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Effect of Physiologic Insulin Resensitization on Stages of Chronic Kidney Disease

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Abstract: Diabetes is one of the fastest growing chronic diseases in the world, and a substantial number of these patients will ultimately develop chronic kidney disease (CKD) leading to a declining quality of life and renal failure. End stage CKD leads to a markedly higher risk of cardiovascular death from endothelial and vascular dysfunction as well as multiple metabolic disorders involving bone/mineral metabolism, and reduced lifespan. Progressive CKD also places heavy financial burdens on patients and health systems. A previous small case study using Physiologic Insulin Resensitization (PIR) showed improved kidney function in several patients. PIR is a distinct treatment intended to improve insulin sensitivity and counter chronic inflammation by attempting to reproduce the natural pulsatile release of insulin in hopes of restoring physiologic insulin signaling processes. This retrospective observational study expands includes more patients over a longer treatment period evaluating on a total of 21 patients with CKD stage 3a or higher (based on eGFR), starting 15-months prior to PIR treatments followed by active treatment periods ranging from 7-28 months. Changes in the eGFR the primary marker of CKD stage progression or change in renal function. Overall, the percentage of patients whose eGFR continued to decline decreased from 57% to less than 10% after PIR treatments. Some patients exposed to PIR achieved an improved stage of eGFR. Retarding or halting CKD progression with PIR has the potential for improvements in QOL and thousands of dollars in annual health savings.

Keywords: chronic kidney disease, metabolism, Physiologic Insulin Resensitization, PIR, insulin resistance, diabetic nephropathy

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1. Introduction

The Centers for Disease Control and Prevention estimates that 37 million Americans have diabetes. Among US adults aged 18 years or older with diabetes, 38.9% have chronic kidney disease (CKD)[1]. The natural history of diabetic kidney disease worsens over time despite improved diabetes control and blood pressure control and the use of Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB), Sodium Glucose Co-Transporters Type 2 (SGLT-2) and Mineralocorticoid and Non-Steroidal Antagonists such as Spironolactone, Eplerenone and Finerenone. While the decline in eGFR and Urine Albumin Creatinine Ratio (UACR) can be slowed, diabetic CKD is neither curable nor reversible. [1] Among US adults with End Stage Renal Disease (ESRD), 39.2% of those cases list diabetes as the primary cause. [2] In 2018, 62,202 persons with diabetes began dialysis. The number of diabetics needing dialysis or kidney transplantation are likely to increase in the future as there are an estimated 96 million people with prediabetes many of whom will become diabetic[i] The cost of caring for those with a combination of diabetes and CKD is significant and the cost of providing care for Medicare recipients with both co-morbidities are doubled compared to than those without kidney disease. These costs in dollars accounts for 23.5% of Medicare's fee-for-service expenditures.[3]

While it is possible that some individuals with stage one or two CKD are able to see an improvement in eGFR at the later stages of 3 or more, "reversal" of CKD is rarely achievable. Unfortunately many diabetics are unaware of their stage of renal function as many do not have annual assessment of their eGFR and are asymptomatic. Tragically as many as 90% of those with CKD are not even diagnosed until they become symptomatic. [4] Better efforts to screen all diabetics at least annually with eGFR and UACR have been proposed by policy experts in the diabetes and renal fields such as the ADA/AACE guidelines for the standard of care in diabetics and the KDIGO heat map use by nephrologists to assess risk of progression to End Stage Renal Disease (ESRD). Early detection would allow more aggressive interventions and perhaps protect vulnerable nephrons from being lost.

Recent modifications in the method of insulin administration to mimic the phased pulses of the pancreas in a normal physiology have been made in an effort to address the root cause of diabetes as well as alleviate the associated comorbidities, such as progressive Diabetic CKD.

The application of phasic insulin infusions referred to here specifically as Physiologic Insulin Resensitization (PIR) have attempted to advance the science of previous contradictory efforts to determine the short and long term effects of small doses of intravenous insulin administration in diabetics. A recent review article explored derangements in the interplay of the insulin/glucagon/ glucose axis in Type 2 Diabetes leading to insulin resistance. [5] With insulin resistance cells are unable to normally take in glucose and metabolize it in a balanced pathway of either growth and repair or to intracellular pathways involved with energy production to maintain cell viability and function. Damage to the kidney is a complication of T2D. CKD is a progressive disease of the kidney leading to dialysis. [7] PIR therapy attempts to mimics the natural release of insulin physiologically in an oscillatory manner utilizing physician directed dosing of IV insulin in both a precise dose amount and interval in a cadence of intervals based on the patients glucose levels and response to calculated insulin amounts which change over the duration of the infusion period. This IV insulin treatment is based on an individual's insulin resistance profile as identified by laboratory data, history, body mass index and underlying comorbidities. The physician seeks to provide the optimal concentration, period, frequency, and wave amplitude necessary to reengage down-regulated insulin receptors that have been exhausted or desensitized to chronic hyperinsulinemia in insulin resistance. This protocol insulin is delivered in a more physiologic manner of oscillatory release to more closely resembles native insulin signaling. The change from chronic unrelenting insulin exposure of the insulin receptor to episodic bursts of very small intravenous insulin may allow a metabolic pause at the receptor level from overexposure of insulin which resulting in its downregulation, to an upregulation of insulin receptors in cells such as the hepatocytes. If true, carbohydrate metabolism would then follow a more physiologic pathway with improvement of multiple metabolic processes in multiple cells and organs including perhaps the kidney. Cellular mechanisms of insulin-glucose balance should result in resensitization of the cells to better and more appropriately respond to insulin and glucose entry into cells. During the treatment, insulin delivery doses and concentration are carefully and accurately monitored. Patients ingest oral glucose prior to and sometimes during the infusion period following a

specific algorithm to target up-regulation of insulin receptors while also reducing the potential of hypoglycemia albeit to very small doses of IV insulin. The frequency of PIR treatments is modulated based on patient response and customized for a given individual considering their insulin resistance profile. The patient "response" is determined individually by a clinician's judgement of the patient's change in objective lab measures (A1C, eGFR, fasting Blood Glucose, Insulin, etc.) and subjective patient questionnaires conducted quarterly. Initial PIR treatment starts with weekly infusions calculated based on the patient's unique profile. Evaluation of the patient during subsequent infusions results in changes in both the frequency and the dosing. A more complete description of the mechanisms involved in this treatment are found in papers by Greenway et al and Villaverde et al. [5,6]

Another small case report using PIR showed small but favorable changes in markers of chronic kidney disease in 3 patients with type 2 diabetes. [6] It is recognized that a correctly powered clinical trial of patients with T2D patients be conducted to determine whether this study's findings could be replicated in a larger sample over an extended time period Given that the disease progression of CKD in T2D has profound clinical and economic implications, further inquiry is warranted, needed and welcomed to determine if this treatment may be an important new option for renoprotection in diabetics with CKD.

2. Results

Twenty-one patients met the inclusion criteria of having at least 2 recorded eGFR values documenting their CKD stage prior to beginning PIR, as well as having been treated with PIR for at least 6 months. The number of months included in the pre-PIR phase varied from 3 to 30 months and was due to variations in the times that patients were under the care of Island Doctors or since they were diagnosed with CKD. The highest GFRs during the period prior to starting PIR revealed that five patients had eGFRs that were stage 2, six were stage 3a, seven were stage 3b, two were stage 4 and one was stage five. The stage 5 patient (patient 21) was on active dialysis before beginning PIR treatment as well as during the course of treatment (See Table 1). The eGFRs measured at the time of starting PIR determined whether the patients' GFRs were classified as stable, worsening or improving depending on whether they had changed their stage of CKD during the pre-study PIR treatment. The data showed that compared to the peak value before assignment to PIR and the eGFR the value at the start of PIR that, of the 5 pre-PIR stage 2 patients, four had worsened to 3a and one to stage 3b. Of the pre-PIR stage 3a patients, three were stable and three worsened to 3b. Of the seven pre-PIR 3b patients one improved to stage 3a. three were stable and three had worsened to stage 4. One pre-PIR stage 4 patient worsened to stage five and one was stable. The stage 5 pre-PIR patient was stable. In summary, of the 21 patients, 12 (57.1%) worsened, 8 (38%) were stable, and one improved in their CKD stage. (See Table 1 and Figure 1). At the initiation of PIR treatment after the pre-PIR evaluation period, the 21 patients in this study presented with the following breakdown of CKD stages: eight stage 3a, seven stage 3b, four stage 4, and two stage 5 (See Table 1).

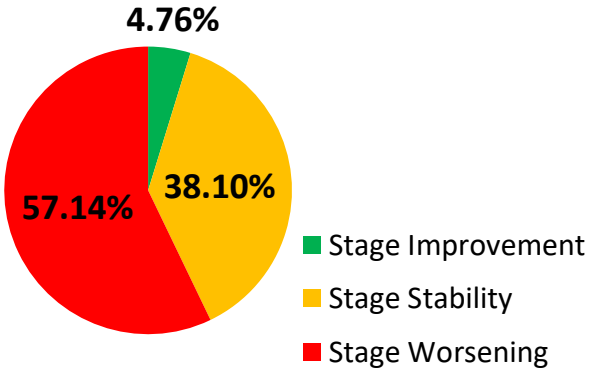

Figure 1. Patient CKD Stage Progression Before PIR

Case	Highest eGFR before PIR	eGFR at start of PIR	Stage at highest point before start of PIR	Months Peak eGFR occurred before PIR	Stage at start of PIR	Relative stability of CKD stage prior to PIR
1	52	58	3a	14	3a	Stable
2	58	58	3a	4	3a	Stable
3	64	58	2	14	3a	Worsened
4	71	57	2	16	3a	Worsened
5	84	56	2	15	3a	Worsened
6	61	55	2	9	3a	Worsened
7	41	45	3b	13	3a	Improved
8	59	45	3a	15	3a	Stable
9	48	43	3a	15	3b	Worsened
10	48	43	3a	2	3b	Worsened
11	67	42	2	19	3b	Worsened
12	40	41	3b	25	3b	Stable
13	43	38	3b	15	3b	Stable
14	36	33	3b	10	3b	Stable
15	58	33	3a	7	3b	Worsened
16	39	28	3b	21	4	Worsened
17	25	26	4	9	4	Stable
18	30	22	3b	13	4	Worsened
19	30	20	3b	7	4	Worsened
20	23	13	4	33	5	Worsened
21	4	3	5	3	5	Stable

Table 1: Changes in Chronic Kidney Disease Stages Prior to Initiating Physiologic Insulin Resensitization (PIR)

The time patients were on PIR varied from 7 to 28 months due to patients beginning PIR on a continuing basis in the study period time frame with individualized treatment plans based on their response to PIR. Broadly speaking, a positive response to PIR was determined by qualified medical professionals as improved lab outcomes, resolution of certain symptoms or complications associated with diabetes, and better health and well-being as described by the patients in validated questionnaires. Typically, patients underwent infusions twice a week lasting 3 hour intervals for several weeks, followed by weekly infusion for 3 months, and twice a month for 3-6 months, with additional spacing between treatments if deemed appropriate based on the patient response as defined above. After at least 6 months of treatment, three stage 3a patients had stable eGFR levels, three improved and two worsened. One of the latter patients had improved from 3b to 3a prior to initiating PIR and reverted to 3b after receiving PIR. Based on percentage, 38% of the CKD 3a patients in the study showed a full stage improvement to stage 2 after PIR treatment, and 75% either showed a stage improvement or stability at 3a.

Table 2: Changes in Chronic Kidney Disease Stages After Receiving Physiologic Insulin Resensitization (PIR)

Case	eGFR at start of PIR	eGFR after PIR	Stage at start of PIR	Stage at end of study period	Stage at high point prior to PIR	Change prior to start of PIR	Change during study period	Months on PIR
1	58	50	3a	3a	3a	Stable	Stable	24
2	58	43	3a	3b	3a	Stable	Worsened	14
3	58	68	3a	2	2	Worsened	Improved	17
4	57	51	3a	3a	3a	Worsened	Stable	21
5	56	51	3a	3a	3a	Worsened	Stable	21
6	55	66	3a	2	2	Worsened	Improved	15
7	45	20	3a	3b	4	Improved	Worsened	22
8	45	62	3a	2	2	Stable	Improved	10
9	43	81	3b	2	2	Worsened	Improved	28
10	43	58	3b	3a	3a	Worsened	Improved	19
11	42	58	3b	3a	3a	Worsened	Improved	7
12	41	45	3b	3a	3a	Stable	Improved	16
13	38	32	3b	3b	3b	Stable	Stable	21
14	33	31	3b	3b	3b	Stable	Stable	10
15	33	45	3b	3a	3a	Worsened	Improved	23
16	28	30	4	3b	3b	Worsened	Improved	9
17	26	27	4	4	4	Stable	Stable	24
18	22	22	4	4	4	Worsened	Stable	20
19	20	23	4	4	4	Worsened	Stable	28
20	13	14	5	5	5	Worsened	Stable	11
21	3	6	5	5	5	Stable	Stable	10

In the seven patients whose beginning PIR was at CKD stage 3b, 71% showed a CKD stage improvement, and all seven patients either improved a stage or did not worsen. Likewise, all four stage 4 patients did not worsen over their treatment period, and one of those four transitioned upward to stage 3b. One of the stage 5 patients became stable after declining prior to PIR, and the other remained stable throughout the pre-treatment and PIR treatment period.

Looking at the entire study group, of the twelve patients who had declining eGFR prior to PIR, seven had improvement in their eGFR and five were stable. Of the eight who were stable prior to PIR two improved and five remained stable. One who had been stable declined. In the cohort of 21 patients, after all patients received PIR for a minimum of six months, the percentage of patients whose eGFR stages were worsening less than 10%. The decreased from 57% to remaining stable in their percentage of patients 38% to 52%, and the stage increased from with an increase in eGFR percentage of patients less than 5% to 43% (See stage increased from Figure 2).

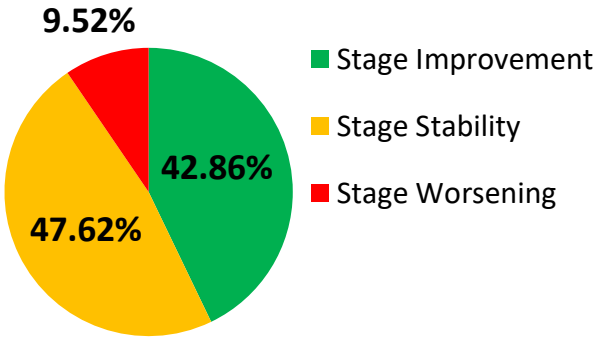

Figure 2. Patient CKD Stage Progression While Active on PIR

Interestingly, the patients with more advanced CKD (stages 3b, 4, and 5) appeared to have a higher percentage of eGFR stability and improvement compared to the entire cohort. In this group, none of the patients had a worsening decline in renal function after beginning PIR, and of the patients that were showing progressive decline, over 60% of them either reversed their downward progression or showed a rise in eGFR and were reclassified to higher stages of CKD. One patient's final eGFR measurement improved two stages (from 3b to 2).

3. Discussion

Previous research has established a correlation between insulin resistance and chronic kidney disease. [8,9] Insulin resistance has been shown to create physiologic impacts on kidney function, including excess cell proliferation, apoptosis inhibition, and decreased endothelial functionality. [10] Because as a basic tenet that T2D patients are insulin resistant it is reasonable to conclude that they may have progressive CKD over a shorter time span associated also with higher rates of hypertension and lipoprotein abnormalities and endothelial dysfunction and inflammation. Therefore, it was not unexpected that four of the stage 2 patients progressed to stage 3a during the pre-PIR period that averaged 13 months. (Table 1)

Changes in CKD stages defined as dropping from stage one to five also have economic consequences. For example, in a fee for service Medicare patient population, Medicare recipients with stage 2 CKD cost on average $39,536 per year in USD (Us Dollars) while those advancing to stage 3 cost an average of $42,190 USD annually. The worst and most costly is stages four and five with the average annual cost rising to $55,479. [11] In the pre-PIR period of the study which averaged 13 months, three of the patients' renal function worsened from stage 3b to stage 4, and one went from stage 4 to stage five. Nine out of the 21 patients (or 42.9%) declined prior to exposure to PIR treatments (Table 1).

However It is remarkable that 9 of 21 diabetic patients improved their eGFR after PIR treatments after a therapeutic period that averaged 16 months. This is particularly noteworthy when one considers that 7 of the 9 patients had a history of declining CKD stages over the average 14 months prior to receiving PIR and that improvement in CKD stages after a patient reaches 3 is uncommon. It is also reassuring that 10 of the 21 patients had stable eGFR during periods ranging from 10 to 28 months.

Equally as reassuring is that all of the patients classified as stage 4 or 5 remained with stable renal function for periods from 10 to 28 months. In a fairly recent study by Caravaca-Fontan et al. in 2017, that followed 915 CKD 4 and 5 patients reported that these patients showed a mean eGFR decline of -3.35mL/min/1.73m^2/year [10] and at a median follow-up period of 16 months after study enrollment, 64% of these patients were on active dialysis, and 16% of the total cohort had died. [12] By contrast, none of the CKD 4 and 5 patients in this study showed a decline in eGFR, and none worsened to the eGFR of 15 ml/min/1.73 m2 or less (stage 5)where dialysis or transplantation would be necessary. If these preliminary results are confirmed on a larger scale these results could have potentially significant cost implications when compared to the costs of dialysis and or transplantation. Bentley and Ortner estimated the average charges for kidney transplants, including charges for 30 days pre-surgical services, organ procurement, hospitalization, and 180 days post hospitalization costs were USD $442,000. [11] Kidney dialysis costs are also significant. Kaplan et al. reported that the cost to Medicare of kidney dialysis ranged from USD $91,716 to $108,656 per year. [12]

The PIR therapy that was examined in this study is believed to reduce insulin resistance via precise doses of insulin at specific intervals to regain healthy insulin signaling pathway functionality. The goal of said treatment is to improve carbohydrate metabolism and counter the chronic inflammation that occurs via mediators such as interluekin-6 and tumor necrosis factor alpha among others. As insulin sensitivity improves, this may allow for the return in normal physiologic insulin action at the post-receptor and improved ATP production via the oxidative phosphorylation cascade within the mitochondria. Considering the results from PIR in these 21 patients, compared to the typical progression of CKD in diabetic patients without PIR, and the physiologic importance of insulin signaling in normal kidney structure and function, it may be possible that the PIR modality exerts a positive impact on kidney function in this T2D patient cohort. Stability or improvements in glomerular filtration may retard or halt the progressive nature of diabetic kidney damage and ultimately may be translated to a substantial cost savings over time by avoiding the high price tag and financial burden on the health care system that arises with progressive CKD, dialysis, and kidney transplants.

A recent review article outlines the mechanisms of PIR and how it may improve insulin sensitivity to counter the complications of diabetes. [5] A brief summary of these elements is outlined as follows: Insulin in

non-diabetics is released from the pancreas in a cyclical pattern, (a fact known for decades). The waveform release of insulin is regulated by a still poorly understood pancreatic neuronal network connecting beta cells in the Islets of Langerhans. An insult (auto-immune, obesity, toxin, trauma, etc.) causes inflammation or damage to the pancreas that disrupts native insulin signaling. When insulin oscillation is impaired, hyperglycemia results and the pancreas must respond by secreting more and more insulin in a failing attempt to normalize elevated glucoses. The resultant hyperinsulinemia acts like a toxin to insulin receptors with a downregulation of insulin receptors, particularly at the hepatic level, due to loss of metabolic pause from constant bombardment of chronic elevated insulin concentrations. Likewise, the pancreatic alpha cell secretion of glucagon is generally also elevated and dysregulated and participates in hyperglycemia. Inadequate receptor function, whether by decreased number or decreased action at the post insulin receptor level is the phenotype of insulin resistance and ultimately leads to diabetes mellitus. Peripheral IV administration of cyclical insulin attempts to restore native insulin signaling that may upregulate receptors and improve carbohydrate metabolism. Improved binding of insulin receptors facilitates the uptake of glucose into cells, where it is processed through oxidative phosphorylation (Krebs cycle) to produce energy (ATP). As energy from carbohydrate metabolism is made more readily available, insulin dependent tissues existing in a chronic state of energy starvation may then be able to undergo growth and repair and reduce chronic inflammation along with the potential to improve end organ damage, including conditions such as CKD.

The prevalence of CKD among diabetic patients affects nearly 40% in the United States, and millions more across the globe. Furthermore, the progression of CKD through its various stages can lead to end stage renal failure (ERF) with need for end organ support that is costly and decreases life expectancy. A focused treatment, such as PIR, shows potential to slow, maintain and possibly reverse the progression of diabetes associated CKD. The potential to positively impact this condition warrants further prospective study, as the benefits to patients and society at large would be immense for the millions who suffer from this disease should this treatment be replicated and adjudicated on a larger study. Improved quality of life, organ function, and productivity while mitigating the costs of end organ failure would truly be a major step forward in treating CKD. This small, retrospective review is a starting point for rigorous prospective studies to determine if adding PIR to the current standard of care would be a material advance in treating this condition. Additional metrics to determine kidney function, such as Urine Albumin/Creatinine Ratio (UACR), will need to be captured in these future studies for even more comprehensive results in future.

4. Materials and Methods

This current study was conducted at Island Doctors of Florida, a medical care provider with over 50 locations in Florida. Patients in this study were recruited from 7 different primary care clinics within Island Doctors into two internal PIR locations based on their home office location. The practice has a capitation agreement to provide care for patients covered by Humana and therefore cost-effective treatments are an ongoing objective of the practice. All patients met the inclusion criteria of 1) an estimated glomerular filtration rate (eGFR) assay less than 9 months prior to starting PIR , 2) having received PIR for greater than six months, and 3) diagnosed with CKD stages 3a, 3b, 4 or 5 at the time of starting PIR defined as eGFRS in ml/min per 1.73 m2 of stages 2 (60-89), 3a (45-59), 3b (30-44), 4 (15-29) and 5 (< 15).

The study was done in two phases. The initial phase evaluated the trajectory of the patients' eGFRs prior to starting PIR. This was defined as the highest value during the pre-PIR period compared to the eGFR at the time of initiating PIR. Based on the differences in the two eGFR measurements, patients were classified as having stable, declining renal function or as improved renal function based on whether their eGFR changed such that they would be reclassified to a different stage of CKD.

The second phase of the study examined changes in the CKD stages after starting PIR. This was done by comparing the last eGFR recorded prior to the start of PIR to the last eGFR closest to the cutoff date of 12/31/22.

Author Contributions: Conceptualization for this study was done by Zachary Villaverde and Richard Grimes. Treatment of patients was done by clinical staff under the oversight of Roy Hinman. Data Collection was done by Zachary Villaverde. Data analysis was done by Richard Grimes and Zachary Villaverde. Manuscript preparation was done by Zachary Villaverde, Richard Grimes, Frank Greenway, Brian Loveridge, Jonathan Lakey, and Stanley Lewis. Manuscript Review and Editing was done by Frank Greenway, Brian Loveridge, and Jonathan Lakey.

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Institutional Review Board Statement: In this section, you should add the Institutional Review Board Statement and approval number, if relevant to your study. You might choose to exclude this statement if the study did not require ethical approval. Please note that the Editorial Office might ask you for further information. Please add "The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code XXX and date of approval)." for studies involving humans. OR "The animal study protocol was approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code XXX and date of approval)." for studies involving animals. OR "Ethical review and approval were waived for this study due to REASON (please provide a detailed justification)." OR "Not applicable" for studies not involving humans or animals.

Informed Consent Statement: Before any patient began treatment with PIR at any of the Island Doctors PIR clinic locations, the patient signed a consent document allowing for the anonymous collection of their medical data for the purpose of studies and publications. All data for this study was collected in compliance with the informed consent document completed by the patients presented in this article.

Data Availability Statement: Participant data used in this study will be made publicly available. These data include participant data that underlie the results as reported in this study, after de-identification. This includes the data used to develop the tables and figures represented. No other documents will be made available. De-identified participant data will be available beginning immediately after publication and ending thirty-six months (three years) after the date of publication. Data will be made available to researchers who provide a methodologically sound proposal and are using the data to achieve the aims as described in the proposal. Proposals should be directed to zvillaverde@islanddoctors.com. To gain access, requestors will need to sign a data access agreement. Data will then be made available via a file sharing link that will expire after one year.

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Conflicts of Interest: Roy Hinman, MD is owner and medical director of Island Doctors, which administers the PIR treatment modality. Zachary Villaverde is a contractor for Island Doctors and a contractor for Well Cell Global, LLC, a company that researches, advances, and licenses the PIR treatment modality to physicians around the world. Brian Loveridge MD is the Chief Medical Officer, and minority owner of Well Cell Global.

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References must be numbered in order of appearance in the text (including citations in tables and legends) and listed individually at the end of the manuscript. We recommend preparing the references with a bibliography software package, such as EndNote, ReferenceManager or Zotero to avoid typing mistakes and duplicated references. Include the digital object identifier (DOI) for all references where available.

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