DAVID C. WHITCOMB: Well, good afternoon. As you know, there has been tremendous advances in pancreatic disease, a disease that has been without progress or without hope for 100 years prior to some recent discoveries in genetics and modeling of complex diseases. Today I'm going to speak about systems modeling and precision medicine because these are interdependent and are critical to the future of managing these diseases.

Before I begin, I would like to just disclose some of the competing interests, since there are many things that I'm involved in, all of which have the purpose of promoting precision medicine for pancreatic diseases. The objectives of today's talk are to define the different goals of traditional Western medicine in precision medicine. Secondly, it's to help recognize the need for disease models in precision medicine. And finally, I'd like to give an example of targeted treatment for pancreatic disease that includes both genetics and functional testing.

To begin with, I would like to draw your attention to our current understanding of chronic pancreatitis, using the traditional clinical characteristics for a diagnosis. So a clinical diagnosis of chronic pancreatitis is to look for variable biomarkers, and these include scarring, which are present in maybe 80% of cases, maldigestion, diabetes mellitus, pain, which is very different in its characteristic and types, and pancreatic cancer, which can occur at the end stage of many patients with chronic pancreatitis.

The diagnosis and treatment is based on using imaging classifications to demonstrate irreversible damage to the organ. The method is to repeatedly use CT scans, MRIs, ERCPs, endoscopic ultrasound, and other imaging techniques as surrogates for pathology in order to demonstrate irreversible damage.

Once irreversible damage is demonstrated, then we begin treatment, which is symptomatic, to try to minimize pain-- but don't give too much, because the patient might be an alcoholic and a drug seeker-- to use pancreatic enzyme replacement therapy, because the function of the pancreas is lost, and insulin therapy when the islet cells, which float in a sea of acinar cells, are also destroyed.

In summary, chronic pancreatitis is a complex, hopeless, irreversible condition that is expensive to diagnose and treat. This is unacceptable. Let me give you an example. What if you saw a 33-year-old woman with five years of pancreatitis-like pain, with new evidence of chronic pancreatitis on a CT scan-- it looks like there might be some fibrosis, maybe a calcification-- and she comes to you, as a world's expert in pancreatic disease.

She only has three questions for you. Why me? What is going to happen to me? And what medicine will stop this disease? After a careful history, physical exam, laboratory testing, review of the CAT scan, you can answer her with confidence everything you've learned. I don't know why you got this, I don't know what's going to happen to you, and I don't know what medicine is going to help you.

This tells us that traditional Western medicine for pancreatic disease has failed. We must do better. Let's look at what we've learned about pancreatic disease using the traditional model, which is based on the germ theory of disease. First of all, it's a pathology-based approach, defining the chronic pancreatitis by the clinical symptoms and what the pancreas looks like on pathology. It is inflammation without infection.

Early chronic pancreatitis cannot be diagnosed because it requires advancement to stages that meet the clinical criteria that are established by convention. Genetic testing has emerged as being important and associated with pancreatic disease, but there is no place to put the genetics in the diagnosis, and it's unclear how to interpret these results when looking at the disease under a microscope. And the management continues to be based on symptoms.

The alternative approach is precision medicine, and I'd like to talk to you more about that today. The framework is mechanism-based. A mechanistic definition looks at the underlying dysfunction. What is happening that is associated with the etiology that's driving the disease that eventually becomes pathology? It requires dynamic mechanistic models. This allows early detection of the underlying problem with high accuracy and specificity.

It requires looking at a holistic approach, multiple risk factors-- such as outlined in the TIGAR-O system-- that gives a clinical context, and multiple biomarkers that may be sorted out using big data approaches, so that the problem in an individual patient can be diagnosed immediately and we can begin the appropriate treatment. Because of the sensitivity and specificity, targeted treatment can begin before there's irreversible damage, and we should be able to minimize both the symptoms and the disease progression, and prevent the development of a disease that no one can cure.

The delivery system is dynamic, with continual updating as we watch the patient and determine from their signs and symptoms whether or not the treatment is effective, or whether or not it needs to be adjusted, so they remain healthy and do not develop the disease that we cannot cure.

Now, the big data is a little bit of a problem, and as you can see, there is a lot of information, both from population, epidemiology, omics data. There's a large number of genetic variables, and already there are additional genes that have been identified associated with diseases. There's modifier diseases. There are multiple biomarkers.

Nobody can understand all of these, integrate them in their head, and keep up to date on it. It's too much. This is a partial list. We have to have new tools that will allow us to immediately consolidate all the information on the patient and give them the right treatment at the right dose at the right time.

Now this requires some models, and a couple of thoughts about models that were inspired by Albert Einstein. He said, everything should be made as simple as possible, but no simpler. And so we don't have to use systems biology, where we look at every single step in the Embden Meyerhof Pathway and try to calculate exactly how many molecules are coming in and out, and what the temperature and the dynamics are.

All we need to know is whether or not the system is working or not. If it is, great. We'll find the one system or two systems that are not working and be able to predict why.

So in a complex human disease, all systems should be assumed to work perfectly normal unless proven otherwise, then focus on the variables underlying the dysfunctional system. Secondly, in common complex diseases, the primary interacting disease variables must be common. Otherwise they will not appear together commonly.

So if there's four variables that are part of a disease that are seen in one in 1,000 patients, they each have to be present in at least 10% of the population for them all to come together, by chance, one in 1,000 times. So instead of looking for a needle in a haystack, we need to see the obvious players that are in the room which, together, make a team that is causing trouble.

Finally, and this is so exciting. It's because of the magic of adaptability with living organisms. A 50% solution to a problem may be a 90% solution to the disease, because we're trying to help the body compensate for dysfunction, not completely replace a dysfunctional part. And we're able to do that through lifestyle changes, targeted therapy, and using what we know about biology to help change the patient from symptomatic to nonsymptomatic, from progression to non-progression.

So how do we use models? Well, we're very used to data-driven models, and in fact, this is where big data comes in. There's an idea that precision medicine can be solved by taking a huge amount of data, throwing it into a computer, and let artificial intelligence think about it until it comes out with a solution to the purpose and meaning of life. And it turns out that there are some advantages in using big data models, but these are data-driven and association-driven.

The association-based approaches in a population can find some principal drivers of disease, things that are so big and so common that they make a big effect, and also networks that are important for the disease. But on an individual basis, it's usually not helpful.

Big data also uses a limited amount of prior knowledge. Everything we have learned about the pancreas and the cells of the pancreas and which ones do which thing and how they function and respond is ignored. All they do is look at the biomarkers and the outcomes in the genetics and try to have it solved. And so the understanding of medicine and biology is not really used in the way it could be to bring insights into disease.

Thirdly, it takes a huge amount of data, and the problem with pancreatic disease is that if you try to get together a cohort of patients, like we did with the NAPS2 study, it took us 10 years to get 1,000 patients, and it was highly heterogeneous. How can you compete with diseases like rheumatoid arthritis or diabetes in which they have 50,000 patients and 100,000 controls? And yet even there, they do not give insight into the disease.

And the third problem is using machine learning. It subdivides the population and tests it against the others and then moves in an iterative way back and forth with training sets in order to come up with predictive algorithms and associations. But unfortunately, when you look at a slightly different population, it doesn't work. It fails outside of the training set, or functions at a much lower level than you would hope. And so there are major limitations to data-driven models.

Mechanistic models are ones in which we assign steps of a process with specific direction and effect size, and we use the understanding of biology to organize them in a dynamic way. So they're very highly causal in their design. It's an engineering problem, not a statistical problem.

The advantage is that we can use the tremendous amount of prior knowledge about how the pancreas actually works and look at components of it. And once you've zeroed in on a component and understand how it works, then you can use your statistics. But you have tremendous statistical advantage because the number of vitamins you're looking at is not in the billions but in the tens, and so your Bonferroni correction is low and the effect size is high. So you can get accurate assessment of exactly what the effect is using a reverse engineering approach.

Once you've been able to put this together and test it on individual patients, you can begin to understand emerging concepts where a component of the system seems to be malfunctioning in some patients that you didn't expect. But now we know exactly where to look, and how to solve the problem, in that subset of patients that have a problem in that area.

The biggest problem is it's hard. It's very difficult, and it takes a multi-faceted team to be able to put the pieces together and organize and to test them in order to get a system that works, and then it has to be integrated into an expert system so that each of the different data sets can be transformed and simplified and organized, and then backed into what we know about medicine.

But the advantage is it can make predictions outside of the training set. So once you have the model, each case that you fail in teaches you more about the disease, allows you to modify the model, and have it even more robust than it was before. So in precision medicine, we need to use mechanistic models, and they need to be dynamic because the mechanistic models are ones that change over time as the disease progresses.

What is the right model? Well, it depends on what system is being evaluated. So, for example, in the pancreas, a model of the duct cell is different than the acinar cell because the duct cell is an ion transport system, whereas the acinar cell is a protein synthesis system, and so each of the models has to be different and dynamic.

Now in order to move forward with precision medicine, we recognize there was a major problem with the definition of chronic pancreatitis itself. And so a group of us got together and debated for a long time about what the problem was with our current definition and how to improve it, and we came up with a mechanistic definition of chronic pancreatitis that was published in 2016 in the journal Pancreatology.

And what this did was recognized there's actually two parts to a good definition. The first one we already had. It describes the features of a thing, and here we recognize that the common features of established and advanced chronic pancreatitis-- that meet the criteria that have been established in 1984 in Cambridge-- include pancreatic atrophy, fibrosis, pain syndromes, duct distortion, strictures, calcification, pancreatic exocrine insufficiency, pancreatic endocrine insufficiency, and dysplasia. So these are the characteristics that we're familiar with.

But what is it? What is chronic pancreatitis? And here we understood that it is a pathologic, fibro inflammatory syndrome of the pancreas in individuals with genetic, environmental, and other risk factors who develop persistent pathologic responses to parenchymal injury or stress. And so not everybody gets pancreatitis. They have to be susceptible, either because of a strong environmental factor that blasts the pancreas, or a weak pancreas in which many small effects are enough to cause injury or stress.

And so now we understand what it is and what the characteristics are. To put this together, we say, is there a process, or is this a sudden thing that happens? And what we learn is that in pancreatitis, such as alcoholic pancreatitis, some individuals get acute pancreatitis, and of those, there's a subset that progress and a subset that don't. About 30% develop recurrent, acute pancreatitis, and of those, about a third also develop chronic pancreatitis.

So there is a strong connection between these different types of pancreatitis in these highly susceptible patients, and we know what the sequence is, and we know they actually are different states of the disease that progress in some people but not others. And indeed, recurrent, acute pancreatitis is known to be a major driver of this disease.

And on this diagram, you'll see on the x-axis is the month after the first attack of acute pancreatitis, and the risk of chronic pancreatitis, shown on the y-axis, is five times higher if you have recurrent acute pancreatitis than if you have just that one episode, which also has an association with the development of chronic pancreatitis. And so we see that there are warning signs, and there's time to intervene to stop the progression of disease in a matter of weeks and months, so we do have an opportunity to make a difference.

So we put together a progressive model, and this tells us the different states. Here are five different states of the disease, and there are factors that put you at a certain position and cause the progression to the next one, and there are biomarkers for each one of these. And it allows us to understand what the process is.

We recognize that the genetic and environmental factors now can be organized into a process that reflects underlying disruption of the normal injury, inflammation, resolution, and regeneration sequence. And so the normal process of regeneration and going back to normal is disrupted, and that's what leads to disease and progression.

We also see that, in these diseases, stages D and E do not have the same features in every person. And in fact, we've shown that patients with pancreatic pain cannot be predicted by their CT scan. So the amount of fibrosis doesn't predict the amount of pain. It actually doesn't determine whether or not they're having diabetes.

It also doesn't predict whether or not they have pancreatic insufficiency. As a matter of fact, fibrosis, which comes from the Stelic cells, which is not even a normal part of the pancreas, has been used for diagnosis and prognosis and it doesn't correlate with anything of clinical significance. No wonder we're struggling with this disease.

So what we're understanding now is each cell type, like the acinar cell, has a characteristic function and a characteristic dysfunction, and each one of them has to be tracked independently. And so we are beginning to understand that the models are a little bit more complex because we actually have to track each of the components of the disease.

So let's look at the duct cell. This is a very exciting area that's been led by the cystic fibrosis groups, and what they have found is that there are genetic factors underlying cystic fibrosis. We all know that. That's CFTR. But in spite of the fact the problem is CFTR, there's a whole bunch of variants, and each one of them has a different effect. But they can be classified by where the problem is located, and what is happening in the development and activation of CFTR that causes normal duct function.

What's interesting is that there are now medications that can be directed to the underlying problem. It's not that, if you have CFTR, anything works. It's that we can now understand where the problem is, what the dysfunction is, and how to treat it to either stabilize the RNA, to improve the trafficking of the protein, or to help in the function so that it does the right thing in these patients. And there are now effective medications targeting each of these steps.

So when we look at pancreatitis, we're used to seeing end-stage disease, and then do genetics in order to find out what the heck happened, and you can't do anything with the results. Furthermore, it's not having a Mendelian disorder. It's a complex disorder with different types of dysfunction that eventually lead to disease. So what we need to do is make a diagnosis early in the disease, not at the end stage but when you first see abnormal biomarkers and symptoms suggesting there's underlying problems.

And that's actually when we should start the therapy. We want to know what the underlying problem is so that we can start the therapy and begin to address the problem that these patients are having so that the end-stage disease is never seen. And your grandchildren, when you talk to them about chronic pancreatitis, you should say, back when I trained, we saw chronic pancreatitis, but because we were able to identify it and treat it early, you'll never see this again.

Just like in rheumatoid arthritis where, when I trained, we saw women with their hands gnarled and unfunctional because of the effects of rheumatoid arthritis. But the treatment before the joints were destroyed allow the patients to go through life, with treatment but with a normal use of their hands, and we want them to have the same type of advances for pancreatic disease.

So for early diagnosis, we've identified all of the different types of environmental and metabolic and genetic factors, and organized them in the TIGAR-O classification system, and there's a new classification that has just come out, a 20-year update, that's available online and open access.

We also are able to begin to organize the different features by the system that is dysfunctional in a management plan that will allow us to address it. So depending on what the underlying risk factor is, we can begin to address it. And many of the risk factors are modifiable, and we know what the combination of risk factors and genetic susceptibilities are so that we can target our therapy and encourage specific types of treatment.

This allows us to focus on minimizing these injury and distress, and also to anticipate the type of problem that these patients are likely to develop if they are having poor response to the initial therapy. So this allows us to begin to identify each patient, but since each one is different, we need to think different than the old fashioned, randomized control trial, because we can never get enough patients to do this, and use a little bit more innovative things, like N of one trial, to find out when the patient is actually responding to the therapy that we've designed for them personally.

Now the problem with precision medicine is that it's a disruptive technology. It's an approach that nobody has ever seen before, nobody knows how to use it, and as with many disruptive technologies, stable systems do not want to be disrupted even though they're dysfunctional.

There's a number of things that have to be addressed in order to solve this problem, and one of them is a technology one. A very interesting paper was published when Obama announced the Precision Medicine Initiative, and this identifies some of the things that need to be achieved from a health policy standpoint, and these are actually important to consider.

The first one is that the medical records need to be linked with the patient and their doctor. There needs to be accurate reporting of the data. We need to be able to connect the research insight and the clinical data set together. We have to understand the approval process so that we can compare and contrast patients, and all the information from individual patients can be seen by themselves rather than as summary data.

There needs to be continual markers over time. There needs to be updating of the information as new data becomes available. We have to have real-time decision support so the physician and the patient know exactly what's going on at every period of time.

It has to be affordable. It has to represent all the ethnic groups and all the ancestries, and it has to have an educational component. Health care workers need to know how to do it but they can't learn the genetics and all the information. And the patients are the ones that know the details about their own disease and experience. They have to be partners in this process.

How can all these be brought together? What are the disruptive technologies that are needed in order to make this happen? How can it all be integrated so that the physician and the patient can work together to solve an unsolvable disease?

Well, I'm happy to announce that within the last 10 years, that technology is available. And as a matter of fact, it's available to you and your patients. We call this a smartphone. And using smartphone technology, it may be possible for the physician and the patients, for the first time, to connect all the pieces, and use precision medicine, mathematical modeling, big data, and in an affordable way to solve a disease that is otherwise unsolvable.

So to summarize what I've talked about today, we recognize that the germ theory paradigm-- the Western medicine, traditional approach-- has failed for complex diseases. It's great for infectious diseases and simple diseases, but for complex diseases like recurrent acute and chronic pancreatitis, it's failed, and a new framework is required.

Physicians caring for patients with idiopathic, recurrent, acute pancreatitis and early chronic pancreatitis, in which the woman is asking, why me, what's going to happen to me, and what can I do to stop this, need new tools. They can't look at them with the information that they're currently given, and answer those three critical questions.

The future is now. What we need to do is to stop using only genetics out of context, and begin using precision medicine, where we can answer those questions and deliver the medicine that is needed. Thank you for your attention, and I hope that you have learned a little bit about precision medicine, and I'm happy to answer your questions. I have my email available. And thank you for your time.