OPTN Pancreas Transplant Committee
Medical Urgency Workgroup
Meeting Summary
March 2, 2023
Conference Call

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Introduction

The Medical Urgency Workgroup (the Workgroup) met via Citrix GoTo teleconference on 03/02/2023 to discuss the following agenda items:

1. Data Review
2. Literature Review
3. Medical Urgency Definition
4. Next Steps and Closing Remarks

The following is a summary of the Workgroup's discussions.

1. Data Review

The Workgroup reviewed relevant data and literature regarding hypoglycemia unawareness, waitlist mortality for pancreas, kidney, and kidney-pancreas (KP) transplant candidates, and pancreas transplant as a treatment for hypoglycemia unawareness.

The Workgroup considered several questions in reviewing the data and literature, including:

- Does hypoglycemia unawareness present a higher risk of mortality and medical urgency?
- Does pancreas alone transplant reduce this mortality and is there any other available treatments?
- How common is hypoglycemia unawareness?
- If the Committee decides to move forward with a definition for medical urgency based on hypoglycemia unawareness, how would hypoglycemia unawareness be defined?

<u>Data Summary:</u>

The Scientific Registry of Transplant Recipients (SRTR) Annual Kidney and Pancreas Data Reports found the following:

- In 2020, overall pre-transplant mortality rates for adult pancreas candidates were about 6 deaths per 100 patient years. This is slightly higher for simultaneous pancreas kidney (SPK) candidates (7 deaths per 100 patient years).
- In 2020, pre-transplant mortality rates for adult kidney candidates were slightly less than 6 deaths per 100 patient years. Closer to about 8 deaths per 100 patient years for kidney candidates diagnosed with diabetes.

Figures 1 – 3 show Organ Procurement and Transplantation Network (OPTN) waiting list removals due to death or too sick to transplant, status at removal, and cause of death.

Figure 1: Number of Pancreas/Kidney-Pancreas Waiting List Removals Due to Death or Too Sick to Transplant, 2017-2021

Removal Reason	Kidney-Pancreas	Pancreas
Death	482	129
Too sick to transplant	405	178
Total	887	307

Figure 2: Status at Removal for Pancreas/Kidney-Pancreas Waiting List Removals Due to Death, 2017-2021

Status	Kidney-Pancreas	Pancreas
Active	124 (25.7%)	34 (26.4%)
Temporarily Inactive	358 (74.3%)	95 (73.6%)
Total	482 (100.0%)	129 (100.0%)

Figure 3: Causes of Death for Pancreas/Kidney-Pancreas Waiting List Removals Due to Death, 2017-2021

Causes of Death for Pancreas/Kidney-Pancreas Waiting List Removals Due to Death, 2017-2021

Cause of Death	Kidney-Pancreas	Pancreas
Cardiovascular: myocardial infarction	42 (8.7%)	2 (1.6%)
Cardiovascular: other specify	49 (10.2%)	14 (10.9%)
Cardiovascular: vascular embolism	1 (0.2%)	0 (0.0%)
Cerebrovascular: other specify	11 (2.3%)	3 (2.3%)
Cerebrovascular: stroke	14 (2.9%)	2 (1.6%)
Diabetes mellitus	6 (1.2%)	3 (2.3%)
Hemorrhage: gastrointestinal	2 (0.4%)	1 (0.8%)
Hemorrhage: intraoperative	0 (0.0%)	1 (0.8%)
Hemorrhage: other specify	7 (1.5%)	5 (3.9%)
Infection	44 (9.1%)	9 (7.0%)
Malignancy	2 (0.4%)	4 (3.1%)
Misc: ARDS	0 (0.0%)	1 (0.8%)
Misc: liver failure	0 (0.0%)	2 (1.6%)
Misc: multi-system failure	7 (1.5%)	6 (4.7%)
Misc: pancreatitis (graft)	0 (0.0%)	1 (0.8%)
Miscellaneous: renal failure	2 (0.4%)	0 (0.0%)
Miscellaneous: respiratory failure	4 (0.8%)	1 (0.8%)
Trauma	6 (1.2%)	3 (2.3%)
Other specify	54 (11.2%)	22 (17.1%)
Unknown	231 (47.9%)	49 (38.0%)
Total	482 (100.0%)	129 (100.0%)

OPTN data shows that 47.9 percent of deaths for KP candidates were due to unknown causes, while 11.2 percent were attributed under the "Other specify" cause. Similarly, 38 percent of pancreas candidate deaths were attributed to an "unknown" cause of death, while 17.1 percent were attributed under "Other specify."

Summary of Discussion:

One member asked if the pancreas-specific data was inclusive of pancreas-after-kidney (PAK) candidates. Staff clarified that this data relates to any candidate who is registered for pancreas alone. The member commented that this is a high number, particularly because these candidates don't have kidney failure. The member continued that it would make sense for simultaneous pancreas kidney (SPK) candidates to have high mortality due to dialysis and renal failure. The member commented that 307 pancreas-alone candidates removed for death or too sick is concerning. Staff clarified that the data is over a four year period. The member commented that the numbers reflected in the data is still high, and

that for pancreas alone, this would be rate of death in type I diabetics without end organ damage. Another member noted that the pancreas alone could incorporate PAK patients.

A member noted that, in discussing medical urgency, comparing someone who needs a pancreas transplant alone with the mortality of someone who simply has type I diabetes, it is likely that pancreas-alone candidates will have a higher risk of mortality.

A member theorized that the high percentage of deaths due to unknown causes, may in part be attributed to hypoglycemia unawareness.

Summary of literature review:

The Workgroup reviewed several articles regarding hypoglycemia unawareness and Pancreas transplant candidate medical urgency. These articles include:

- Cryer, 2012, "Severe Hypoglycemia Predicts Mortality in Diabetes:"[1]
    - Estimated that between 4% and 10% of deaths in patients with type one diabetes could be attributed to hypoglycemia.
- Seaquist et al, 2012 "Impact of Frequent and Unrecognized Hypoglycemia on Mortality in the ACCORD Study:"[2]
    - Authors found increase in number of hypoglycemic episodes was inversely related to risk of death.
    - 31% reduction in risk of death associated with each additional report of hypoglycemia.
    - Reduction in mortality risk more pronounced among those experiencing a previous severe hypoglycemic event.
- Martín-Timón et al, 2015, "Mechanisms of hypoglycemia unawareness and implications in diabetic patients:"[3]
    - Hypoglycemic unawareness (HU) was observed in 40% of type I diabetes patients and with less frequency in type 2 diabetes patients.
    - HU increases risk of severe hypoglycemic events up to 6-fold.
    - Treatment of HU may include optimized insulin treatment, several kinds of pharmacological interventions, and islet transplantation.
- Franchini et al, 2016, "Hypoglycemia in children with type 1 diabetes: unawareness is a concrete risk:"[4]
    - 23.4% of patients with T1D had HU, 15.3% uncertain awareness, and 14.1% experienced one episode of severe hypoglycemia "Severe episodes of hypoglycemia and unawareness are not associated with an increased risk of all-cause mortality or cardiovascular death in patients with type one diabetes."
- Sejling et al, 2016, "Association between hypoglycemia and impaired hypoglycemia awareness and mortality in people with type 1 diabetes:"[5]

[1] Philip Cryer, "Severe Hypoglycemia Predicts Mortality in Diabetes," Diabetes Care 35(9), Sept 2012
[2] Seaquist et al, "The Impact of Frequent and Unrecognized Hypoglycemia on Mortality in the ACCORD Study," Diabetes Care 35, Feb 2012
[3] Martín-Timón et al, "Mechanisms of hypoglycemia unawareness and implications in diabetic patients," World Journal of Diabetes, July 2015
[4] Franchini et al, "Hypoglycemia in children with type 1 diabetes: unawareness is a concrete risk," Current Medical Research and Opinion, 2016
[5] Sejling et al, "Association between hypoglycemia and impaired hypoglycemia awareness and mortality in people with type 1 diabetes," Diabetic Medicine, 2015

    - "Severe episodes of hypoglycemia and unawareness are not associated with an increased risk of all-cause mortality or cardiovascular death in patients with type one diabetes."
- Harlan, 2016, "Islet transplantation for HU/severe hypoglycemia:"[6]
    - Literature review examining islet transplantation as a treatment for HU and severe hypoglycemia.
    - "Significant survival benefit for patients with T1D receiving SPK transplants but increased mortality associated with solitary pancreas transplants."
    - Chronic episodic hypoglycemia dulls compensatory response, resulting in unawareness.
    - "Although T1D with recurrent severe hypoglycemia is associated with significant morbidity and increased mortality, the absolute mortality risk is quite low."
- Sharifi et al, 2022, "Hypoglycemia Unawareness: challenges, triggers, and recommendations:"[7]
    - Continuous Glucose Monitor (CGM) with an alarm is a reliable and suitable treatment options for patients with hypoglycemia unawareness.
- Reno et al, 2018, "Severe hypoglycemia-induced sudden death is mediated by both cardiac arrhythmias and seizures:"[8]
    - Hypoglycemia mediates sudden death in two distinct ways: seizure associated respiratory arrest and arrhythmia associated cardiac arrest.
    - "When seizures were reduced and arrhythmias were reduced in pharmacological combination, overall mortality was completely prevented."
    - Preventing arrhythmias and seizures necessary to prevent hypoglycemia induced sudden death.
- Lin et al, 2019, "IAH continues to be a risk factor for severe hypoglycemia despite use of CGM system in Type one diabetes:"[9]
    - Gold, Clarke, and Pedersen-Bjergaard questionnaires demonstrated prevalence of IAH/impaired awareness to be 33.3%, 43.7%, and 77.0% percent respectively.
    - Amongst patients using CGM > 6 months, 24.5% were found to have at least one episode of severe hypoglycemia in the preceding 6 months.
- Lin et al, 2020, "HU and autonomic function in diabetes:"[10]
    - 25-40% of T1D have impaired hypoglycemic awareness (IAH), with stable prevalence over 2 decades.
    - CGM is an effective tool to reduce hypoglycemia and severe hypoglycemic episodes in T1D patients, including those with IAH.
- Rodriguez et al, 2010, "CGM after SPK and Kidney Alone Transplant:"[11]
    - Cross-sectional study of 48-hour glucose concentrations (N=23).

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[6] Harlan, 2016, "Islet transplantation for HU/severe hypoglycemia," Diabetes Care, 2016

[7] Sharifi et al, "Hypoglycemia Unawareness: challenges, triggers, and recommendations in patients with hypoglycemic unawareness: a case report," Journal of Medical Case Reports, 2022

[8] Reno et al, "Severe hypoglycemia-induced sudden death is mediated by both cardiac arrhythmias and seizures," American Journal Physiology, Endocrinology, and Metabolism, 2018.

[9] Lin et al, "IAH continues to be a risk factor for severe hypoglycemia despite use of CGM system in Type one diabetes," Endocr Pract, 2019

[10] Lin et al, "Hypoglycemia unawareness and autonomic dysfunction in diabetes: Lessons learned and roles of diabetes technologies," Journal of Diabetes Investigation, 2020

[11] Rodriguez et al, "CGM after SPK and Kidney Alone Transplantation," Diabetes Technology and Therapeutics, 2010

    - Glycemic excursions were higher in the KA group compared to the SPK cohort, with no difference in incidence of hypoglycemia between these groups and the controls.
    - SPK transplantation is effective at normalizing glycemic excursions.
- Kendall et al, 1997, "Pancreas transplant restores epinephrine response and symptom recognition during hypoglycemia in type one diabetes patients with AN:"[12]
    - Stepped hypoglycemic clamp studies in pancreas recipients to assess response during hypoglycemia.
    - Successful pancreas transplant improves epinephrine response and normalizes hypoglycemia symptoms in patients with long standing diabetes and autonomic neuropathy.
- Rubin et al, 2022, "Relationship between hypoglycemia awareness status on Clarke/Gold methods and counterregulatory response to hypoglycemia:"[13]
    - Examine type one diabetes patients (N=78) via both questionnaires and underwent a hyper-insulinemic clamp.
    - Clarke and Gold highly correlated with each other (r = 0.82), but 32% of subjects classified wrong by Clarke vs. Gold.
    - Subjects who had partial loss of symptoms or epinephrine response more likely to be classified inconsistently.
    - "IAH classification may be discordant between Clarke and Gold questionnaires, and hypoglycemia awareness status on both questionnaires poorly predicts hormonal and symptomatic response with moderate blunting of symptoms."
- Speight et al, 2016, "Characterizing problematic hypoglycemia: HypoA-Q:"[14]
    - "Preliminary validation shows the Hypo-QA has robust face and content validity, satisfactory structure, internal reliability; convergent, divergent, and known groups validity.
- Kaur et al, 2021, "Impact of successful pancreas transplant on patient reported hypoglycemia outcomes:"[15]
    - Observational study of patient reported outcomes after a year after transplant in T1D patients.
    - "Pancreas transplant recipients reported reduced fear of hypoglycemia and improved hypoglycemia awareness over a period of one year, even in patients with partial graft function."
- Van Meijel, 2020, "High prevalence of IAH and SH among people with insulin-treated type 2 diabetes: Dutch Diabetes Pearl Cohort:"[16]
    - Observational study of Dutch diabetes Pearl cohort of type two diabetes patients to assess presence of IAH.

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[12] Kendall et al, "Pancreas Transplantation Restores Epinephrine Response and Symptom Recognition Dureing Hypoglycemia in Patients with Long-Standing Type I Diabetes and Autonomic Neuropathy," Diabetes, Feb 1997

[13] Rubin et al, "Relationship between Hypoglycemia Awareness Status on Clarke/Gold Methods and Counterregulatory Response to Hypoglycemia," Journal of the Endocrine Society, 2022

[14] Speight et al, "Characterizing problematic hypoglycemia: iterative design and preliminary psychometric validation of the Hypoglycemia Awareness Questionnaire (HypoA-Q)," Diabetic Medicine (33), June 2015

[15] Kaur et al 201, "Impact of Successful Pancreas Transplantation on Patient Reported Hypoglycemia Outcomes," 2021

[16] Van Meijel, "High prevalence of impaired awareness of hypoglycemia and severe hypoglycemia among people with insulin-treated type 2 diabetes: the Dutch Diabetes Pearl Cohort," BMJ Open Diabetes Research and Care, 2020

- Authors of this Dutch study found that type II diabetics utilizing insulin treatments had a prevalence of hypoglycemic awareness of about 1 in 10.

Summary of discussion:

One member noted that some of these articles predate the use of continuous glucose monitoring (CGM). Staff explained that these articles span across a range of time.

A member commented that the pediatric population is unique. The member wondered if these larger population studies are adjusting their data for attempt to control diabetes. The member explained that it could be that patients with hypoglycemia unawareness are faring similarly to patients who don't manage their diabetes at all. The member added that hypoglycemia unawareness is harmful, even if not associated with an increased risk of all-cause mortality or cardiovascular death. Another member agreed.

One member noted that survival benefits of SPK transplant can be attributed to the receipt of the kidney transplant for SPK and PAK recipients. The member asked if the Harlan 2016 article found increased mortality, and staff summarized that the article pointed to an increased mortality associated with recurrent severe hypoglycemia, but a generally low absolute mortality risk. The member recalled the Workgroup previously deliberating on how best to define recurrent severe hypoglycemia, and that further discussion would be needed to determine a definition.

An SRTR representative shared that another paper Harlan had contributed to, "Survival After Pancreas Transplantation in Patients with Diabetes and Preserved Kidney Function" (Venstrom et al, 2003), related to the overall mortality of SPK transplant recipients relative to solitary pancreas transplant recipients.[17] The SRTR representative explained that this paper was impactful to pancreas transplantation, as it showed that there was no increased survival benefit for PAK or pancreas alone transplant (PTA) relative to waiting on the list, but there was for SPKs. The SRTR representative continued that this was rebutted a few years later by RW Gruessner et al, which looked at the same cohort and corrected a few statistical anomalies to show actual survival benefit after 1 year post transplant, accounting for early mortality post-transplant.[18] The SRTR representative explained that SPKs had immediate benefit, and for solitary pancreas, the mortality curve shifted in favor of transplant at one year post-transplant.

The SRTR representative added that Cryer 2012 is still the standard when discussing mortality risk, and that this author previously wrote an editorial on another article which showed a 3.4 fold increase in mortality for patients who have hypoglycemia unawareness as opposed to those that did not. The SRTR representative explained that this was a 5-year analysis utilizing self-reported hypoglycemia unawareness. The SRTR representative added that the annual mortality due to hypoglycemia in diabetic patients as a proportion of overall deaths ranges anywhere from 4 to 10 percent, meaning that 1/20th or 1/10th of diabetic patients die directly due to consequences of hypoglycemia unawareness, and this was in type I diabetics. The SRTR representative also pointed out that there is a stroke risk from hypoglycemia unawareness, and that this has been studied well. The SRTR representative cited a 2 to 8 percent annual stroke risk from recurrent hypoglycemic episodes, and noted that the stroke risk is

[17] Venstrom et al, "Survival after Pancreas Transplantation in Patients with Diabetes and Preserved Kidney Function," JAMA, 2003: https://jamanetwork.com/journals/jama/fullarticle/197759
[18] Gruessner et al, "The current state of pancreas transplantation," National Review of Endocrinology, 2013: https://pubmed.ncbi.nlm.nih.gov/23897173/

significant.[19] The SRTR representative continued that there have been indications and goals for beta cell replacement therapies in relation to solitary pancreas and islet transplantation, published by a consensus group, the International Pancreas and Islet Transplant Association in combination with the European Pancreas and Islet Transplant Association.[20] The SRTR representative explained that this consensus conference included endocrinologists, immunologists, and transplant clinicians who aimed to come up with unified indications for solitary pancreas and beta cell replacement.

A subject matter expert (SME) in endocrinology and diabetology noted that this is currently the age of CGM as a treatment for type I diabetes, and the prevalence of CGM utilization ranges from 30 percent in children and up to 70 percent of adults living with type I diabetes. The SME noted that the prevalence of cardiac arrhythmia disturbances in people with severe hypoglycemia is minimal, and some of that data has not been made public. The SME continued that CGM could likely adequately prevent complications of hypoglycemia unawareness for many in the pancreas transplant candidate population. The SME noted that it would be interesting to see a study comparing CGM to transplant in terms of treatment of type I diabetes and related complications. The SME continued that this literature points to the use of CGM to treat hypoglycemia unawareness and severe hypoglycemia.

One member commented that this concept seems loosely correlated to medical priority adjustments for hepatocellular carcinoma for liver transplant candidates, where these candidates have high risk of death with the transplant, but without the transplant, there is a higher mortality related to metastatic cancer later on. The member continued that this concept could apply here, and added that these patients should not be penalized or put at greater risk by waiting as long as other candidates for a pancreas transplant, particularly if they have identified that they are appropriate candidates for transplant. The member also noted that CGM use will not cure hypoglycemia unawareness directly, though it can help to manage or reduce the risk of complications such as severe hypoglycemia. The member added that patients who have been referred and listed for transplant are likely a more at risk population.

2. Medical Urgency Definition

The Workgroup discussed hypoglycemia unawareness as a potential definition for pancreas medical urgency. The Committee were asked to discuss the following questions:

- Does hypoglycemia unawareness present a higher risk of mortality and medical urgency, relative to other Pancreas, Kidney, or KP transplant patients?
    - What is the relative mortality of KP, PA, and Kidney transplant candidate patients?
    - How urgent is hypoglycemia unawareness in these patients? Does it contribute to increased mortality?
- Does pancreas transplant, alone or in SPK, reduce this mortality? Are there other available treatments?
    - Is pancreas transplant a suitable treatment for hypoglycemia unawareness?
- How common is hypoglycemia unawareness?
    - Among the transplant population, and among the general population?

[19] L Smith et al, "Exposure to hypoglycemia and risk of stroke," Ann N Y Acad Sci, 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6214717/

[20] Rickels et al, "Defining outcomes for beta-cell replacement therapy in the treatment of diabetes: a consensus report on the IgIs criteria from the IPITA/EPITA opinion leaders workshop," Transplant International, 2018: https://onlinelibrary.wiley.com/doi/epdf/10.1111/tri.13138

- If the Workgroup decides to move forward with a medical urgency definition based on hypoglycemia unawareness, how are we defining hypoglycemia unawareness/severe hypoglycemia?
    - CGM data? Clarke, Gold, or Hypo-QA scores? What if the candidate does not have access to CGMs

Summary of Discussion:

An endocrinology SME commented that a patient with hypoglycemia unawareness who has never used CGM or other diabetes management technology should likely attempt to manage their diabetes this way for some time. The SME also noted that some pancreas candidates have tried everything available to them and still have these issues, and that these patients should be receiving priority for medical urgency. The SME explained that this is a population of patients who have tried this technology, and still have the danger of hypoglycemia unawareness and its complications. The SME noted that some may disagree that hypoglycemia does not increase the risk of mortality or other issues, but that the population of patients described is important. The SME explained that type I diabetics in their twenties or thirties may be safer, particularly because their cardiovascular status is not necessarily damaged or brittle. Other patients in their 40s or 50s that have been diabetic for the last 40 years are at risk to experience high mortality and morbidity from severe hypoglycemia.

The Workgroup Chair offered that the issue of discussion is not whether hypoglycemia unawareness is an indication for pancreas transplant, as the determination of candidacy for pancreas transplant will have been made by the program. The Workgroup Chair continued that the concern of this Workgroup is whether patients with hypoglycemia unawareness should be able to petition for additional priority, and what the definition of hypoglycemia unawareness should be.

The Workgroup Chair noted that the literature has found that pancreas transplant alone and SPK transplant do reduce mortality, and that there is evidence to show that pancreas transplantation can improve hypoglycemia awareness. The Workgroup Chair asked the Workgroup if they felt comfortable with those two points. A member responded, noting that there are mixed feelings in the pancreas community with respect to hypoglycemia unawareness. The member noted that the question at hand is whether patients with hypoglycemia unawareness are more medically urgent. The member asked how much priority these patients would receive, not only on the pancreas match run but also in the context of pancreas allocation relative to other multi-organ combinations.

Staff noted that the importance of medical urgency as an attribute of pancreas allocation would need to be determined by the OPTN Pancreas Transplantation Committee. Staff added that the level of priority can be smaller than it is for kidney allocation, and that the priority can be taken in context. Staff added that the Workgroup could recommend that the medical urgency definition is weighted highly or less highly, but that the ultimate decision is in the hands of the Pancreas Committee. Staff added that there is limited data on this, and the SRTR would not be able to model this.

One member pointed out that there are very few indications for solitary pancreas transplant, which includes hypoglycemia unawareness. The member continued that in terms of increased priority, the solitary pancreas patients are at a disadvantage because the SPKs have received a higher priority in current allocation system. The member added that these patients who have hypoglycemia unawareness and may even be hospitalized for it should likely receive some sort of increased priority.

A member shared an article by McCune et al (2023) which found that "pancreas transplant provides superior glycemic control to CGM and remains the optimal therapy for appropriately selected patients with diabetes."[21]

One member noted that there seems to be consensus that patients with hypoglycemia unawareness should receive some priority, but expressed concern about how this could be operationalized. The member continued that there are many factors that need to be considered, including CGM use, defining recurrent hypoglycemic events, and how to define urgent hypoglycemia unawareness as well. The member recommended looking into other ways to define pancreas transplant priority.

An SME stated that there should be consideration for those patients lacking effective management of their diabetes, as giving these patients access to the right kind of endocrinologists significantly helps address issues with hypoglycemia unawareness, wide glycemic excursions, and other diabetes management problems. The SME continued that it will be difficult to indicate that this is a much needed priority for transplant candidates. The SME recommended qualifying additional priority for patients with hypoglycemia unawareness by requiring a complete evaluation by a skilled diabetologist using CGM. The SME cautioned that it could be difficult to discern who meets this criteria.

A member noted that a large portion of the pancreas transplant population may qualify as medically urgent due to hypoglycemia unawareness, as it is one of the main indications for pancreas transplant. The member continued that it could be that many solitary pancreas patients would receive increased priority. The member also commented that it is also possible that people petition the incoming Pancreas Review Board with medical urgency cases outside of a definition that the Workgroup finalizes for medical urgency. The member commented that there is not likely going to be sufficient data to satisfy the entire community, but that there seems to be an understanding of the need for some kind of medical priority for pancreas transplant patients.

Staff shared that the Pancreas Committee is in the process of building a review board structure, and that the review board could provide some structure or a level of clinical review in determining whether medically urgent priority is appropriate. Staff added that the review board could provide a way for programs to request additional priority for patients who may have a higher medical urgency, but don't exactly meet the definition based on hypoglycemia unawareness.

One member warned against prioritizing pancreas alone candidates over SPK candidates, noting that this could potentially incentivize changes in listing practices. The member added that SPK recipients have the largest improvement in survival, and that the system should not disadvantage SPK candidates as a group.

Staff asked the Workgroup if they feel they have a sense of how common hypoglycemia unawareness is in transplant populations.

An endocrinologist SME remarked that it could be close to 100 percent of pancreas transplant patients who experience hypoglycemia unawareness, based on their experience. Another member noted that pancreas transplant is also performed for patients outside of hypoglycemia unawareness. A member agreed, adding that accelerated microvascular complications are among other indications for pancreas transplant.

[21] McCune et al, "The best insulin delivery is a human pancreas," Journal of Clinical and Translational Research, 2023: https://onlinelibrary.wiley.com/doi/full/10.1111/ctr.14920?campaign=wolearlyview

A member expressed concern about how this definition of medical urgency can be operationalized. The member added that even if a lot of the life-threatening urgency of hypoglycemia unawareness can be ameliorated by other therapies, not all patients will have access to those therapies. The member emphasized that there are inequities there that should be considered, particularly if there are stipulations involved regarding requirements to work with an endocrinologist or state of the art therapies. The member added that many rural patients don't have access to an endocrinologist. The member added that though it is an interesting concept, it could be difficult to operationalize this fairly. Staff offered that the Workgroup could include lack of access to an endocrinologist or other therapies as part of their definition.

Staff asked the Workgroup if they recommend moving forward with a definition of pancreas medical urgency based on hypoglycemia unawareness. The Workgroup Chair noted that this is the fundamental task of the Workgroup, to determine whether this recommendation should be made.

The Workgroup agreed to move forward with definition of pancreas medical urgency, with 10 members voting to move forward, and 2 members disagreeing with the concept of building a definition of medical urgency based on hypoglycemia unawareness. One member who voted yes shared some reservations with operationalization. The SME recommended that the Workgroup does not move forward with a definition of medical urgency based on hypoglycemia unawareness.

Staff asked the Workgroup how this definition should be operationalized. The Workgroup Chair recommended going through each issue at a time, and determine whether there is enough consensus in how to address these topics.

An SME responded, explaining that the counter-regulation that exists in hypoglycemic individuals relates to four hormones, two of which – cortisol and growth hormone – are delayed in response. The SME continued that epinephrine is an important counter-regulatory hormone in terms of hypoglycemia, and epinephrine depends on whether there are sufficient glycogen stores to generate glucose delivery to the stomach circulation. The SME added that glucagon doesn't play much of a role in hypoglycemia responsiveness in patients with type I diabetes. The SME continued that people with partial hypoglycemia responses are hard to define. The SME recommended that the definition should require that these patients are utilizing CGM and management therapeutics, and that epinephrine response is evaluated in a structured circumstance, including specifically a diet rich in carbohydrates. The SME continued that many studies have controlled and induced hypoglycemia in patients to evaluate their epinephrine response, and that this can be done safely. The SME concluded that, this would be the best way medically to define hypoglycemia unawareness and the capability of that patient to respond to a hypoglycemic environment.

A member remarked that their patient population likely would not be able to do all of this, and that most of their patients don't have access to CGMs. The member continued that having a low glucose is very different than hypoglycemia unawareness, and that it is unclear what role the CGM plays in proving unawareness. The SME remarked that use of a CGM speaks to adequate management of diabetes before they are evaluated for pancreas transplant. The member remarked that this is the value of pancreas transplant, as many patients do not have and may never have adequate management. The member noted that they have a large patient population with very limited health literacy, and that these patients are often completely reliant on their programs for their care and diabetes management. The member added that once the patient receives the pancreas transplant, it is much easier for them to manage their graft than to manage their diabetes. The SME agreed, adding that issues of access and long term care still apply for pancreas recipients living in rural areas.

Another SME recommended combining these approaches, including use of CGM and awareness scoring. The SME remarked that they are not in favor of watching for epinephrine response, as it may not be practical for most clinical areas. The SME added that a physician's testimony or endocrinologist testimony could also be included.

The Workgroup Chair noted that the access to specialized endocrinology across the country is not uniform, and that for some patients, it is easier to access a transplant surgeon than an endocrinologist. The Workgroup Chair remarked that this definition will need to be simple. If the definition is too complicated, it becomes unmanageable for the transplant program. The Workgroup Chair remarked that the transplant evaluation is challenging enough, and that the definition will need to be minimally invasive.

Staff summarized Workgroup comments, noting that there is a recommendation to show some evidence that the diabetes is attempting to be managed in other ways and a recommendation to include some kind of criteria showing the patient has a proven issue with hypoglycemia unawareness.

The SME remarked that, from a scientific perspective, this needs to be better defined, and that there may need to be a simpler definition which could lead to effective management. The SME added that scientifically, there is a science that would be interesting and important to define.

An SRTR representative noted that it is hard to argue with the scientific basis proposed for defining hypoglycemia unawareness, but that CGM access is not universal by any means. The SRTR representative commented that anywhere from 20 to 100 patients out of 1000 have access to CGM, and that this number varies widely depending on type of insurance, race, and other factors. The SRTR continued that equity issues are highly prevalent in access to diabetes management technology, and that anything requiring CGM use explicitly will carry over and amplify these equity issues.[22] Staff offered that lack of access to CGM could potentially also replace CGM use, and that this could address some equity concerns.

One member recommend a simpler approach, with descriptive clinical narrative that does not require sophisticated lab testing. The member remarked that prior to the Median End Stage Liver Disease (MELD) score, programs had more subjective evaluation, and that this was sufficient evaluation when there were no appropriate ways to calculate severity of illness. The member continued that just because the Workgroup cannot currently finalize a fully vetted formula should not prevent the Workgroup from developing a simple, utilizable definition.

The Workgroup Chair proposed that a CGM only helps to mitigate the hypoglycemic issues, and doesn't resolve or cure the issue. The Chair remarked that in this perspective, the patient still has hypoglycemic unawareness, but there is a monitor to manage diabetes. The Workgroup Chair offered that the CGM is not a necessary component of this definition.

One member expressed concern for a definition that is too open, as this could lead to wide inconsistencies in use. The member continued that this would require a level of trust that could also result in changes in provider behavior and decision making.

Another member shared that, in their experience, solitary pancreas patients generally are referred by endocrinologists. The member commented that they don't see it as unreasonable to require that the patient be managed by an endocrinologist if they haven't been managed by an endocrinologist before.

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[22] "Health Equity and Diabetes Technology: A Study of Access to CGM by Payer and Race Executive Summary," American Diabetes Association: https://diabetes.org/sites/default/files/2021-10/ADA%20CGM%20Utilization%20White%20Paper.pdf"

The member added that a patient who has been in the emergency department because of their hypoglycemia, that these would be severe complications. The member added that these patients ultimately end up defining themselves, and that complete subjective recommendations may not be necessary.

Staff asked the Workgroup how they felt about continuing to explore a definition of pancreas medical urgency based on hypoglycemia unawareness, noting that this may involve data collection. Staff also noted that the Workgroup could instead recommend data collection.

One member expressed concern in collecting granular enough data that medical urgency could be defined. The member remarked that there may not be data available on the risk of the patient's hypoglycemia unawareness. Another member agreed, noting that the lack of data may make building a definition with consensus very challenging.

An SRTR representative commented that this was the struggle during a consensus conference focused on determining what data was needed to establish need or indication for a solitary pancreas transplant. The SRTR representative continued that there is not much data that could be collected from a transplant database that would provide much urgency based on hypoglycemia unawareness. The SRTR representative remarked that the Workgroup could decide on tools that are easy and practical to operationalize, and that this could involve a combination of self-reported measures, such as a questionnaire or scoring system, and documentation of having at least used available medical therapies to ameliorate unawareness issues. The SRTR representative continued that this would require new metrics to implement this, as there is not scoring system being collected in any of the reporting forms for pancreas. The SRTR representative pointed out that starting off with data collection without a definition will not likely provide much more additional information or clarity in the next few years. The SRTR representative recommended that this definition utilize existing consensus data and practical guidelines, with fine tuning going forward.

7 members of the Workgroup agreed to move forward in attempting to build a consensus-based definition. 1 member abstained, and 2 voted not to move forward, but instead focus on building data. One approving member expressed hesitation and concern. An SME recommended collecting data instead of moving forward with a definition.

Upcoming Meetings: TBD

Attendance

- **Workgroup Members**
  - Antonio Di Carlo
  - Colleen Jay
  - Dean Kim
  - Dolamu Olaitan
  - Maria Helena Friday
  - Jessica Yokubeak
  - Randeep Kashyap
  - Reynold Lopez-Soler
  - Muhammad Yaqub
  - Anita Patel
  - Parul Patel
  - Ty Dunn
  - William Asch
  - Todd Pesavento
- **SRTR Staff**
  - Bryn Thompson
  - Raja Kandaswamy
- **UNOS Staff**
  - Joann White
  - Kayla Temple
  - Kieran McMahon
  - Lauren Mauk
  - Lauren Motley
  - Sarah Booker
  - Austin Chapple
- **Other Attendees**
  - Betul Ayse Hatipoglu
  - Robert Eckel