JOHN TILBURT: Good afternoon. Welcome to CCaTS Grand Rounds. I'm Jon Tilburt from General Internal Medicine and the Center for the Science of Health Care Delivery. About four years ago, we started a new training program for clinicians interested in patients centered outcomes research. And one of the first applicants we selected was Matt Rank, who's our speaker today.

Dr. Rank is a consultant in allergy, asthma, and clinical immunology at Mayo Clinic Arizona; an assistant professor of medicine. He attended the University of Wisconsin-Madison for undergraduate and medical school, completed an internal medicine in pediatrics residency at the Ohio State University and Nationwide Children's Hospital, and then a fellowship in allergy and immunology at Mayo Clinic Rochester. He also recently completed the Health Care Delivery Scholars Program, and we're excited to hear what he has to share with us today.

I will say two things about Matt. One was I was very sad when he moved to Arizona. The other thing is I won't hold his buckeye status against him. And I'm super excited to hear him sort of show and tell some of his experiences in his recent, very prolific scholarship. Matt.

[APPLAUSE]

MATT RANK: Thanks John. Really glad to be here, be back in Rochester, and to talk about some of the things we've been working on. I see a number of familiar faces in the audience, people that have supported our research. And I think we'll see how some of it's come together. I'm going to be talking about asthma, which is the disease that I mostly spend time doing research on. And I'm going to talk about overtreatment of asthma and in particular, overtreatment.

And I'm talking about a method for addressing overtreatment, which is reducing somebody's asthma medication. And we're going to call this stepdown of asthma medication. And we've really been researching this in a lot of different ways, and I'll show you those different ways. But I think I want it to make it clear to you with the outset that this is not a talk about getting people on more medicine or addressing people who have problems with their asthma. This is about what to do with people that are doing well, and where to go from there.

Neither the organizers of this course nor myself have any disclosures to make. Four learning objectives for today. One, I want to talk just a little bit about background information, some population level trends for asthma outcomes, asthma costs, to try to explain why I think this subject matters. Second, I want to quantify risks associated with reducing asthma medicines. We've spent a lot of time trying to do this.

Third, I want to talk a little bit about how the scholars program that John outlined, his influence, some of the research we're doing, and some of the methods that I learned within this scholars program to help answer some of these questions. These are things like secondary database analysis, systematic review, survey research. I think you'll see how we use those different methods to try to get at these clinical questions as I progress through the talk. And finally, I want to reflect a little bit about being a clinician in this scholars program, what we've been able to accomplish, and what we haven't been able to accomplish. And hopefully, those of you in the room that are in a similar junior position that I am can learn some lessons from what we've done.

This is just a brief slide to introduce the Health Care Delivery Scholars Program, of which I was a member until this June. It really is designed to support the career development of residents, faculty, and Fellows. The focus is really on learning research methods that can be applied, research methods that are associated with the science of health care delivery or health services research. There are several components to the program. There's mentorship. There's coursework. There are frequent interactions between the faculty in the program and the scholars. And the program length varies between one and three years. Most people are in the program for about two years.

And then, I want to give a little bit of background about asthma. When you're a clinician that sits and spends a lot of your time talking to patients with asthma or reading everything about asthma, you get some tunnel vision. And the organizer of this course reminded me that not everybody spends 80% of their time treating asthma patients. So I wanted to take a step back and make sure everybody sort knew what I was talking about when I say that.

There are four main symptoms that people generally will have if they have asthma, not necessarily all of them, but usually some of them. And those are wheezing, coughing, shortness of breath, and tightness in their chest. This is a chronic disease. It's a problem that lasts years, not days. But it's a dynamic disease that changes over time, which is really important when you think about adjusting somebody's medicine, particularly downward, which is what we're interested in. The prevalence of this disorder is high. It's the most common chronic disease in childhood at between probably 8% and 10%. And it's up there for adults. It's about 8% of adults that have this problem.

We have reasonably effective treatments available. Inhaled corticosteroids are the mainstay of treatment for patients with chronic asthma. And they've really been available since the mid to late 1970s, and have been sort of pushed and translated, disseminated into practice over the 1980s, 1990s. And we have several currently available products. But there's still a problem with translating some of the guideline recommendations, and there's a problem which I'm going to share with you about-- perhaps the guideline recommendations for stepping down asthma are not fully developed.

So while, again, I'm going to spend a lot of time talking about reducing asthma medicine, but there's still a lot of problems with getting people on the right treatment for this condition. There're still undertreated people that we still can't reach, and that's really what I spend the bulk of my day doing in clinical practice-- are seeing children and adults who are having problems with their asthma and getting them on more medicine. So I want to just make sure everybody understands that concept before I completely narrow my focus and stepping down now.

This slide is an example of what many clinicians have seen as the template to manage asthma. It's a step down and step up chart of which medicines you may use depending on how much trouble your patients are having with their asthma. If you're having problems in Step 2, go to Step 3. If you're having loads of problem at Step 2, skip to Step 4. The research that's been done to construct this chart is almost exclusively built on studies involving choices of stepping up medicine. And there are a fair number of trials that have addressed these questions. But going in reverse-- going from, say Step 2 to Step 1, the trials that have been performed to do that are far fewer.

So I'm going to try to talk. This talk is really designed as a chronological description of some of the ideas that we've had, some of the people that have worked with us to help develop these ideas starting from about four to five years ago and working to about present day. So the origins of this concept of using the least amount of medicine to control symptoms and limit future attacks is really the central management principle of asthma in medicine management at least.

We, in our practice, identified-- what we're pretty confident was, pretty strong influence over treatment of asthma-- meaning these are patients who are doing very well, were on very high levels of treatment. There have been no efforts to adjust their medicine over time. These medicines were expensive. Patients were telling us this. They were going to the pharmacy and saying, I didn't have the money to get my inhaler this month. It was so expensive. And there was a disconnect because they were doing so well. And so, there were these people that weren't stepping down that probably should be stepping down or reducing their medicine.

And I began to wonder about cost trends, about outcomes, and about perhaps there's a problem with overtreatment that we've not really paid a lot of attention to. Really, the last 20 to 30 years of asthma research has been dedicated to identifying the undertreated and helping them. I think that's a pretty important priority, but people haven't really paid quite as much attention to the other end.

So the other thing I want to do is I walk through this again, is point out some people who have been involved, and some of the idea origins, some of the research methods. And I also wanted to put this in the framework of a translational medicine context. And I owe this idea to Jon Tilburt who looked at these slides and said, hey, this is a translational medicine grand rounds. The type of research you're doing spans a couple of these different translational levels. Make sure you put this in context for the people in the audience, to try to at least give them a roadmap of where you are in this whole translational medicine, I guess, T1 through T4 structure.

So I'm going to just talk. So T1, I'm talking about basic science research that you're testing for clinical effect; T2 testing interventions in controlled settings, really developing guidelines; T3, applying guidelines to practice; and T4, what interventions to improve population global health. I actually want to show you that, really, T2, T3, and T4 are areas that I think were working in, and talk first about the gaps that we've identified, and then the efforts we've made to fill some of those gaps at each of those levels.

I mentioned this already, but there are lots of organizations and some pretty important ones that have written as guidelines. And they come up with levels of confidence, levels of evidence, and we're all familiar with looking at these things. The current state of recommendations for when you should step asthma medicine down is based on very low levels of evidence. So that's a T2 gap, and probably a T1 gap as well.

Furthermore, it's unclear how to apply recommendations to reduce asthma medicines, who to apply them to, who's at high risk, who's not. So that's a gap in identifying the proper patients and the proper health systems in place to make that happen, which also leads to T4 gap, which is, our system as it currently is for most-- most systems, that is-- aren't well designed to meet the needs of patients who have a chronic dynamic disease when they're doing well.

And I'll show you some hard numbers to back up that statement. in this period of our development, I had several mentors-- Barbara Yawn, Jim Li, Jerry Volcheck, Kirohito Kita-- who were helping me understand and frame some of these different ideas. There were others too. These are some of the main folks. And that was early. We started doing some studies, looking at some national databases, some secondary database analysis studies. And that's when I began to have an interest in this area of science of health care delivery. I was working with Nilay Shah, Megan Branda, Juliette Liesinger, Kaiser Lim. And we looked at a national database called the Medical Expenditure Panel Survey to understand what the outcome and cost trends in asthma had been, to try to get a better sense of what the gaps may or may not be.

This is an example of the main finding of the cost trends that we've found. And what I want to point out here is that comparing the 1990s to the mid 2000s, there is a difference in total costs. And the total costs are higher in the 2000s. And I want to point out that the main driver for this are medications. We weren't surprised by this, but it was helpful for us to frame this, and frame our focus on medication choices and asthma as something that may have a really important impact on the population health in the end.

If you look a little bit closer at this, there are two specific classes of medications that have driven this. OK? The two in the red are the leokotrine modifiers and the ICS, which is inhaled corticosteroids. The one that I mentioned are sort of our mainstay of treatment that have been available now for 30 plus years. Those products are coupled with another product called a long acting beta agonist, and they're called combined treatment. Those two products-- those two classes of medication went from very infrequently prescribed to being the first and second most commonly prescribed asthma medication during that time. And so that also gave us an idea about some of the changes in trends of asthma medication prescription and another thing for us to think about in terms of costs and outcomes.

I want to take a little bit of time to use a source that I haven't usually used, which is an investigative journalist source. But I think they've touched upon some of the main issues and controversies that happen with these trends. And I think this will help all of us understand the context. So in 2001, per this investigative journal report, a pharmaceutical company introduced the first combination product of inhaled corticosteroid lined to beta agonist. And their statement was-- the executive was talking to all their sales force said, there are people in this room who are going to make an ungodly sum of money selling this product. And that's true. 13 years later, it turned out to be very true.

Now looking back 10 years, I think this statement also helps put this in perspective a little bit as well. This is from the same report-- a statement by Fernando Martinez, a very well-respected and well-known asthma specialist who said that the problem is, there are hundreds of thousands of people who have pretty mild asthma that should just be prescribed a simpler treatment that are being prescribed these medications. So now, we have this problem where people are getting more medicine than they probably need. But we need some type of solution and how to help these people who are potentially being overtreated for whatever the reason is, whether it's aggressive marketing, whether it's-- who knows what the reasons are. But we need to have some way of trying to figure out how to make this better. I'll tell you what the FDA did in a couple of slides. They had some ideas on this. But really, I think this calls for a solution of between patients and clinicians, a communication, a risk assessment, and a long term solution on how to help these folks.

Now back to our studies. So we looked at around the same period-- the mid 1990s to the mid 2000s-- and said, well, it looks like asthma care is more expensive. It looks like these particular medications are driving the costs. What about outcomes in the same period looking at these databases? And the first thing I'll tell you is we could not detect any major different outcomes in those two periods. The second thing I'll tell you is that we had a surrogate marker for adherence to guideline prescribing that was only mildly sensitive to some of the new medication classes that looked like there was a slight uptick. So there's a slight uptick in guideline-adherent medication prescribing for asthma, but the attack rates were the same.

We're not the only ones to show those trends. This is from NCHS Data Brief. If you look at these particular lines across 2001 to 2009, they're all pretty flat. The asthma outcomes have not changed much in the last decade. There maybe a slight decreasing trend in mortality. That's a whole another talk in controversy about whether that's a true effect or not. So, these are some of our early studies. These are the things we're thinking about and worrying about and wondering about. We didn't know exactly what these data meant. These are observational. We could say this-- the cost of asthma care increasing. We're not the only ones to show them. A lot of other people have done similar type analyzes and confirmed our findings. And we confirm theirs. The outcomes don't look any better. Clinical trials would say if you use these medicines in appropriate patients, their outcomes are better.

So what's the explanation? Is it overuse, which is our driving hypothesis, meaning there are these patients who have very mild asthma who are getting a lot of asthma medicine that would do the same regardless if they had the medicine or not? Or is it just this strong undercurrent of these patients who are so sick, they're not getting their medicines, they have all these other factors, and they're the drivers of the outcomes? At this point, I was fortunate enough to join the Health Care Delivery Scholars Program with the goals of writing grants, developing new research methods. And mentorship teams was firmed up-- Nilay Shah, my primary mentor, Jon Tilburt, Eric Hess, the program leads-- and begin to think, OK, now I have this new opportunity to ask more questions, do more research.

And I thought, well, what should we do to approach this? So how can we try to understand overuse? How can we try to understand stepping down and what the risks are-- which is, stepping down is kind of like our tool for addressing this. And we really decided to focus on stepping down. I'm going to review this again, even though I mentioned this in the guidelines a little bit. But this is kind of what things look like in about 2012 or so when we started looking at this, or maybe even 2010 and '11.

What the guidelines say, the international-national guidelines say is if you've been stable with your asthma for three months, think about stepping on your medicine, OK? And that low confidence, low evidence-- it's what the experts that were sitting at the table thought made the most sense. T2 gap. Real life. So in many practices, there is such a short time to address the patient's concern that if something is going well, it never even gets on the agenda. So if you start a medicine, they're doing well-- how's it going with the inhaler? Fine. Great! Refill. There's just not necessarily the structure and time and place to do that.

Furthermore, even if there was time, most of the visits that are done for asthma-- this is what Barbara Yawn showed in Olmsted County here-- over 80% of the visits for asthma are when kids or adults are sick with asthma, not a great time to talk about reducing their medicine. That's a time when you need to step up their treatment. Furthermore, there hasn't been a lot of funding flowing to this type of research because if you look at the totality of asthma trials and asthma studies, the majority is funded by the pharmaceutical companies who are interested in studying new treatments for asthma. They're not really interested in funding us to help patients get off their medicines. I think that just makes sense. And so, that's another gap in our knowledge.

So this is what I mentioned about the FDA. So in 2010, the FDA has paid a lot of attention to this. There's a few reasons for that. One are those combination inhaled corticosteroid long acting beta agonist products have long been controversial, since for about 15 years now. And they have a black box warning that is extremely controversial whether it should be on there or not, but it's there. The FDA has been worried about this. The FDA is worried about how many people were taking these products who may not need them. So they changed the label for these medications in 2010 to say, stop the use of this if possible. Once asthma what control is achieved, maintain the use of an asthma controller medication such as an inhaled corticosteroid alone. So they're legislating through their labeling.

So this brings me to some of the work we've done as during the scholars program. I was fortunate enough to take a course and have some mentoring about knowledge synthesis research. Some very smart researchers, including Dr. Li this at our institution, here were involved in a project that said, fine, the FDA made this statement. Let's look at the evidence. Let's do a systematic review, let's do a meta-analysis, and let's see what those risks actually are for making that step down change. What they found was-- really a dearth of evidence is really what they found. But I'm going to show you some of the details. I try to take a lot of my data slides out to make this more of an overview talk, but I have a few numbers in here because I think they're important.

So if you look at all the studies that have ever been done to answer this question, there were about 500 patients in each group that were identified. One of the most severe outcomes in asthma is needing to go to the hospital emergency department because you're having so much trouble. And so, when they looked at that outcome, there were 11 in the group that stepped down and five in the group that didn't. The reason I point those numbers out, that's a very low number of observations. You can see the relative risk calculation is 2, but the confidence interval is huge. This is a nonsignificant finding. You can't really know if there's an increased risk.

If you look at some of their other endpoints-- so using a systemic corticosteroid is a marker of having an asthma flare-up or having enough asthma that it's a problem. That wasn't significant. There was a slight significance in symptom days of 9%, but there was a fair amount of heterogeneity in that finding. There were significant differences in asthma control and asthma specific quality of life. But the total effect size of those differences were really small, so clinically, may not be so important.

So the FDA legislating this step down-- we don't know because I'd say that the knowledge synthesis is pretty indeterminate. We embarked on some of the knowledge synthesis of our own. I showed Dr. Hagan, who's in the audience here today, this picture as he was a major part, as long as many others in this room of leading these efforts. And I want to show you two results of what we found.

The first is, if you take an inhaled steroid, and you've been doing well, and you just cut the dose back, your risk of having an asthma attack based on this knowledge synthesis is about 1.25-- crosses 1. You see the confidence intervals, looks like pretty safe overall. Maybe we'd like a few more studies to ensure that this is truly safe, but overall OK. If you go from being on an inhale steroid to completely stopping, your risk is clearly elevated. It's about 2, and you can see the confidence intervals there.

There are other systematic review products we're working on, including asking about the risk of substituting leukotriene receptor antagonists for an inhaled steroid. That question was being asked and answered for a lot of reasons, not the least of which is that leukotriene receptor antagonists are now available in generic forms and are awfully cheap relative to the cost of other asthma treatments. There's only been one trial that's addressed that question.

And then we've been really interested lately in what happens if you're on an inhaled asteroid steadily, and then you back off and just use it when you feel you need to-- an off-label indication for this inhaler. And there have only been two trials that have addressed that. And we'll have those forthcoming. So that's other people's research that we're sympathizing. In the course of things, we wanted to generate some of our own data, some of our own information. And we turned to a couple of different research methods and have had various people help us along the way-- survey research, quality improvement research, and then a self-examination of one of the practices within Mayo to try to understand better what the outcomes of reducing medicine within that practice are. And so, the collaborators-- Tim Beeby, Kunal Shal, Jeanette Ziegenfuss, David Elon, Deb McWilliams-- all played a key role in making some of these studies happen.

So what we found with our survey. We found a couple of things. One was really related to quality improvement. And that is when patients perceive their health quality delivery to be good, it doesn't seem to correlate at all with what's being reported as a quality measure to the state or to other organizations. That was one finding. And we thought, one of those that you catalog in the back of your head when you think about designing an intervention for asthma and measuring its outcome.

The second thing we found-- which I don't think surprised any of us-- [INAUDIBLE] confirmed our suspicion. Most of the people that are reducing their asthma medicines are not asking their doctors or nurses or their pharmacist about this. They're doing it on their own. That's a risk because the patients may not know if they're at a higher risk. And doctors will have a little better idea if they're at a high risk, but maybe not even a perfect idea either. But we don't want the little boy who just got out of the hospital to go home and decide to step his medicine down on his own with his parents. We want to be the ones to do that. And for us, that's a target, right? That's a problem. If we're designing interventions to increase and improve the use of de-escalation of care, we need to meet the patients where they're at. OK.

This is what we found in the Pediatric Asthma Management Program, which is a program that's from here in Rochester. We found that most children who stepped down are successful. Many children who look like they could step down aren't doing it. The children who didn't look like they're OK to do it and did it anyways look pretty good still. And then we found that the most important predictor of step down was the time of year or the season in which they decided to step down.

So now we're doing some of that work. Now we're back to a secondary database analysis. We were fortunate enough to land a grant from the AHRQ to look at this a little bit more closely. And we were fortunate to establish some outside collaborators, Michael Schatz and Bob Zeiger, who are known experts in asthma database research, and then allowed us to form this three site team trying to answer some of these questions.

Furthermore, I also had an opportunity to be a content mentor for Mike Gionfriddo-- who's here in the room and supporting us here-- which ended up being a fantastic opportunity for everybody involved. Mike's been interested in de-escalation of care in chronic disease and thought that the asthma model that we were looking at seemed to make sense to study. And he's been doing qualitative methods and research methods to understand decision making processes in asthma, to better understand what's happening. He's interested in decision aids for stepping down, and he's been heavily involved in our secondary database analysis work as well.

So here's what we learned so far from the study that AHRQ gave us money to look at. In patients who meet our predetermined guideline-concordant definition of asthma stability, those who step down their asthma medicines have similar outcomes to those that don't. And we controlled for every possible variable we can think of. It looks the same. And that's important because in asthma, adherence to medications and other factors that don't often show up in clinical trials are detected in these type of comparative effectiveness research studies. So it's an important finding that encourages us further that stepping down asthma medicines in real life is probably OK for most people. We did, however, find a difference in costs, which is really our primary question here. The patients who stepped down had lower costs than the patients who didn't step down. And it's because of the cost of the asthma medications.

So once you start talking about one topic over and over again, people start asking you to write review articles about that topic. And we were asked to write a review article about stepping down asthma medicine. And normally, that's a tasks that you may associate with a low overall academic yield that-- here's a review article, not my original research. But it kind of forced me and other folks who working on this to think about us a little bit differently and to think about the problem. And this is what I learned from doing the review article. I decided to make this really simple diagram and envision this-- kind of like a front stoop of the house. You know the two steps coming in? And then I made a little teeter totter on top. And then I thought about the pressures or the force on either end of the teeter totter, and I thought the things that we have really focused on were asthma exacerbation and loss of asthma.

We were really focused on the risk. We were focused on the reasons not to do it. What I hadn't thought as much, and nor have other people, thought about these other factors. The cost, I thought about. But I haven't thought about medication side effects. I haven't thought about the treatment burden it is to take your inhaler and follow all these things I haven't really thought about patient family preference a whole lot when I've been doing this stuff. And I was kind of shocked when this happened.

In fact, a good colleague of mine was preparing a talk like this. And the talk was called "The Risks and Benefits of Stepping Down Asthma Medication." We were looking at it. The whole talk was about risks. And so, we hadn't really, again, given the two-sided thought. On the benefit side, there's only been one study that asked this question. And that study said that after you've stepped down, your quality of life looks better. And then I thought about all the potential side effects of some of these asthma medicines. In general, they're are pretty well tolerated. I don't lose sleep of overprescribing them to the hosts of asthma patients I manage. But there are side effects. There are immediate side effects, like hoarseness. But there are also side effects that may be less readily apparent, that patients wouldn't know about until they happen to them.

So for example, there's pretty good data that there is some growth suppression with giving-- if you give kids high enough doses of inhaled corticosteroid, there is some growth suppression. That's a risk. That's something we take into context when we prescribe or don't prescribe or what dose we use. But that's a risk. Patients wouldn't know that because they wouldn't know they're getting shorter until they got shorter. There's a risk of pneumonia, right? Probably a risk of pneumonia. We don't know for sure. It's somewhat controversial. But if you have an increased risk of pneumonia-- and especially in older population-- you're not going to know about this risk until you get pneumonia. And then, this whole black box warning thing is out there still. Whether that's a real signal or a false signal, eventually we're going to get some answers to that.

So we did some more secondary database analysis, this time with the Optum labs data warehouse. And we picked up some additional collaborators-- Ryan Johnson, Jeff Herrin. And we wanted to try to understand what factors help predict the patients that do well. So we're now into this mode where we want to do individualized risk prediction. The one factor that we pre-hypothesized-- the one that we thought that would matter the most-- is how long a patient's been stable before you decide to make this decision. So remember, the guidelines said three months. Wait three months until you're stable. And I talked to a lot of asthma experts out there. And they say, well, that doesn't make sense because it matters if they've been three months over their worst season. It matters-- I'd like to see them go through a whole year before I do anything.

And so, we really wanted to test that pre-step down length of stability as a factor. And Optum let us do that. This partnership ended up being very helpful for us. We were able to identify over 25,000 individuals who stepped down their controller medication by 50% or more, and had continuous data-- one year pre and two year post-- to really allow us to get some longer views of the asthma outcomes, and then to judge the asthma predictors beforehand. And we had the key data we needed-- pharmacy dispensing, the encounters with health care providers that allowed us to construct our definitions of asthma stability.

And this is one of our main findings. This is a time-to-event curve. And basically, what we did was we divided the cohort into four groups-- those who were stable for less than 4 months; 4 to 7; 8 to 11; 12 or more. And were able to follow them out over time to see when they first became unstable. And you can see this. And this particular definition for instability-- are no in-patient visits for asthma, no emergency department visits, and no systemic steroids. So that was our chosen end point. We have these charts for all kinds of endpoints. And I think you can see that the lines are clearly separate; and that it's on a dose gradient; and that those folks in the gold who are stable for more than a year are stable longer afterwards too; and that of all the predictors we've identified for predicting how well somebody will do within this observational data set, this one's probably the strongest. There are some other ones that came out as well.

So we concluded the length of stability beforehand influences the length of stability afterward. Again, sometimes I feel like I'm just confirming what other people already think and know, but this really hasn't been studied before. We really didn't know this before for sure. It just makes sense after you read the conclusions. Individuals and their providers can cautiously apply this data. This is some information that can be used. It's better than the vacuum that currently exists. And we're really focused now on refining and validating a clinical prediction rule that includes additional predictors that weren't available in our observational data.

So I'm moving on to summary here. See how I'm doing on time-- excellent. So I'm going to move on to summary here and leave plenty of time for questions and discussion. I'm going to go back to our learning objectives and talk about the things that I think are the take home messages. First, describe recent population-level outcome, cost, and trends. I think it's pretty clear from our data and from others that medication costs have increased in asthma. And the outcomes for asthma have been similar over the time-- the population-level outcomes in the US, I should say.

Quantify the risks associated with stepping down. I think there are some stepping down events that happen that are clearly associated with more risk. Those risks may be overstated in clinical trials and less apparent in comparative effectiveness studies. Those different ways of stepping down medication-- going from this level to this level-- may be different. And we don't know that for sure because there haven't been enough data points to really get confident estimates. I would say the overall data suggest that this is a reasonable option for patients with stable asthma in many cases, and that is happening right now. Regardless of what we're recommending to our patients, it's happening. And if we want to influence this in a positive way, we need to think of some creative ways of reaching these patients.

Second summary. So recognizing how these research methods that we've learned in the Health Care Delivery Scholars Program can be useful in answering some of these clinical questions. So I think our risk estimates are better now because we've done this knowledge synthesis. I think that's a nice contribution. I think through the comparative effectiveness research for the secondary database stuff is extremely useful for some practical risk estimates as well. I think also using the secondary database analysis and identifying predictors is getting us closer to an individualized prediction of who will do well. And I think our survey research confirmed and gave us some foreshadowing that we need to think about how to reach these patients because many of them are not in our offices when they're doing this.

And third, apply the lessons of an aspiring health services researcher to all of your own research activities. I don't know how well it'll translate, but these are the things that I learned along the way that I think were helpful. And these are things that are, I think, more general advice that probably all of you have heard already-- that within a program like this, having an active mentorship and somebody who's constantly looking over your shoulder is key. The formal coursework, which is one such course advertised here beforehand. The formal coursework and the methods through the CCaTS was really helpful to perform these studies. Because not only do-- because really, I need to learn those methods. Not my mentors, but I need to learn those methods so I can own them and know what the data mean and take full responsibility.

And then, learn by doing. So I learned the most by writing grants rather than listening to how to write grants. Talks. I learned by doing them. And then, team leadership by being responsible for leading teams. I learned that by doing, and I have a lot more to learn. And then, really the gist, the main point-- which is, I think, probably a commonly recited research truism-- is that you have a clinical question, and you want to try to understand what the answer to that clinical question is, the more tools you have to pick from, and the vary tools you have to pick from, the more likely you are to apply the right method to get your question answered efficiently.

Some of these questions we're talking about could be answered very nicely-- in large scale, comparative effectiveness, perspective trials, in randomized trials. But that's extremely expensive, extremely inefficient. And some of this other methods that we're talking about here can help us begin to understand this in a way that will lead to the definitive studies. So with that, I'd like to thank all of you for your attention. I'd like think mentors, collaborators-- named and unnamed. And I'd also like to formally think the Mayo Clinic Robert D and Patricia E Kern Center for the Science of Health Care delivery for supporting me during my time as a scholar.