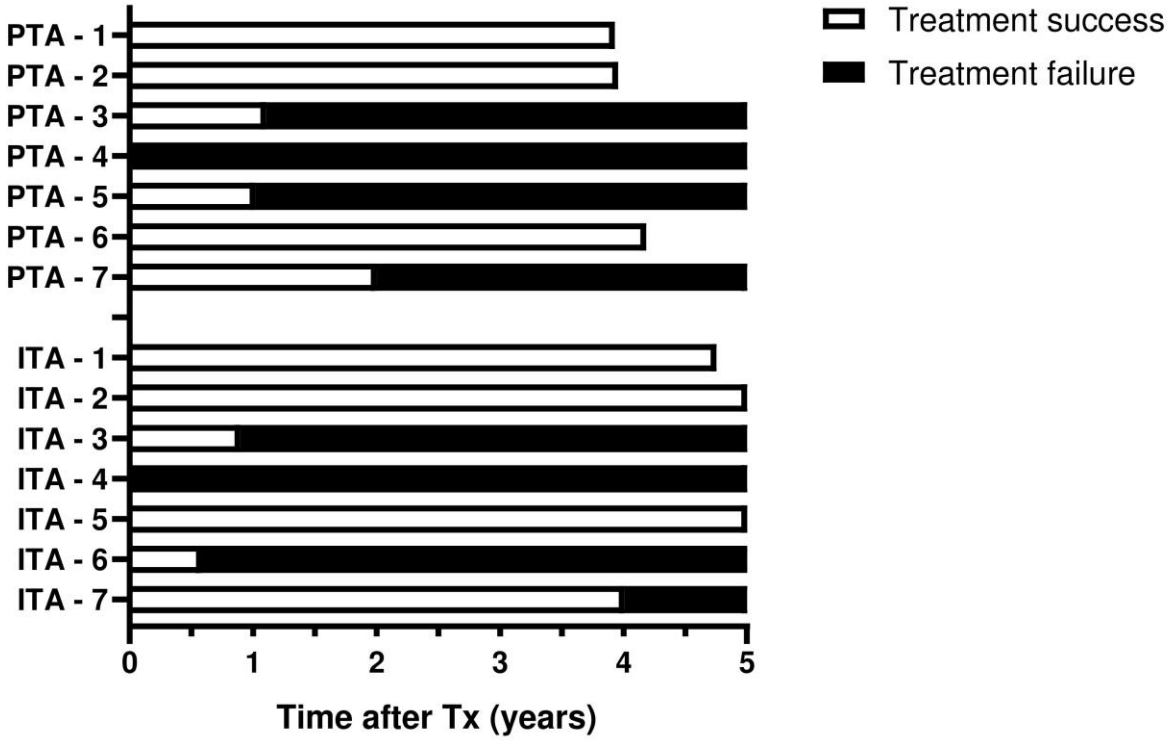

Figure 3

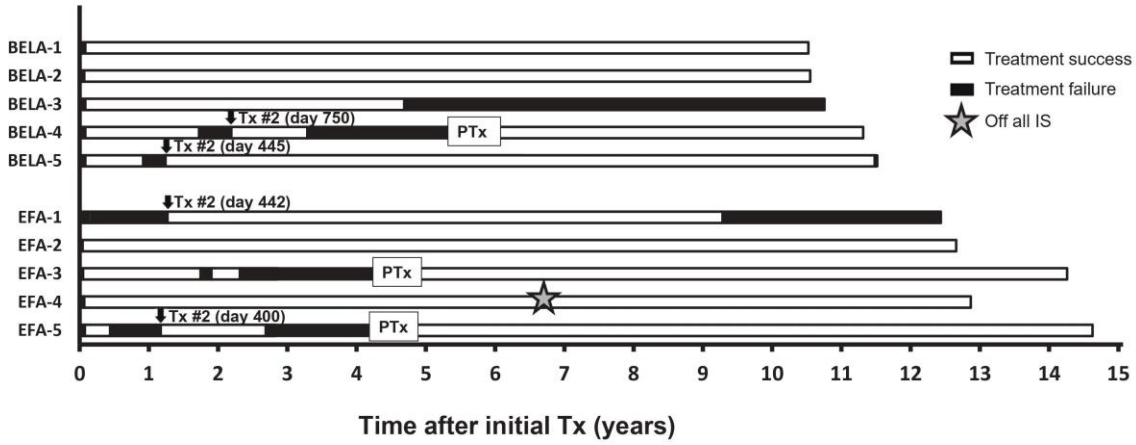

Figure 4A

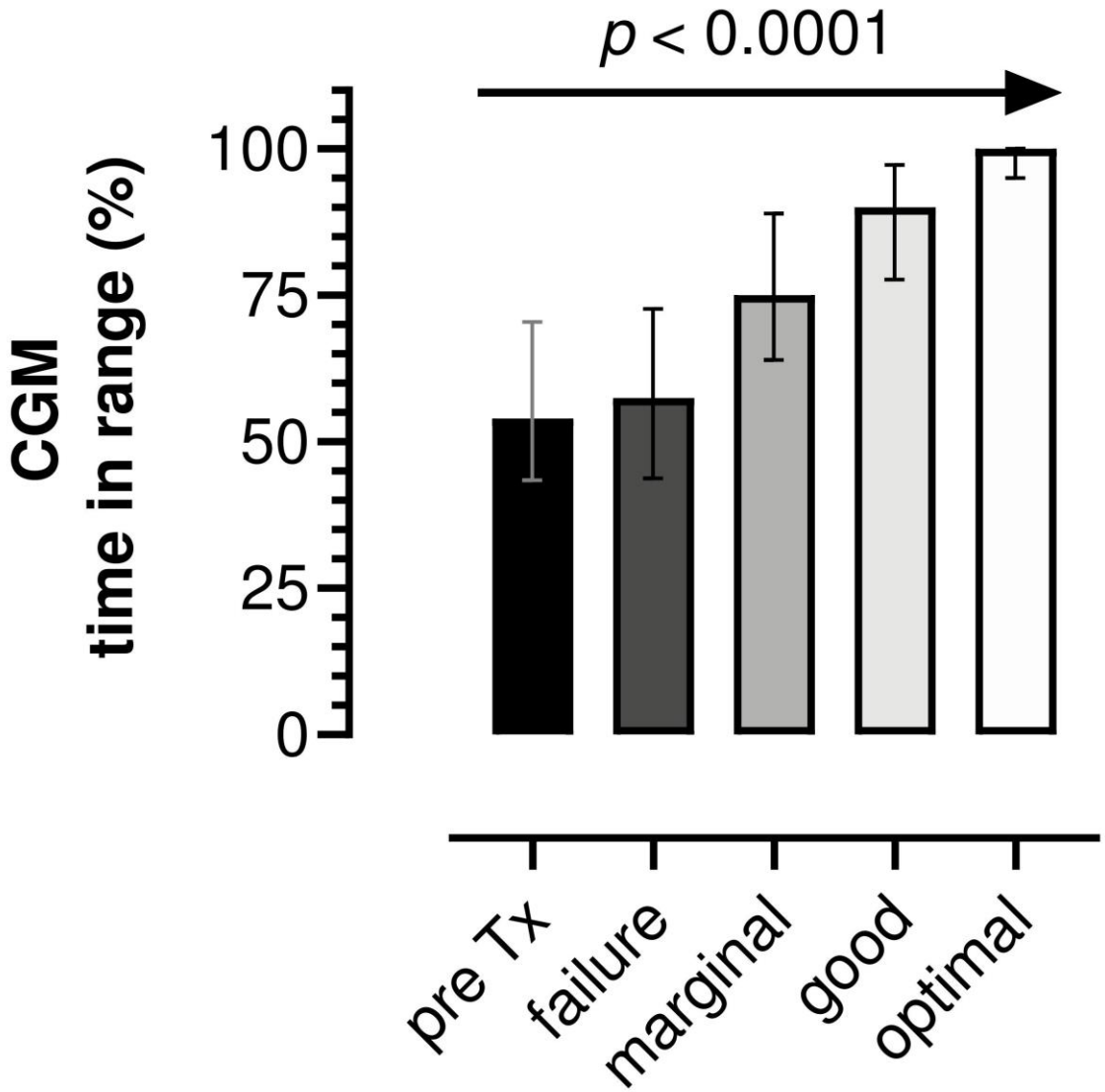

Figure 4B