Exhibit A

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I have been asked to review the case of Larry James Thomas, who, at the time of his death was a 46-year-old male who was admitted to CHI St. Luke's Health of Houston, Texas, on July 30th, 2015 for the purpose of coronary artery bypass grafting (CABG) surgery. During a workup for a potential renal transplant, Mr. Thomas was discovered to have coronary artery disease. This is a common complication of diabetes and this precipitated his admission for CABG surgery on July 30, 2015.

My opinion is being sought regarding what role, if any, an episode of *hypo*glycemia (low blood sugar levels) that occurred on July 31st 2015 played in Mr. Thomas' subsequent prolonged hospital stay and eventual death on November 28th, 2015. In order to adequately answer this, several questions need to be explored:

(i) What are the effects of *hyper*glycemia (high blood sugar levels) on outcome after CABG surgery?

(ii) What are the effects of anesthesia and cardiopulmonary bypass on glucose levels?

(iii) What are the effects of commonly used medications in the perioperative period, specifically those used in the cardiac intensive care unit, on glucose levels?

(iv) What is the recommended treatment for *hyper*glycemia in patients during and after CABG surgery?

After these topics are explored, I will attempt to create a timeline of the events surrounding the episode of *hypo*glycemia. I will then offer my opinion regarding the

management of Mr. Thomas' glucose levels during his surgery and immediate postoperative course.

What are the effects of hyperglycemia (high blood sugar levels) on outcome after CABG surgery?

Nearly 40% of patients presenting for CABG surgery have diabetes. With this high incidence of diabetes, it is natural that some patients will have hyperglycemia at some point during their operative course. It has been known since the 1980s that hyperglycemia in the perioperative period is associated with worse outcomes than those patients who did not have hyperglycemia[1,2]. Several studies have shown that elevated glucose levels during and immediately after cardiac surgery lead to increases in the incidence of stroke, wound infection and heart attack[3]. Other studies have demonstrated that the mortality rate of patients who are hyperglycemic is increased when compared to those who do not have hyperglycemia[4].

Collectively, the medical literature would suggest that the presence of hyperglycemia in both diabetic and non-diabetic patients results in adverse perioperative outcomes[5]. These studies were observational in nature. The natural question to follow of course is: does the lowering of blood glucose levels in the perioperative period of patients undergoing CABG surgery decrease the incidence of these adverse outcomes. It is possible that hyperglycemia is a marker of adverse outcome, but normalizing serum glucose concentrations may have no effect on the incidence of these adverse outcomes. I will answer the question on the efficacy of lowering serum glucose during CABG surgery in section (iv). But first, it is important to discuss the role of surgery in producing hyperglycemia.

What are the effects of anesthesia and cardiopulmonary bypass on glucose levels?

The human body depends on a continuous supply of glucose to produce the energy required for normal cellular function. Glucose is often called the fuel of life, due to its importance in human metabolism. Other energy sources such as protein and fat are converted to glucose in the cell, demonstrating the importance of glucose as the energy broker of the cell. While some organs are less reliant on glucose supply for normal function, others, such as the brain, rely almost exclusively on glucose in order to maintain normal function. The brain is one of the first organs to be affected by hypoglycemia. Low glucose levels initially cause subtle reductions in mental processing, with lower levels leading to unconsciousness, seizures and eventual brain cell death.

As might expected for such an important substance, the human body has developed an elaborate system to maintain normal glucose levels at all times. Specifically, the actions of two hormones play a key role in the regulation of serum glucose: insulin and glucagon. The description of how these hormones maintain normal glucose levels is beyond the scope of this discussion, but simplistically, insulin tends to lower blood glucose levels while glucagon tends to elevate glucose levels.

A brief discussion regarding the effects of anesthesia and cardiopulmonary bypass on glucose metabolism is however relevant in order to understand how the hypoglycemia that occurred with Mr. Thomas likely arose. When exposed to the stress of surgery, patients essentially exhibit a 'fight or flight' response. Hormones such as cortisol and epinephrine are released in response to the stress of surgery. With respect to the control of blood glucose, these hormones have the net effect of increasing serum glucose. In patients without diabetes, these

hormonal effects are counterbalanced by endogenously (i.e. arising from the person) secreted insulin in order to maintain normal blood glucose levels. Due to the underlying disease process of diabetes, the ability of the body to maintain normal glucose levels is lost in these patients, and these patients often develop hyperglycemia in the perioperative period.

With respect to CABG surgery, patients are typically placed on cardiopulmonary bypasss (CPB, or a heart lung machine) during the operation. In the spectrum of operative interventions, CABG surgery is one of the most physiologically stressful on the human body. As such, the stress response is magnified and hyperglycemia is commonly seen during CABG surgery in both diabetic and non-diabetic patients.

Based on his underlying diabetes and the stress of cardiac surgery, it is not surprising that Mr. Thomas developed hyperglycemia during his CABG surgery. Since Mr. Thomas' hypoglycemic episode occurred in the *post-operative* period it is important to examine a few of the factors that may have contributed to this event, specifically the response of the body after the stress of the surgery and the role of drugs Mr. Thomas received in the postoperative period on glucose metabolism.

What are the effects of commonly used medications in the perioperative period, specifically those used in the cardiac intensive care unit, on glucose levels?

As mentioned above, the stress of surgery causes a hormonal response that tends to elevate the blood glucose level. In order to counteract this hyperglycemia, the body secretes large doses of insulin in order to return glucose levels back to normal. These high levels of insulin were likely present in Mr. Thomas in the immediate postoperative period.

During his anesthetic and during his initial admission to the intensive care unit (ICU) Mr. Thomas was placed on two drugs, (norepinephrine and epinephrine) that both have the tendency

to increase blood glucose levels[6]. These medications, and the aforementioned surgical stress response likely contributed to the high blood glucose levels that precipitated treatment in the operating room.

Mr. Thomas was also placed on Propofol, which is a sedative drug that is commonly used in the ICU. While this drug has no effect on glucose levels, its administration is important in this case as patients on sedative drugs do not manifest the same signs of hypoglycemia as those who are not sedated. Conscious patients who are hypoglycemic have typical manifestations of this condition. Propofol obliterates these manifestations and the only way of determining hypoglycemia is by doing serum blood glucose measurements. This last point (serum glucose measurements) is important when I discuss the timeline of Mr. Thomas postoperative course.

What is the recommended treatment for hyperglycemia in patients during and after CABG surgery?

As mentioned above, hyperglycemia has been associated with adverse perioperative outcomes. The natural follow-up question was: does treating hyperglycemia reduce the incidence of adverse perioperative outcomes. The best way to study this question is through the conduct of a randomized controlled trial (RCT). In a RCT patients are randomly assigned (essentially by a flip of a coin) to one of two different treatment groups. One group of patients receives active treatment for their condition and the other receives a placebo. With respect to a clinical question, RCTs generate the highest levels of certainty in medicine. In the case of glucose control and CABG surgery, there have been several RCTs that have examined the question of whether administering insulin reduces perioperative adverse outcomes.

The results of the studies on insulin administration on the outcome of cardiac surgical patients are controversial. This is due to several factors including trial design, blood glucose levels that were targeted, type and route of administration of insulin, and whether the patients were diabetic or non-diabetic.

When there are conflicting studies in the literature, clinicians are often left with a dilemma in terms of how to treat an individual patient. In these situations, it is often helpful to look to guidelines that are created by medical specialty societies in order to determine what is the best course of treatment for an individual patient. These guidelines are often created by a group of medical experts in the field who debate the merits of the different studies on the subject and come up with consensus statements regarding treatment.

With respect to blood glucose control during cardiac surgery, the Society of Thoracic Surgeons in 2009 published a paper entitled: *Blood Glucose Management During Cardiac Surgery*. This paper is one of the only ones I could find when reviewing the medical literature that gave guidelines on the treatment of blood glucose during CABG surgery.

These guidelines make two very important recommendations on the control of blood glucose during the operative period. First, the recommendation is for the administration of insulin by an infusion, rather than a bolus (which was done in this case), during cardiac surgery if the blood glucose level is >180 mg/dL. Second, the recommendation is that blood glucose be monitored every 30-60 minutes, or as frequently as every 15 minutes during periods of rapidly fluctuating glucose levels.

In the next section I will construct a timeline of Mr. Thomas perioperative course and hope to demonstrate that his immediate postoperative course would be considered to be that of

fluctuating glucose levels and this warranted more frequent blood glucose monitoring than was performed.

Timeline of perioperative events

I have reviewed the salient parts of Mr. Thomas' voluminous electronic medical record as they relate to his intraoperative and postoperative events on July 31st 2015. I feel a reconstructed timeline offers the best insight into what transpired. The following timeline is my best effort to construct the events surrounding his operation and his immediate postoperative course (see next page):

Time	Event
1609	Case begins
1610	Glucose 154
1622	Norepinephrine started
1653	CPB start
1706	Glucose 210
1732	Glucose 273
1740	Epinephrine started
1747	Insulin 10 units IV
1752	CPB stop
1817	Glucose 251
1820	Insulin 10 units IV
1856	Glucose 150
1857	Propofol infusion started
1852	Norepinephrine stopped
1906	Case ends
1916	Handoff to ICU
1917	Anesthesia post op Note
1942	Glucose 90
2003	Glucose 93
2201	Propofol stops
0000 (approx.)	Patient Not waking
0030 (approx.)	Blood glucose <20
0300 (approx.)	Seizure activity

I have several concerns with respect to the management of this case. These concerns relate to the dosage and timing of insulin given to Mr. Thomas, and the subsequent glucose monitoring he received.

As mentioned previously, there is evidence that lowering postoperative glucose levels in patients undergoing CABG surgery has been shown to reduce postoperative adverse events. The evidence for the treatment of blood glucose levels in the operative period is less robust. However, most anesthesiologists faced with elevated glucose levels in this situation would elect to treat them, so in my opinion, the treatment of elevated blood glucose would be consistent with

the standard of care. However, Mr. Thomas received two large doses of insulin in a relatively short period of time.

A typical dose of insulin in this situation would be in the range of 0.05 to 0.1 units/kg. Mr. Thomas weight the day of surgery was recorded as 94.9 kg, so he received a total dose of 0.2 units/kg. While I appreciate that his first dose of insulin did not appear to have had the desired effect of lowering his blood glucose level, my opinion is that the second dose of insulin was too large and was given too soon after the first dose. Based on published pharmacokinetics, intravenous insulin begins to take effect within 10-15 minutes and the effect lasts for a median of 4 hours (range 2 to 6 hours). Based on this information, it is possible that the insulin Mr. Thomas received still had clinical effects at 2200hrs to midnight on July 31st.

Furthermore, the second dose of insulin was given after CPB was stopped and close to the end of the case. The glucose level measured at 1856hrs (150 mg/dL) would be considered to be in the normal range and would have likely assured the anesthesiologist that his insulin administration achieved its desired effect. A concerning fact however is that the blood glucose level had dropped by 40% from the previously measured one. Upon arrival to the ICU, the initial blood-work (measured 46 minutes after the previous one) demonstrated another 40% decrease (see figure 1). These large decreases were occurring at the end of the case when the surgical stress was abating and stress hormone levels (and subsequently glucose levels) would be expected to be returning to normal.

There is no documentation in the medical record as to whether the receiving medical staff in the ICU (either nursing or physicians) were made aware of the insulin doses and times when given. The only mention of the insulin dose by a physician is at 0105hrs on August 1st by Dr. Dwarakanath after Mr. Thomas is found to be unresponsive and profoundly hypoglycemic (page

16 of the EMR). Many ICUs have a formal transfer of care or handover process when a patient is admitted in order to ensure pertinent intra-operative events are communicated to the receiving medical team. Without knowing the policies of this particular ICU I cannot comment on whether or not this handover took place. However, considering the lack of any documentation of such a handover and blood glucose only being measured once postoperatively, I can only assume that such a handover did not take place.

Patients admitted to the ICU typically have intravenous fluid ordered at a type and rate in ml/hr in order to avoid dehydration. Since Mr. Thomas had not had anything to eat or drink all day long he was prescribed a fluid called Lactated Ringers by Dr. Carillo at 1923hrs (4668 of the EMR). This appears to be the only intravenous fluid he was provided. This order is significant in that Lactated Ringers contains no glucose. The standard of care for postoperative diabetic patients would be to administer an intravenous fluid that contains glucose. So, while the effects of intraoperative insulin were still active in his body, Mr. Thomas did not receive a sugar source that could have prevented hypoglycemia.

My other concern with the care Mr. Thomas received has to do with the frequency of blood glucose monitoring in the postoperative period. As mentioned in the timeline, his blood glucose was checked twice in the immediate postoperative period at 1942hrs and 2003hrs. From my reading of the EMR these two readings were from different sources. Presumably one was from a bedside glucometer (a point of care test) and the one from 2003hrs was from a central hospital laboratory. There are no further glucose measurements in the chart. There are physician notes that mention a blood glucose level of <20 mg/dL and that these levels are being uploaded into Epic (which I assume is the hospital's EMR), but this low blood glucose level is never formally recorded on the patients chart.

Considering the large dose of insulin that Mr. Thomas received and the subsequent rapid decrease in his blood glucose levels, and the lack if administration of a sugar source in his IV, my expectation as a critical care physician is that blood glucose monitoring would have occurred more frequently, in the order of every 30-60 minutes in order to rule out hypoglycemia. It is important to note that Mr. Thomas was deeply sedated on Propofol in the first 2 hours after his surgery. This would have blunted any physical signs of hypoglycemia leaving only blood glucose monitoring to discover this lethal complication.

Mr. Thomas had his Propofol discontinued at 2201 (5886 of the EMR). He was apparently unresponsive from the time this sedative drug was discontinued until shortly after midnight when he was discovered to be hypoglycemic. This prolonged period of time (2.5 hours) when he was unresponsive after surgery should have triggered an assessment by the medical or nursing staff as to why he wasn't waking up.

When faced with a postoperative patient who is slow to wake after an anesthetic, there is a list of things that an anesthesiologist or an ICU doctor should be thinking of. One of those is an overdose of narcotics or sedatives. Mr. Thomas received fentanyl (a narcotic) at 1527 and 1611 (3897 of the EMR). The total dose of this drug administered was 500 micrograms (or approximately 5 micrograms per kilogram). The last dose of this drug given at 1611 would be expected to have completely left his system within 3-4 hours.

Mr. Thomas also received midazolam at 1521 and 1735. Based on published pharmacokinetics for this drug, I would also expect that this would not be contributing to Mr. Thomas' lack of wakefulness in the postoperative period.

Based on published pharmacokinetic values for Propofol, 50% of this drug should be eliminated in approximately 30 minutes. At 50% of this drug's initial concentration, I would expect some movement or wakefulness by Mr. Thomas.

Another cause of 'slow to wake up' in this particular surgery is a stroke. I cannot find any documentation of his neurologic assessment in the postoperative period.

Mr. Thomas lack of wakefulness in the postoperative period should have triggered a search for its cause. There is a paucity of documentation from his admission to the postoperative unit to the time when he is discovered to be hypoglycemic. It is unclear how long Mr. Thomas was hypoglycemic for. But based on his seizures and the neurologic outcome he suffered, the period of time was likely substantial.

It is my opinion that several individuals involved in this case have breached the medical standard of care. At numerous points during the care of Mr. Thomas, had the medical standard been upheld, this tragic outcome would not have occurred. Furthermore these breaches in the standard of care, in aggregate, were the proximate cause of Mr. Thomas' adverse neurologic outcome and his eventual death. I will now outline these breaches in medical standard of care and identify the individuals who were culpable.

In summary, my opinion is that Mr. Thomas' tragic neurologic outcome could have been prevented. It is also my opinion that Mr. Thomas did not receive the standard of care for the following reasons:

(i) Large dose of intraoperative insulin: Dr. Bryan Deaver is identified on page 3898 of the EMR as administering the first and second doses of

insulin. Based on the above descriptions of the half life of insulin and the effects of cardiopulmonary bypass and surgery on serum glucose levels, the cumulative dose of insulin was too large for the clinical circumstances. An anesthesiology resident administering this drug should have a robust knowledge of its pharmacokinetics, and the physiologic changes that occur during CPB with respect to glucose homeostasis.

(ii) Timing of second large dose of insulin: Dr. Deaver administered the second dose of insulin 37 minutes after the first dose. This dose was administered too soon after the first dose, and based on published pharmacokinetics, before the first dose would have its peak effect. This was the intervention that led to Mr. Thomas' demise, but as I will point out below, there were several other events that occurred that contributed to his death. Under Texas law, there may be more than one proximate cause that leads to an injury. I believe that this is the case here.

(iii) Lack of supervision: Dr. Deaver appeared to be under the supervision of Dr. Kishan Dwarakanath. Dr. Dwarakanath would be responsible for all the actions taken by Dr. Deaver during the operation. According to page 3897 of the EMR, Dr. Dwarakanath was 'immediately available' and 'frequently monitored' Mr. Thomas during the case. Dr. Dwarakanath should have realized that the insulin dose given was excessive and that the

second dose was given too close to the first. Dr. Dwarakanath could have taken measures to ensure that hypoglycemia didn't occur in the immediate postoperative period by either starting a glucose infusion, notifying the postoperative ICU team of the large doses of insulin given and recommended frequent monitoring of blood glucose, or some combination of both. This lack of supervision and lack of appropriate handover (see below) also breaches the standard of care that I would expect of an anesthesiologist in this situation.

(iv) Lack of documented handover to receiving staff in the ICU: It is unclear from the EMR if it was Dr. Deaver or Dr. Dwarakanath who provided the handover to the receiving ICU team (both physicians and nurses). There is no documentation in the EMR of any handover being given to the ICU team. I base this conclusion on the lack of any mention of the intraoperative insulin given in any of the admission notes to the ICU. This would have to be considered a critical piece of information that needed to be conveyed to the receiving ICU team. Without it, their management of Mr. Thomas would be compromised. The lack of this vital intraoperative information being transmitted by Dr. Deaver and Dr. Dwarakanath would be another proximate cause in Mr. Thomas Death. It also breaches the standard of care with respect to the appropriate handover of medical care from an anesthesiologist to an ICU team.

(v) Lack of frequent glucose monitoring in the postoperative period: Based on my review of the EMR it appears that. Mr. Thomas only had his blood glucose checked twice in the postoperative period. This was at 1942 and 2003 hours. There are no other records of blood glucose being checked until Mr. Thomas is found to be not waking up after surgery. Either the bedside nurse or the attending physician would make the decision regarding the frequency of blood glucose monitoring in the postoperative period. In the absence of a physician order, it is within the scope of practice of an ICU nurse to initiate blood glucose monitoring if they felt it clinically important. In an immediate post operative diabetic patient who was not receiving a glucose source in his intravenous fluids, it would be my expectation that a bedside nurse in the ICU would monitor the blood glucose *at least* hourly until some degree of stability in those measurements had been established. From my reading of the EMR, it appears that Alexander Inawat was the bedside nurse responsible for Mr. Thomas. In my opinion, even in the absence of a physician order to do so, it would be the standard of care for a bedside nurse to monitor blood glucose more frequently than was performed in this case. Again, this would also be a proximate cause in the adverse neurological outcome that Mr. Thomas suffered, in that, had more frequent blood glucose monitoring been performed, hypoglycemia would have been discovered much earlier and therapeutic interventions (namely glucose administration), could have been instituted.

(vi) Delay in pursuing a differential diagnosis for his slow emergence from anesthesia: It is unclear from the medical record which physicians were responsible for the care of Mr. Thomas in the ICU. However, based on the pharmacokinetics of the sedative drugs he was receiving, he should have woken up from his anesthetic relatively quickly after these drugs were discontinued. The fact that he didn't should have triggered the care team (both the bedside nurse and the physician responsible for his care in the ICU) to pursue a differential diagnosis as to why Mr. Thomas wasn't waking up. It would be the standard of care to send off screening blood work (including glucose levels) to determine if there was a metabolic cause for slow emergence from anesthesia and to perform a cursory neurological examination to help determine the cause of his slow emergence. There was no documentation of concern for his slow emergence until several hours after his sedative drugs were discontinued. He was thus left hypoglycemic for a prolonged period of time, and this caused his neurological injury that lead to his death. This delay in recognizing his slow emergence would also breach the standard of care and be considered a proximate cause of his injury.

In reviewing this case, it is surprising to see how many times an intervention could have occurred (such as appropriate insulin dosing, fluid choice in the postoperative period, glucose

monitoring, examining a patient who is slow to wake from anesthesia) that would have prevented Mr. Thomas fatal hypoglycemic episode.

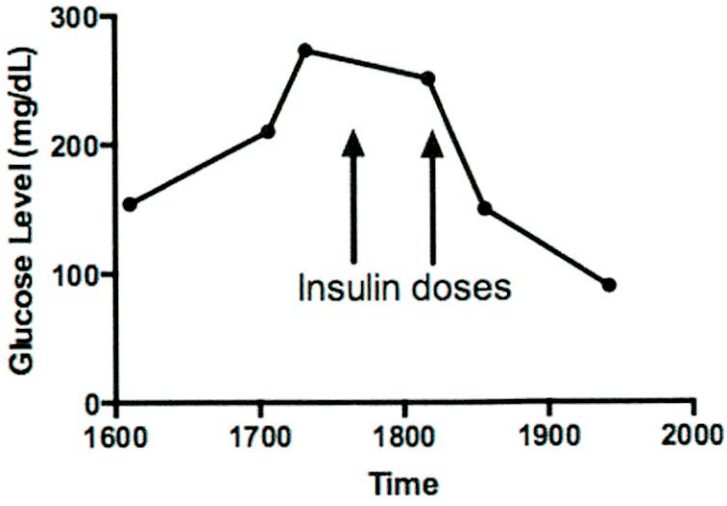

Figure 1: Blood glucose levels during operative and postoperative phase. Of note, there are two subsequent 40% decreases in serum glucose in the postoperative period.

Respectfully Submitted,

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