Speaker 1:	00:01	Translating Mechanisms to Management Award Challenges and Opportunities in AKI Diagnositic by John Kellum
New Speaker:	00:01	Jeff Gray was a brilliant scientist. I had the pleasure of working with, and many of you in the audience too had the chance to work with him at two different companies. In fact, he actually started out doing some amazing antibody engineering work at a company called Biosite, which is known for commercializing the BNP test for heart failure. And then later, we started a company called Astute Medical and we focused on AKI and I think everybody in this room agrees AKI is a really important area and needs a lot of innovation. Jeff was involved heavily in trying to elucidate and understand the mechanisms behind it, very often would emerge from this office with his hair sort of sticking up and it meant that he'd been trying to figure this out because it's a very complex area. And unfortunately we lost him to a malignancy in 2015 and I think he had such a tremendous impact on everyone around him.
Speaker 1:	00:58	He left two brothers, a young son and an enormous group of admirers who just appreciated not only what he could do, but the way he did it. And, we spoke with some friends and colleagues and thought leaders about what we should do and we said, let's do something positive. Let's create an award that looks towards really what his goal was, was to really take things forward to improve clinical practice. And that's where we came up with the idea for this award. And I want to thank Ravi for, for doing this every year and for the selection committee. It's now our fourth award and I am pleased to be here, to welcome this year's recipient because, I am not sure how to describe the volume of work that he's done in this field. It's immense. The publications, the lectures, the patents, the innovative contribution to this field is immense and we're not sure he actually sleeps. But, we do know if there's something new in AK. Dr John Kellum is on the scene and I would like to ask you to applaud Dr John Kellum, this year's recipient.
New Speaker:	02:59	Thank you very much for all those kind words. I'm deeply honored to receive this award. Not only, because it's a very humbling acknowledgement of some of the work that we've done over the years. but also because I guess I'm probably the only recipient of this award who knew Jeff, personally. And you know, sometimes you encounter people who have a very unique way of thinking about things and it leaves a mark on you. And it's interesting because, I first met Jeff, probably around 2012, maybe somewhere in that range. And, coming to work, with the folk at Astute and I still do a lot of consulting

with them. And when I entered the building, you know, there's a few sort of automatic things that go through my head.

Speaker 1:	03:50	Like I know where the expresso machine is and, I know where Jeff's office was and I would always pop in and say hello, and find out what he was working on. it's just kind of a poignant reminder of the fragility of life in general and the contributions that many of us, many people, make and the good fortune that we have to meet those individuals and the impact that they have, on our lives. So I Miss Jeff a great deal. So I was asked obviously to give some remarks, its traditional give a lecture on this topic. and so I decided to talk about not just the opportunities, in AKI Diagnostics but also some of the challenges. I decided to focus on some things you might not be aware of.
New Speaker:	04:44	So my disclosures are there. I am obviously going to talk about technologies that are made by these companies. Interestingly, Astute Medical and some other companies have licensed some technology out of the University of Pittsburgh. I'm not actually going to talk about any of those technologies because none of them have been commercialized yet, but I am going to talk about other technologies that these companies make a. So first of all the opportunities. So clearly I'm going to talk about NephroCheck, I am going to talk about, this biomarker TIMP-2 and IGFBP7, this biomarker panel that is effective in identifying patients with acute kidney injury. This biomarkers you well know a performs very well for detecting something in the kidney that often leads to a acute kidney injury and it does so in the next 12 to 24 hours.
Speaker 1:	05:33	And this something is actually, one of the most interesting things about this discovery is not just that it's a biomarker that works, but that it really taught us something new about what goes on in the kidney. And you see here that it has been validated in various cohorts outside of the original studies that we did. This is some work from Alex Zarbock group and cardiac surgery. and importantly, it not only works to identify these patients, but you can use that information to treat patients differently. And this is evidence that you can do that, that you can take a KDIGO bundle, which is what Alex has done in essentially apply it to patients who have, a biomarker positive test and not apply it, importantly to patients that don't have a, positive test. So ruling out patients, is just as important as identifying patients that are appropriate for, the therapy.
Speaker 1:	06:32	The, logistics of this or, the inner workings of this protocol involve, something this last session spoke about in great deal

which was getting the fluids, inotropes and vasopressors right, and that matters obviously much more in patients who are developing acute kidney injury or are high risk for acute kidney injury than it is in patients that their kidneys are functioning normally. And what Alex was able to show is that you could dramatically reduce the rate of AKI in this very enriched population. About a third of patients in this cohort, were test positive. And then if you randomize those patients to a KDIGO bundle, you could dramatically reduce the rates of AKI, and even the rates of severe or moderate to severe AKI shown in red. And as I said in this editorial, this is critical because it does two things for us.

Speaker 1: 07:24

First of all, it's shadow shatters the myth that there's nothing we can do about AKI. You hear physicians say this simultaneous and it's very interesting that to hear it because you hear people on the one hand say there's nothing we could do. And on the other hand we do everything. And so it's very interesting because, the reality is that neither of those comments are true. We shouldn't do everything for every patient. That's not good medicine. We should do the right things for the right patient, we should do the right things at the right time. And this study demonstrates that that's possible and that it does in fact impact the development of AKI. This is some work that you haven't seen because it hasn't been published yet and I don't think it's been presented anywhere, but the test actually goes beyond restratification at the very high levels when it's persistent.

Speaker 1: 08:16

So this is the essentially diagnosis of acute kidney injury that can be made when multiple tests are very high. So not only is the test, a risk stratifier, but it at the very high level, and particularly when it's persistent, it's actually diagnostic of acute kidney injury. And this is critical because we know at some level, some of acute kidney injury is hard to diagnose with traditional. We don't do biopsies, we don't do, any kind of invasive tests in these patients if they, are to die, we can do postmortem examinations, but, the subclinical AKI that occurs in many patients. And so we need better diagnostics, not just for restratification, but probably most importantly, I think is the discovery. And this actually is Jeff's figure. Jeff designed this figure, it was first of all written on a napkin, and then it was transferred to a piece of actual paper and then it became a PowerPoint slide.

Speaker 1: 09:20

And then finally we had an illustrator at the Mayo Clinic, with Kianoushs Kashani actually developed this figure. So this iconic figure, I would say of the NephroCheck test, was a figure that Jeff created, this is a figure that we worked on together. But

really this was Jeff's creation. And what it shows is that a variety of different stimuli can produce the release of these two biomarkers TIMP-2 and IGFBP7. And the reason it says that they're in response to cell stress is that we've subsequently demonstrated that this is not an injury marker, that it really goes up with cells stress. So let me just quickly introduce you to cell stress. this can be thought of as being a bit of a psychiatrist for the kidney.

New Speaker: 10:15

in a way it's a response to a non-lethal cell injury or noxious stimuli. It may include a protective response or pattern or down regulation of non-vital cell functions. And the reason we know it's stress is that we can stimulate this by just making the cells unhappy. So let me just, draw your attention to down in the lower right hand corner, you can see that LDH goes up. The C is for control. The N is for nutrient deprivations, the starvation of the cells and O is for oxygen and nutrient deprivation. You kill the cells when you deprive them of both oxygen and nutrients, but you just make them unhappy when you deprive them of nutrients. And if you go to the upper left hand corner, when you then give them back nutrients, it's kind of like a reperfusion injury in a way.

Speaker 1: 11:08

Again, it doesn't cause injury, but it does cause a brisk release in both the proximal tubule and the distal tubule of these biomarkers. And we've shown this in clinical scenarios as well. This is Alex Zarbock work again this is a remote ischemic preconditioning model in which we've taken humans and conducted remote ischemic preconditioning by putting a blood pressure cuff on their arm, blowing it up, causing the muscle to release damage associated molecular patterns like uric acid, myoglobin, hmgb1 we can measure those and have done so in the plasma in the urine. And what happens is when those molecules go to the kidney, they make the kidney unhappy, the kidney begins to react. And of course in very concentrations it's damaging to the kidney. But in these low concentrations, the kidney doesn't appear to be damaged.

Speaker 1: 11:58

We see damage markers on the right, which is NGAL they don't go up, the patient doesn't develop AKI from remote ischemic preconditioning, but they do respond with this increase in the test, in the biomarkers. And the biomarkers go up really quite rapidly in response to this maneuver. And then that's protective to subsequent stimuli that is injurious to the kidney, such as a cardiac surgery event. And the idea then is you stimulate this protective event. It then protects the kidney from the subsequent event. So that's obviously very novel. That's very new. We didn't know any of this, some time ago. There are

other mechanisms for remote ischemic preconditioned, they're important too, but this is a humoral mechanism that we've identified. We've also wondered whether these biomarkers TIMP-2 or IGFBP7 could be targets, right?, and initially we thought, well, this is a protective mechanism, so inhibiting them ought to be harmful.

Speaker 1: 12:59

But in several experiments, both done in my lab and this worked on with my, colleague in China, we've demonstrated that in fact, when you knock down TIMP-2, but not IGFBP7 but just TIMP-2 in a sepsis model, it's actually protective and there's a reduction in injury to the kidney, both as evidenced by creatinine, we've also done this in HK-2 cells which have decreased apoptosis and in the most convincing experiments where we've actually transfected kidneys in live animals using a lentivirus vector knocked down the TIMP-2 subsequently then giving this animal sepsis cecal ligation and puncture There is again, a reduction in injury to the kidney if I had a pointer I could better point, but you can see, I think even without, being a pathologist that the lower left hand corner is sort what the kidney looks like in CLP

New Speaker: 14:05

all that vascularization in the tubules and in the, knocked down situation. In the lower right hand corner, you can see without being a pathologist, you can see a whole lot better kidney histology. But we haven't stopped there. So we conducted another study with Astute Medical called the RUBY study. And this was because, and it's actually, I have to tell you the story. I'm the very first time I met Chris Hibberd, and I met him, with his partner in crime, Paul McPherson at a bar, that's all good stories start at a bar. I met him at a bar to get a beer, after the ASN in Philadelphia. And Chris said to me, he said, we're really looking to develop a marker, which ultimately became NephroCheck.

Speaker 1: 14:55

We're interested in developing marker for AKI And I said, you know, that's great, but you really should develop a marker that tells me in a patient who has AKI whether they're going to get better or not, because I have therapies for that. I need to know whether to put the patient on renal replacement therapy. I need to know whether to hold tight and wait and see, I really need this information. And Chris said, we'll get to that. But will you help us with the AKI story first? And so that led us, ultimately, to conduct the RUBY trial and Mitch Chawla was the Co-PI of the NephroCheck studies and the SAPPHIRE TOPAZ and we flipped roles in this study, largely because I didn't want to be Pi because I had actually had some technology that I thought was a competitor, in this space.

Speaker 1:	15:41	And Astute Medical looked at it, it didn't pan out. But what did pan out is a biomarker, that I'm going to talk about on Friday that we're calling Nefroclear. So NephroCheck tells you that AKI is likely Nefroclear, tells you whether or not that AKI is going to resolve and if it doesn't resolve, you're in persistent AKI and we know that's associated with long term as well as short term hazards. And your clinical decision making is informed largely by whether you think a patient is going to recover from kidney injury. And this is the performance of this test. Obviously I don't want to steal my own thunder for Friday, so I'm not telling you what the marker is. but keep calm the wait is almost over on Friday. I'll tell you, what this marker is, it is a very interesting mechanism, behind this marker that I think you'll appreciate.
Speaker 1:	16:34	So, we have, lots of opportunities. So in half of this talk I spent time talking about the exciting opportunities, AKI risk, AKI diagnosis, AKI persistence. there's technology out there that looks interesting with regard to etiology, we had some talks on that yesterday. Long term recovery is potentially another question because just identifying short term resolution may not be the whole game. We may want to know what happens down the road. so I think there are a variety of other opportunities in this space and I hope that the team that that Chris Hibberd put together, with Paul McPherson manages to continue this work in the new company --------- but there are challenges and people don't often talk about these challenges. So, I wanted to use this time to acquaint you with some of the issues that I think are out there that you may not be aware of.
Speaker 1:	17:28	The first frankly, is the regulatory burden, it used to be possible to get approval for a diagnostic and it's still largely possible, are becoming less possible in Europe to get approval for a diagnostic that simply does what it's supposed to do. Imagine getting approval, for a thermometer where you had to show outcomes studies, or you had at least show that not only did it measure the temperature of the patient, but that what clinicians did with that information was on the whole useful. It's a really high bar and it becomes very challenging. so the requirements that the FDA puts on these things are now becoming progressively more, difficult to manage and therefore costly. NephroCheck costs about a $150 million to get to this stage. And as a result, there's very few diagnostics that we have available. Think about what's available as novel protein diagnostics in acute hospitals, medicine in the us market in the last 20, 30, 40 years, we have about one to two a decade.
Speaker 1:	18:40	This is hard and it's expensive. And as a result, it's very challenging. There's another problem and that's us. It seems to

be fashionable amongst clinicians, to play politics with clinical innovation to say, I'm skeptical, they get a pat on the back that seems for being skeptical no one comes back later and says, you didn't use this brand new innovation that you are going to have in your hospital because you did not lobby for and your patient suffered. No one says that. They say, Oh, good job. You're holding the costs down in your hospital by being skeptical. I am as skeptical as anybody. Those of you who work with me clinically, know, that I'm very skeptical. Those of you who worked with me in research, know, I am extremely skeptical, but I try to have an open mind. We polled clinicians, nephrologists and intensivist and we asked them this question about AKI.

Speaker 1: 19:39

We said, how high is the need for a test that predicted AKI at least 12 hours in advance of serum creatinine, nephrologists, 77% said very high. 11% said high, intensivist 62% said very high. 26% said high. Almost nobody said this wasn't necessary. And yet you hear when you provide the data and you show that the test works, they say, we already know in AKI will occur. No you don't. we already do everything. No, you shouldn't. Anything that costs more than $5 is just not affordable. And it's really amazing. clinicians are just the worst when it comes to health economics, I've actually heard clinicians say things like, well, chest x-rays are cheap, but clinical diagnostics are expensive. Do you know what a chest x-ray costs? Well we don't because that's a --- to us, right? No one knows what that costs.

Speaker 1: 20:36

But Google it. Kaiser thinks that it costs $240 a chest x-ray, how much value do you get out of a chest x-ray that you'd get daily on your ICU patients? And how often do you avoid diagnostics? It cost considerably less than that. that may well be effective in managing your patients. We have another problem, which is this bunch. Okay. This is the Supreme Court in the United States. if you're not following politics, the Supreme Court hadn't made a landmark decision that I think few people realize how important it is in our field. This is going to dramatically, it already has dramatically created a chilling effect on diagnostics and it's going to continue to do so. This was a unanimous decision in 2013, against Myriad, and the decision was Myriad had discovered the BRCA2 and BRCA1 genes, a test for them and what the Supreme Court said was well that is great but you know these genes they occur in nature the fact that you discovered a test that detects something that occurs in nature is not patentable

Speaker 1: 21:39

That was their decision and this is bled over. This of course, became a bit of a political ping pong because it's the BRCA2

gene that's associated with breast cancer. And that was construed as being a woman's rights issue, but it's had enormous impact on the diagnostic field because lower courts in particular have interpreted this information as evidence that we should not provide patents on anything that occurs in nature. So Mayo Collaborative Services sued Prometheus Laboratories because Prometheus Laboratories, developed a test to see whether or not a chemotherapeutic agent was going to cause toxicity. And somehow the Court decided that well, even though it's a chemotherapeutic agent that you're adding to the body, that somehow that's not patentable, give you even a better example.

Speaker 1: 22:50 In June of 2015, the Federal Court ruled against the company that developed a test from maternal cell free fetal DNA. So rather than measuring by amniocentesis, simply getting a blood sample and seeing if a patient has trisomy 21, would be a huge value and that test will never be on the market in the United States. It'll never to be available to anyone because the Court ruled that that's something that occurs in nature and you can't patent something that occurs in nature and the company didn't fight it because remember it cost $150 million to get the test on the market. What's it going to cost to fight it to the Supreme Court? They decided it wasn't worth it. They packed up and they went away. This is a huge problem for us because the value proposition, and patent protection is getting lower, less weighty, if you will, while the cost and the FDA requirements are getting larger, this is going to get companies that might be interested in developing diagnostics just to be not interested.

Speaker 1: 23:57 And if we compounded that a sort of medical nihilism that our community sort of has about many things, then it's even worse than the few that remain will say, well, we're just going to work with the oncologist. They really seem to care about biomarkers and treating patients that, might not have a very good outcome and spending a lot of money, to achieve those outcomes. And yet, despite all of that, the opportunities have never been greater. The promise of personalized medicine, is really quite great and not just for therapeutics and not just for things related to genes and regulation of gene products, but also all the things we care about. The idea that you can synthesize information from the Biomonitors that we have in place to drive better renal replacement therapy will be totally invalidated.

Speaker 1: 24:51 If some patent attorney says, well, those bio signatures are things that occur in nature so they can't be patent. And if they somehow managed to get a patent, and our clinical colleagues say, well, that costs $100 more to have that sophisticated

		dialysis. We're not gonna even think about whether it works. Because I get Kudos from my hospital administrator if I just be the wall against new technology, this is what we're facing. There are many opportunities. This is another example, in which patients have, and this is, segue from Sean Bagshaw, lecture. Getting the fluid removal right is something we could do much better with that kind of advanced technology. And there seems to be hazard on both sides, too much fluid removal, too little fluid removal, both cause hazards. So in conclusion, I would argue that the application of precision medicine to acute disease will provide robust opportunities for medicine and industry to collaborate.
Speaker 1:	25:59	Diagnostics are essential to the promise of precision medicine. We have an amazingly powerful therapeutics and we don't know how to use a lot of them. We don't know what patients to select them in. Important barriers to development of precision medicine, and precision organ support include the requirement for much better diagnosis, less about the genes and more about the real time gene expression. Sure. And we'll talk about precision medicine later today. I think at lunch, narrowing the value proposition for in vitro diagnosis is absolutely essential. It's gotten way out of control and countering medical nihilism is part of that. Many more. AKI Diognostics are needed and I hope to help the field work on it together, so thank you very much.
Speaker 3:	30:55	. .