Breakthroughs in Reproductive Health: Leading the Way for Personalized Fertility Medicine

Over the last few decades, breakthrough advancements in the field of fertility has helped many infertile couples start a family successfully. Innovations like non-invasive tests that can identify genetic abnormalities and multi-gene panel tests have brought personalized medicine to reproductive health. We are talking to reproductive endocrinologist Dr. Aimee Eyvazzadeh, embryologist and founder Dr. Piraye Yurttas Beim, and neuroscientist Dr. Alan Horsager, about how recent technologies can help physicians help their patients reach their family building goals in a more focussed way.

Full Transcript:

Shweta Mishra: Good evening and welcome to Cure Talks. I'm Shweta Mishra, your host, joining you from India. We are living in an era of personalized medicine where we are increasingly recognizing the value of right treatment to the right patient at the right time. Over the last few years breakthrough advancements in the field of fertility has helped many infertile couples start a family successfully. Innovation like non invasive test that can identify genetic abnormalities, multi-gene panel tests that have brought personalized medicine to reproductive health. This evening we are talking to Harvard educated reproductive endocrinologist, Dr Aimee, more famously known as the Egg Whisperer, embryologist and founder of Celmatix, Dr. Piraye Yurttas Beim, neuroscientist and CEO of Episona, Dr Alan Horsager about how recent advances in personalized medicine can help physicians help their patients reach their family building goals in a more focused way. My co-host for today's show is Emily Dubinfield who became a mom through surrogacy and blogged about her fertility journey at fieldfertility.com. I welcome you all to CureTalks. Dr Aimee, Dr Beim, Dr Horsager and Emily and I extend a warm welcome to all our listeners and I would like to remind them that we will be discussing questions sent in via email at the end of the show. So please email your questions to shweta@trialx.com and if you want to ask a question live, please press one on your keypad and we will bring you on air to ask them. You can also post your questions on could curetalks.com website as you listen to the talk. So I'll start with you. Dr Aimee, could you please set the ground for our audience by telling us in layman terms what the word personalized medicine mean in general and in the context of a infertility and why is that important?

Dr Aimee: Absolutely. So personalized medicine is when treatment is customized for individual patients and when we're using personalized fertility medicine it means that your doctor is digging deep into finding out as much as possible about you and looking at all your fertility factors and then taking all that information and developing a treatment plan based on what's learned. So rather than just trying treatment and seeing saying it's going to work, really finding out what your fertility factors are is the premise of personalized fertility medicine.

Shweta: Alright, thanks. Thanks. Dr. Aimee, Dr Beim you were on the front lines of the personalized medicine revolution during your doctoral work in embryology at Memorial Sloan Kettering and Weill Cornell. What was your motivation behind creating this multigene panel and Fertilome? And also tell us about the Say The F Word campaign and why did you start it?

Dr Beim: Hi .. so as you mentioned, I really had the benefit of being on the front lines of seeing personalized medicine, the way that Dr Aimee described it, really become a standard of care in oncology and the inspiration, for me to found Celmatix and for us to develop the fertilome test began really years ago when I realized that the same technology and the same paradigms, were really not coming to reproductive health. This was a time during which the human genome had recently been decoded. And the feeling was that in the case of oncology, they really had to invent the technology and bring personalized medicine to the field. So

oncology and personalized medicine really grew up together. My feeling was we already have a playbook, we have a path, oncology has really led the way, but we have to do is take these tools and just apply them to our field. And so to me that felt like something that was really important to do and I didn't see anybody going after that until I felt that it was important for me. Also on a personal level, the year that I founded the company, I turned 30. And like many women, I was using age as the primary guiding post of when I should start worrying and thinking of it more about my reproductive clock. And I had friends at that age starting to get married, starting to try to conceive and I saw that in their early thirties they were already struggling. And so I knew that, that from a technological standpoint, we could do better. And then from a personal standpoint, I knew that we had to, so that was what inspired me to start the company and for us to really start down the path of what ended up being over seven years of groundbreaking research to identify the genetic factors that to date have, in a clinically validated way showing the greatest association with different reproductive conditions.

And we're really proud that in 2017 we launched this task, we got full regulatory approval for it here in the United States. and, now that we're looking to scale this and make sure that every individual who really like Dr Aimee said wants to dive deep and really understand why this is happening to them or whether they're at risk for this to happen to them. We want them to have access to those answers. And we think that one of the things that is still a hindrance beyond the technology, beyond the fact that the fertilome genetic testing is now available, is that women still feel like fertility is something that they can't really talk about or even bring up with their physicians. So on the path to developing the test, we also did a lot of research and surveyed women, millennial aged women about how they think about their health, their reproductive health. And we were really surprised and also saddened to learn that over 60% of the women that we surveyed said that they don't talk to their friends about fertility at all, even though it's something that's on their mind. One of the statistics that we found just really chilling was that, one in five women in this population who had experienced a miscarriage had not even told their partner that it had happened. And so, I think for us, we realized, we saw a lot of the women's empowerment movements that have really been gaining momentum over the last year. And we said we have to, we have to do something. We have to create a platform to start removing some of the stigma that is holding women back from getting the help that they need, talking to their closest loved ones, or partners, and even talking to their physicians. We learned that a quarter of women and others have shown this as well, who are trying to have a baby to have not even been broached the topic with their Ob-Gyn. So we want women to proactively start taking control of their reproductive health and we want us to start a dialogue. So we started the Say The F Word campaign. It's a hashtag campaign. We also have a website called the wesaythefword.com and we are partnered with a number of other great allies including Maven and Progeny and we are pledging to donate a dollar up to $25,000 to women's organizations that were also partnered with, including Planned Parenthood, the Women's March Resolve, the Endometriosis Foundation of America. And so we're really excited just, in the first couple of weeks we've already had thousands of women pledge to say the f word and have started to really share their stories, including women who have shared, for example, that they haven't yet even thought about whether they want to have a family one day, but they certainly know they want the option. And so it's been really exciting to see from women who are experiencing devastating miscarriages, the really difficult journey of going through fertility all the way to women who haven't even yet, begun their journeys and we're starting to bring those stories into the light. And that's really exciting for us.

Shweta: Thank you so much for your answer Dr Beim. Dr Horsager I'll move on to you. Could you please explain what the field of epigenetics is and, and in what ways can it be related to infertility and what does the information that Episona provides the health of patients and their specialists?

Dr Horsager: Sure, appreciate your having me on the show and just to carry on with what Dr Beim was talking about if women's reproductive health is difficult, it is a difficult topic to broach, men's reproductive health is even more so in many ways. So I really appreciate what she is trying to do there. So we really got into this opportunity realizing that there was a real absence of ways of evaluating men's reproductive health. You essentially have the semen analysis which is looking at count, morphology and motility. So are sperms present, are they swimming properly and the shape of those cells is that does not look normal. And unfortunately that's a fairly poor indication of infertility. And there's actually been a growing body of work

and in epigenetics and specifically in reproductive health and men's health over the last decade or so, and genetics is, is essentially the study of a system of molecules that sit on top of the DNA to regulate which genes are active and inactive within that affect gene expression. So in each cell of your body, the genome is essentially identical, but the reason there's different cells do different things in and have different phenotypes is because of epigenetics. So different genes are expressed in different cell types. And then this normal molecular pattern that sits on top of the DNA that can be disruptive. And when it's disrupted that can lead to problems with health. And in our particular instance, we're looking at disruptions in the sperm and that we see are related to infertility and we see that manifest in two different ways. One is around things that might impact fertilization. And then even more interestingly, we see these disruptions happen in genes that are important for embryo development. So we see even if you do get to fertilization, successful fertilization, there's still maybe very big difficulties in developing the embryo properly to result in a pregnancy and a live birth that may be the result of a problem in the sperm genome. And so that's really how we inform, on the clinical process and the clinical treatment process is by understanding problems, first recognizing is there are problem on the male side, even if a sperm, a semen analysis, looks normal. And then does that suggest there might be problems with fertilization issues or might there be problems with embryo development and that helps clinics, clinicians politically guide their treatment.

Shweta: OK. Yeah. Thank you so much for your answer Dr. Horsager. With this I invite Emily on the panel. Emily Dubinfield please ask your questions to the panel.

Emily Dubinfield: OK. Great. Thank you so much. Hi I really appreciate this and I love what you're doing, what CureTalks is doing. So hi to all the doctors. So just really quickly, I really, really appreciate this panel and this topic today and I on a personal note really, really resonate with Dr Beim and Dr. Horsager with what you're saying about female infertility and saying that f word as well as male infertility. So Shweta asked me to be on the panel today because I am an infertility survivor, if you will. I have a miracle baby who was born via surrogate. She just turned three years old, but six years ago we started on our path to have a child and like so many of your patients then I know so many of your listeners, my husband and I were doing everything right. Young, healthy couple, I was 30 years old, had a regular period and we could not get pregnant. And at first, my husband went in for his sperm test. This is now six years ago, and it looked like he was the problem and my husband was devastated and later doing a lot more tests turned out he, you know, the issues on his side were solvable and I was really, really the issue. Extremely challenging and so I've put together a bunch of questions that come from my personal experience,, in hopes that a lot of our listeners today will resonate with it. So thank you guys for being so open and being here today and I have questions for each of you. I'm gonna kind of jump back and forth, but I love to create this and have this be as interactive as possible. So if I ask a question to one of you and somebody else wants to answer, please jump in and we'll go for the next 20-ish minutes or so. And then I know Shweta had some more questions at the end. So Dr Aimee Hi, happy to be another Cure Talk with you. So I mentioned just a few minutes ago that, when my husband and I were going through infertility treatments with through three years of it, but we're now going back three to six years and I know so much has changed in the field of fertility, in that time just in my time, but I'm really curious and I'm wondering if you could further help set the stage for the panel discussion today of how have you seen the role of new technology changed from when you first started practicing to now?

Dr Aimee: Yeah so I've seen tremendous changes. I've been practicing now for 10 years. This is my 10th year in practice since graduating from infertility fellowship. So you can imagine all the things that I've seen starting with changes in the technology and for those of you who don't know what PGS, that's where you can check an embryo to see if it has a balanced set of chromosomes. And we've seen that technology going from ELISA to now NGS or next gen sequencing. So, imagine using a magnifying glass to using a microscope, that's kind of the analogy that I use were still not a 100%, but we're, we're getting closer and closer so there are patients that I can say that I can help today that I wasn't able to help even let's say two years ago in 2016. So it's the development of tests like Episona, Fertilome that have given me information about patients that I would have never known that I could have had in the past that having today has really helped a lot. So for example, being able to have a personalized transfer window through testing on someone's lining. That's the air ERA test or the test looking at their endometriosis. Also carrier screening technology, we were doing genotyping in 2008 now sequencing and then more recently looking at

mitochondrial DNA levels and in the embryos and measuring that and being able to give someone their implantation rate of success based on not just how they're embryo look and the chromosome, but also about how much energy an embryo has. So all of this together has really made tremendous changes in how we can take care of patients and has really moved forward the field of personalized fertility medicine because without these tools it was just really just trial and error, just do this and if that didn't work and try this, but that didn't work. But now with this technology we're able to just kind of change how you approach patient care and it's really awesome and exciting.

Emily: Yeah. Thank you so much for sharing that. I think for all the men and women who are listening today and thinking about their hopes and being hopeful and just knowing that medicine is advancing all the time. It's just amazing for you to think that you couldn't help the patients 2 years ago that you could maybe help today and that makes you think of what you could do and a year from now. So I think that there's a lot more hope. I know I really felt that, 10 years ago my husband and I wouldn't not have a biological child. So it's, you know, really impressive and everything that's going on and I'd love for you to take another minute and maybe expand a little bit about your particular practice, and also maybe among your colleagues too. Are you seeing other reproductive endocrinologists hesitant to implement some of these new tests or whatnot? Or what about your clinic? It sounds like you were super embracing all of this, but I'm just curious as a patient and figuring out what doctor to go to what should they be asking and what's your clinic doing that you think is maybe standing apart from the rest or from some of your other colleagues?

Dr Aimee: Yeah basically I coined the phrase called the Egg Whisperer diet and no it is not a diet, I am the worst cook, it is not a recipe for something, it is a really simple approach that all patients can take when thinking about their fertility care so it's really easy, so D stands for diagnosis. When I really dive deep using all these personalised fertility medicine tests that we've talked about. The I stands for IVF or you don't need to do IVF, you can just do treatment . The E stands for endometrial testing before transfer and then the T is transfer. So I can just talk about this Egg Whisperer diet then patients everywhere can realize that these tests are available for them and then they'll be in good position to be as successful as possible and have less heartache before they, less heartache and less trauma because we all know that fertility treatments that don't work, it's really, really stressful when that happens. So my goal is, by finding out early what treatment is best for a patient, they can then do things on their own without anyone's help. But I know it's hard to believe that a doctor would want to see less patients and do less treatments. But I totally do, like I tell patients, I want to teach you what it would take for you to get pregnant at home without my help so that if I ultimately need it to help you with, let's say, IVF when the best position to be successful. So for example, look at the Episona test and we learned that a man sperm quality is low, we see what the issues are, then we can put them through a sperm fitness challenge that could possibly help, let's say supplements, exercise, simple lifestyle stuff like no pizza and beer and stuff like that.

And then whenever we end up doing treatment, if we end up ultimately having to do IVF, we know that we're going to have more beautiful blastocysts that we won't look back and say, hey, why didn't we know this up front before we just spent say $20,000 plus on a failed cycle. I wish someone would have taught me this up front and that's my goal. I want to talk to people about what all the tests are that they can do ahead of their treatment. They can get themselves in the best shape of their lives, be really informed, going forward, do enough cycles so that they have the embryos that they need for their future family so that they're going into it with all the knowledge and information they need for them.

Emily: I think that is so well said and if somebody who's so open about her infertility journey and surrogacy journey. I have perspective, parents or people who are struggling to conceive all the time coming to talk to me and I can't tell you. I mean, just this week I've probably heard people complain of, I wish my doctor had told me this or, now this new doctor is telling me this or, and this is now within the last 2 years, so I love the DIET explanation. Are there certain things you would say to somebody when they are first with you, I know it's a little off topic, I just want to go there. So I think it's such an important nugget, are there some key questions that people must be asking when they start with their fertility doctor?

Dr Aimee: No, the first question I ask my patients, the first thing that I ask when someone sits in front of me,

I say, what do you think is wrong? Because people have a really good gut feeling. Like I have when I feel like there's something like I'm attacking the embryo and I know that for some doctors that might not make them feel comfortable, but I can tell you through the tests, like Fertilome, I can say, wow, I just looked at your fertility gene test and you're right, there's so much going on with your immune system and if I didn't have this test, how would I know what to do? How would I know what tests to do, what to offer you? And so that is actually one of the first questions that I ask people. And then the other thing is it's not just about eggs. So it's just three things, eggs, sperms, tubes. So I look at everything because you can't go to donor egg and then never have looked at the sperm and just assumed everything was going to be great. And then you find out that from, like you shared was an issue that could have been addressed like years ago. So that's kind of my approach – really listening to the patient, doing focus tests on what they bring to me is what they feel the issue is, and then ultimately look at everything and not ignore something like a Fallopian Tube, even if you're doing IVF, because we know that having a hydrosalpinx for example, or having scar tissue in the uterus can affect the success of future transfers.

Emily: Right. Absolutely. Thank you for sharing that. And you dive perfectly into I'm going to jump back or I'm gonna jump over to Dr. Beim. Thanks so much for being here. And I know Dr. Aimee, you were just speaking a little bit about the Fertilome tests and Shweta mentioned it to at the beginning and I know this is your test and I would love for you just to take a little bit and tell us more about what it involves and why should women talk to their clinics about having this multigene panel done. And some are like Dr Aimee, but perhaps others aren't. So I'm hoping you can arm our female patients with this information today. So I'll let you take it from here.

Dr Beim: Absolutely. So, I think you really hit the nail on the head earlier by saying that you've had so many friends come to you and say, I just found this out or I just went to this other doctor and, why didn't I know this earlier in the process? As you know infertility treatment it's hard on your wallet, it's hard on your marriage, it's hard on your emotions, it's hard on your body, right? Yeah. So if you're about to go into battle, and you want to come out on the other end with the outcome that you're hoping for, for all of that investment across the board, our feeling has always been from day one, why wouldn't you want a very personalized biological level view of what is going on with you? So, Dr Aimee mentioned that differences in genes related to immune function, for example, are covered on the panel. You really want to know of the genetic factors that have been clinically validated to date, so of the things that we know the most about in 2018, why wouldn't you want to know that before investing all of the other time and energy or all of the follow-up diagnostic tests. There's dozens of tests that can be run on you. Getting a genetic level view of what maybe going on under the surface also can help guide you to the first diagnostic tests that you should invest in. And so I think doctors like Dr Aimee, I think they have it exactly right that they want to get that full picture. And so what's great about the Fertilome test is that it's a simple blood or saliva test that can be taken any day of your cycle and it's done in a physician's office and what it looks at are the genes that have been associated with gene alterations that have been associated with the most common reproductive conditions. So a woman taking the test can learn if she's at risk for a condition like PCOS, endometriosis, recurrent pregnancy loss, premature menopause or also gain insights into the genetic factors that may be contributing to unexplained infertility, which it sounds like your infertility fell into that category for a while after you guys had realized that, it may not just be on the male side. You started to dive deeper on your side. And so what we want is we want people to get there faster and we know that a lot of unexplained infertility, for example, is endometriosis that's gone undiagnosed or not all PCOS is cookie cutter. Women can be right at the edge of where their hormone levels look borderline or normal, but it may be that they're actually in a much more accelerated path to a diminished ovarian reserve. So they may not respond as well to fertility drugs or they may get pregnant easily in their first IVF cycle, but when they come back in two years or three years and they want to expand their family, they may get the bad news that they already have such low ovarian reserve that they're not going to respond to treatment.

So it's about giving women the power of that information up front. And so we want women to be empowering themselves with this information instead of, some physicians, they take the approach of, well, I've tried everything and I truly don't know what's going on. I'm going to try to Fertilome test. So there was a really interesting story of a woman who shared her story with a journalist recently in an article that was very

touching to hear. She had experienced seven pregnancy losses, including 4 failed IVF cycles in the process and finally got to a physician who said, we have the same tests called the Fertilome test. He ran it. He saw that she had an alteration in a gene that was really important for the process of implantation and he changed a simple thing in her protocol and she now has her first ongoing pregnancy. I have gone through one devastating pregnancy loss and when I read her story, I was moved to tears, my husband saw me crying and said what's going on? And I just shared the story with him and he was very moved too because I just couldn't believe what she had gone through and how easy it was almost to like have that insight, make that change and then she was able to get pregnant. And I don't want to say to people, Oh, if you take the Fertilome test, your doctor is going to know exactly what to do. That's not what I'm trying to say, but to Dr Aimee's point, the needle moves every single year. And so, something that wouldn't have been possible just a few years ago is now possible. And so it's one of those things where no test, the Fertilome test, no doctor can give you all the answers, but what we can do is we can keep moving the needle forward. So this is a patient who the system was not meeting her needs for years. And then this new test came along and in her case, that's how she was able to get there. And so we want physicians to be embracing, the best technology that they can possibly be offering the patients right now who are walking in the door.

Emily: So well said. And I can't tell you how many people I know who have gone through years and years and years of heartache and then find out, oh my gosh. And so, thank you for sharing that and sharing that story. I think it can resonate with so many people who are listening are going to listen to this. So actually, just to add a little bit onto my personal story too, I ended up, fairly early on just through blood work, through AMH and FSH, follicle count, being told I'm in early menopause. I was 30 years old and so that was a huge part of our infertility struggle. Um, and it was just through the ultrasound and two blood tests that came when my doctor wanted to run all these tests on me and I was like, what are you talking about? My husband's the problem. I'm fine, I'm young, I get a period, I know flow and I was really shocked to find that out and IVF hardly ever worked. It's a miracle that, our daughter is my egg and we didn't have to have a donor egg. But I'd like to take a moment if you will, and talk about how your tests, compliments maybe those blood tests or how it does it even better, how does the Fertilome better diagnose if you will, let's say early menopause in my situation or PCOS or endometrial issues?

Dr Beim: Absolutely. So, I think you used the right word, which is it compliments, so we're not saying that genetic risk factors should be replacing other tests. But it helps you, again, focus on which tests you should be giving to a woman and maybe when in her life. So let's say premature menopause, which is the example that you gave and it's one that I can relate to because I also, in my early thirties, I was struggling to conceive, I had just experienced a devastating pregnancy loss. And then, during the course of getting a workup found out through the exact same set of tests that I was also on the road to early menopause. And that was a devastating diagnosis to have in your early thirties when again, like you said, I had a completely normal cycle and I thought everything was fine. And so fast forward I was actually one of the first people to take the Fertilome genetic test. It's something I dedicated almost a decade of my life too. So I went into be one of the first people to find out, and I tested positive for one of our premature menopause markers. For me, it was such a healing experience to test positive for that marker and it led me to speak to my family and learn that my paternal grandmother may have gone into menopause early. And that's something that, I mean, who has talked to their dad about when their dad's mom went into menopause, like, this is something where here I am an expert in the field and I never had that data point about my own medical history. OK. So, this is something that it helped me feel, like it wasn't my fault anymore because I felt a lot of guilt and shame when I got that diagnosis and I felt very guilty that it was "my fault" that we were having trouble. I beat myself up about what I did to make this happen and so to find out that actually I was like wired to excel at a lot of things, but it turns out that my ovary was on the end of the spectrum of humanity, of not functioning for as long as other women. And so, what me and my partner were able to do with that, me and my husband is we knew we wanted to have a bigger family and we knew that we had to make this the number one thing in her life. So, we really focused on trying, we didn't leave a lot of space in between our babies.

And so that's how I was able to action on that information. Now, what was interesting in my case is that my AMH test, which I ran through my Ob-Gyn, I got a message from my doctor saying all, your hormone tests were normal. And this was around the time when we were struggling because I really knew the data,

because of my work with Celmatix. I said, but I want to know the number, and she told me the number and when I got the numbers, that's what I knew I had to see a specialist because I knew that it was the last point on the scale that was considered normal for any woman. And there I was at 32 with that number that would have been normal for a four year old but was not normal for a 32 year old. And so that's kind of when we went into the process and learned that if we were to go down the path of IVF, it was very, very unlikely to work because I would not be a good responder to hormone stimulation, etc. So very similar to your story. So what I think women can, well first of all, I think these markers have great utility for someone who's at the beginning of their infertility journey where, for example, we hear a lot that women are so eager to just get to a pregnancy. Just great. We have an embryo, let's go for it. We've waited a long time for this and what we're seeing physicians are able to do is to get women to just pause for a minute and say, ok, I know you want this pregnancy. I know you want it next month, but you have this marker. you've got borderline hormone levels. I'm worried. I'm worried about getting you pregnant right now. Or I'm worried about getting you pregnant with non-IVF because what I can't do if I get you pregnant with clomid or injectables and IUI is I can't then save embryos for when you come back to me and a few years. So what we've been seeing, women who know that maybe right around the corner, their cliff is much sooner potentially than other women. They can then be much more proactive and put more embryos away. So we see that. We also know that if we can get this information to women earlier in their lives, then they can adopt a healthier lifestyle which we know that a certain lifestyle factors like smoking, things you put on or around your body and that you're exposed to, can accelerate ovarian decline. So if you already know you're wired to be on the early end of ovarian decline, there are actions you can take earlier in your life to try to give your ovary it's best chance. Just like if you know you're at risk for cancer, there are actions you can take lifestyle wise. For some women they can freeze their eggs, where they can freeze more eggs, maybe then they were planning to originally, they can try to conceive earlier than they had originally planned. And importantly they can start to plan financially. I think one of the things that makes the process so devastating for people is that they are blindsided by it. It's like the blindsided by a mortgage, like, hey, I know we were fine and then I just found out that to have anywhere to live, I have to come up with a mortgage in a month. How do I do this? And so…

Emily: Right but the means of a mortgage you do sort of know I think the hard part in fertility treatment as you go, I'll have to do one round of IVF. Well, three or four rounds later you find out it didn't work, and you don't know that it doesn't always work.

Dr Beim: Exactly. And I think for somebody who knows that they're likely going to need to go down that path and now we see women who are literally changing their job because they tested positive, they know that it's either going to be much harder for them than the average woman to have fertility treatments work for them or to get pregnant on their own or they need egg freezing and they're going to work for companies that are, they know have great egg freezing benefits or have great fertility benefits and if you know earlier in your life, you can start to put money away like you do. You start as a parent, you start planning and saving for college if you know that you're at risk for this kind of stuff, then there's actions you can take. So I think that bringing us out of the zone where there's this one size fits all, 30, 35, 40, these are the age points that a woman really seizes landmarks in her life. A lot of women, those landmarks for them are 20, 25, 30 or 25, 30, 35. And so having the information that they have that genetic risk, while again, it's risk, if you don't put a seatbelt on, it doesn't mean you're going to die in a car crash, but it's a risk. If you smoke, it doesn't mean you're going to get lung cancer, but it's a risk. And having these genetic markers are a risk as well and we think it's tremendously empowering for women to have that information earlier in the process.

Emily: So talking about earlier and Dr Aimee I want to bring you in for a quick question and Dr Horsager I know, I know you're still there, I want to get you in one quick second. So when you talk about earlier and also because if we're gonna be a candid question to you in a second about the age. So men and women, we know we want to have children both sides. So we have tests like the Fertilome test. I'm going to start there, Dr Aimee do you see that this is something that Ob- Gyn should be doing with women of what age and Dr Beim, what would you say about that in terms of ideal age for women to get empowered and then Dr Horsager I want to talk about also for men to get empowered, or is this really something that only fertility doctors should be administering? So if we could just get maybe two or three of you to comment on that and then we can go from there.

Dr Aimee: So what I would say is that I strongly believe that every woman should be offered to have fertility health check up, not just once in her life but many different intervals in her life – when you are starting birth control pills, get a fertility health checkup, when you're going in for your birth control pill reset after a year, when you are getting your IUD placed, when you're coming back for your postpartum check, get a fertility health check-up. These are all opportunities to learn about this precious commodity that we call fertility. And the thing is that women are seeing their Ob-Gyn. So the more we can teach them and empower them and engage them, the better, they should be offering.

Emily: What is that checkup?

Dr Aimee: That checkup is getting your fertility levels checked. Getting a fertility history done, talking about your fertility risk factors, endometriosis, fibroids. That's what it is. It's a thorough infertility questionnaire, most of the Ob-Gyns already had those questionnaires in their office as many of them are using electronic medical records systems. So they have a question here already and then if, if someone doesn't know the answer to the question, then you refer to your local fertility doctor, reach out to someone that you can trust and run a patient by. So that's a lot of that Ob-Gyns do around here. They have a question they call me, I'll answer them, they'll send their patients here. But if someone let's say isn't comfortable doing a fertility health check-up, any reproductive endocrinologist in their area is fine.

Emily: Do you have anything you want to add in terms of like ideal age for knowing more about your genetics?

Dr Beim: Absolutely. I couldn't agree more with Dr Aimee, I think one of the overwhelming feelings I felt and that we hear so many women feel is, I did what my job was. I showed up at my Ob-Gyn every year since the age of 14. Like I did my work, and so I would understand if I had neglected to go to an Ob-Gyn for 10 years, why this would be a surprise to me at 32 that I'm already headed down the path of premature menopause. What makes so many women feel so cheated is that they did everything right. They showed up, and then they still got blindsided by this. And so I agree. We do have to empower Ob-Gyns to start the conversation. It's one of the reasons that we have started our F word campaign is that we want Ob-Gyns to realize that their patients don't feel empowered to broach the topic. And so maybe they need to nudge a little bit and we believe that any woman who is already experiencing infertility definitely should have a Fertilome test. But we think that anybody who has a family history of infertility or reproductive conditions that can lead to infertility, like endometriosis or PCOS should also have a Fertilome test. And I think the paradigm that Dr Aimee is talking about where family history with respect to fertility or reproductive condition should be worked into that abnormal recurrent consultation when women are considering egg freezing, they should have a Fertilome genetic test. And importantly, any woman who, as part of her life plans, is as plan A, you know, that's her plan is to postpone kids she should have a Fertilome test. This is a thing that women should have this information as a baseline just so that they realize that the real power and proactively managing their reproductive health is not just postponing having children, not just having an IUD put in or having that whole prescription. But really thinking about the other end of the coin. A lot of women assume, OK, the default setting is fertility and I need to focus on not having a baby too early before I'm ready. And then when they're ready, they say, ok, I'm off the pill for a month, restore the default setting. And then they get very frustrated when they realize maybe it wasn't a default setting and maybe being on the pill while it didn't cause their infertility. Maybe it masked years of reproductive conditions. That now they've added maternal age as an additional risk factor on top of that. So we actually think that this should be in the Ob-Gyn because we think more women should have access to this information earlier in their life.

Emily: Thank you so much. So, Dr Horsager, I would love for you to comment on kind of all of this and how the egg, if you will, there's so much focused right on women of being able to carry and egg and the egg is so important. But as we know, sperm is so important and it's also something that a lot of men are really ashamed of. And, I know when our doctor and let us look at my husband's sperm under a microscope and you could see like multiple tails and multiple heads, who knew that from could be so funky, if you will, for that, nonscientific term. So, with your Episona test, and how all these at-home tests are becoming really mainstream. I know we've got our 23andme kit for the holidays. So if you could just spend some time and

educate us all about sperms, the importance of these tests and at what point a man or a woman should tell her husband or if you will, about this and the importance of it.

Dr Alan Horsager: Sure, sure. One anecdotal comment to make is that PCRS last year, it is our fertility conference held in spring and I can't remember already but there was a reproductive endocrinologist speaking and they were commenting that frequently the couple, the male partner, the first doctor they see in their adult lives is a reproductive endocrinologist. He went on to say men don't go to doctors really at all. There's a clear, unless there is a broken leg involved essentially. So I think we have a, we have a unique problem on the male side were educating and engaging them I don't think can only be done through the clinic. I think there is a big effort that needs to be done online where I think men do, still do quite a bit of research and, and I think would engage in their health more at least in the privacy of their own home. So that's one thing that we thought was very important to be able to provide our test beyond the clinic. So we actually have the opportunity for patients if you will, or users to access the test through our website. It's very much like a color genomics test where they order it, it's still physician reviewed and then it's approved and it gets run through our lab and then they get the results. And then if they are working with a physician, those results are then passed on to the position as well as the patient. But I think men like to stay in the privacy of their home and we wanted to really tackle that, I think one take it to it up a level two. I think one thing that's not Just thinking about how sperm contribute, if it's, I don't think it's always appreciated that that 50 % of fertility problems are at least are partially or wholly responsible from the start. I think everyone really equates reproductive health and fertility health with women's health. And I think that's certainly changing. But it's in the way that it's been historically thought of. Certainly to some degree with the physicians, but certainly with the patients too. So that's another thing that we are really engaging in as it's trying to build an educational platform to help people understand how men's reproductive health fits in the overarching theme of fertility.

Emily: Yeah, I think that's so, so important. And everything you've said, I hear a lot of two and in the community we're in, if you could dive even a little deeper into it in terms of what is revealed on the test and are you just seeing the tests come into play at the point of a couple trying to conceive or you trying to educate men earlier, kind of like with Dr Beim was talking about.

Dr Horsager: Yeah, I think. So the way the tests, what we do now is we look at a specific type of of epigenetic mark called DNA methylation. And so that DNA methylation, of course, there's a normal pattern. We look, we have a fertile baseline that we compare to each individual patient to, and then we look for deviations from that pattern. And we looked in about a, well, we looking at essentially hundreds of genes frankly. But, we, we currently reporting on about 24. Those 24 genes are broken up into two categories of genes that are associated with a sperm function. And that's everything from spermatogenesis to capacitation to the actual fertilization of the egg and then there's a whole other category where we're looking at embryo development. So that's the actual proper development of the embryo as well as the, essentially the immune profile of the immune system of the embryo, which is important. So we really looked at those two categories.
We're really trying to understand, ok, if, if there are problems with sperm function, maybe you want to get that patient to IVF and specifically to IVF ICSI, where you're injecting sperms straight into the eggs, earlier in the process. And then if there are problems with embryo development, it's essentially a counseling tool for the most part where you're letting patients know this could be a more difficult road, it might take longer. So they understand what might be causing their problems with IVF if they're unsuccessful, but there, there is some evidence that suggests we might find some ways around it. So we actually have a handful of interesting cases where we've abnormalities in a gene and gene set that's involved in the development of the embryo and there is some thinking that this might be something that's causing recurrent pregnancy loss at least in a subset of patients. And we've touched on a few patients this way now and there is one, we have a video on this, so if you go to our website, you can see a nice patient testimonial. They had gone through several rounds of IVF which were unsuccessful. They then moved onto a surrogate, with an egg donor and, that was still unsuccessful. And then they did our tests and they found that there were problems with the immune system, that gene that we think is helping with the immune system development of the embryo. And so that patient was put on a light immunosuppressive, well the surrogate was and the husband's sperm and an egg donor, they would hopefully able to carry to term and they had twins. And this was a patient of Dr

Aimee. So she can certainly certainly chime in here, but that was a very compelling use case for us. So that's something we're exploring more deeply. And, we have an abstract submitted to tPCRS this year, but, that's something we're going to explore it and publish on later on.

Emily: I think that's a great point and I'm really glad you shared that and I think that's sort of a consensus among every one of these tests and what they can reveal. And I know we're getting into some of our final moments here and I know Shweta has a few last minute questions, but I want to start with you Dr Horsager, in terms of, the crystal ball if you will, or what you're looking at. I have a three year old daughter, a little miracle baby. Can you help predict what fertility will be like for her and 20 years if you will, like what is going to be available to this generation from your perspective and I want to just kind of rapid fire this. So like a quick minute answer from each of you, Dr Beim and Dr Amy. So I'll start with you Dr Horsager.

Dr Horsager: So I think I'll take it from the sperm epigenetics. I come at this from a neuroscience perspective. So I came at it because I was very interested in these epigenetic alterations that occur in sperm. How are these ultimately inherited across generations. Can this help us understand disease risk in the offspring? And so if you look at the literature is actually developing support for this idea that the changes in sperm epigenetics might actually help you understand or predict risk of specific neurodevelopmental diseases such as autism, schizophrenia and bipolar disorder. So that's something that's particularly interesting to me. And then also I think in terms of other disease, there's allergies, so there's some interesting evidence that suggest that allergy might be an interesting target as well. So I'm imagining that you have an analysis done on the sperm and then you can begin to understand what diseases your offspring might be subject to.

Emily: Thank you. Dr Beim I'd like to ask you 20 years from now, what's the fertility field going to look like?

Dr Beim: 20 years from now every woman who's on the pill is also going to have something spiked into her pill formulation that's going to protect her ovarian reserve and protect her fertility. So that she's not just postponing it, but she's also protecting it. 20 years from now women are from their earliest Ob-Gyn visit are going to know what they're at risk for and they're going to get a personalized fertility plan, that's going to be unique for each one of them. It's going to involve some interventions in some cases sometimes it's about managing lifestyle sometimes it's about just closely monitoring things. But they're going to feel in charge and they're going to look back at us, like, I look back on my mother who tells me about how she couldn't go to the grocery store and buy pads, to me, I just couldn't do what? You have to make your own path, it sounds like it's like the wheel hadn't been invented, and I think, your daughter's going to look back and say you went through what mom? And just, that's what gets you out of bed every morning is to bring that future to a reality.

Emily: Amazing. Dr Aimee?

Dr Aimee: I would say that my, my dream would be in 20 years from now, that there will be no such thing as needing an egg donor that women aren't going to worrying about. Yeah, I would like to. I mean, I want women to be their own egg donors, but I predict that we will have technology where we can generate an egg cell. I guess I'll use the word artificially and we're gonna see genetic testing and modification revolutionized how we take care of people. So there are a lot of things that we're going to laugh about that we did 20 years ago in 20 years, especially surrounding how we mature eggs potentially outside the body, how we want to potentially go through an egg freezing the future. But right now this is the best that we have and we need to take advantage of.

Emily: Absolutely. Shweta I want to turn it over to you to make sure we've answered all the questions we need to for today.

Shweta: Thank you Emily. That was a great round of questions that you had. Dr Beim I want to come back to you and ask you about your future research initiatives that you are involved with right now. And also if you could share some ongoing clinical trials around these tests that people can participate in.

Dr Beim: Absolutely. So we're not ready to share the details, but one of the things that we want to be doing in the new year is to be taking these success stories that we're hearing from physicians who are using our test where they are trying, like the story we heard from Dr Horsager where the Dr Aimee's of the world are creating novel protocols, novel ways to attach these genetic insights to moving the needle forward for these patients. And we want to leverage the amazing research network that we've built. We have an initiative called the personalized reproductive medicine initiative that's brought together over a dozen of the leading, infertility centers and academic centers in the US. And so we want to leverage that network to start making those linkages and moving these stories from one or two Fertilome babies as we call them here to really making the standard of care. So in the past, BRCA testing was not standard of care and breast cancer. Now we couldn't imagine not having that as a tool in the toolbox. So we'll be working on that. And the other things that we're excited about are also expanding and really starting to move into, trying to understand the male contribution and trying to move upstream. One of the things that we're noticing in our research is that a lot of the genetic factors that make it more likely for you to have an infertility condition or have trouble establishing a pregnancy also put you at risk for successfully carrying that pregnancy to term without complications. So things like preeclampsia, etc are very much in our line of sight at the moment because they're also related biologically.

Shweta: Ok thank you. So would you also like to comment on the clinical trials that people can participate in, in this field?

Dr Beim: So what I will say is, keep an eye on our website. We will be making some announcements soon. We were really excited last year to partner with 23andme, I think that came up earlier and the genetic testing company on launching a fertility community right now. We were oversubscribed and that was amazing. We were oversubscribed for that study and we're now tracking those women across 18 months. And we'll be announcing more studies that people can participate in later this year.

Shweta: Alright. Thank you for the answer Dr Beim. Dr Horsager I would like to ask the same question to you about the clinical trials that are ongoing around genetic tests that men can use and participate in those clinical trials.

Dr Horsager: I think I probably don't want to give too much detail, but we are looking at a couple of different interventions. One being a surgical intervention and one being a drug intervention. So I guess I would say if people feel like that would be beneficial for them to participate in a clinical study with us, we'd be certainly willing to talk to them and talk to their physician about their participation. So, right about that.

Shweta: All right, thank you so much for your answer. And I guess we have some questions on our website from the listeners so I'll be asking them. The first question says we have two kids and want another one, but we are having a hard time conceiving since last year. Do you think these genetic tests can help us in any way? Dr Aimee you can start with an answer and then Dr Beim and Dr.Horsager can follow.

Dr Aimee: Absolutely. I mean what I would say is it's a bumper sticker. I'm just joking and don't necessarily have it on my car, but paternity doesn't equal current fertility and so just because sperm was awesome when you had that baby, things can change. Things can change with our egg counts as we age, just like things can change with the sperm. And the other thing that patients find surprising is when I say let's do Fertilome and they say, but I've had two kids. I say this is genetic information. Things can change as you get older. Just because you have this gene doesn't mean that you're not going to have problems now, years after you had your first baby. So I think that there definitely is value. They'll still do a full workup even if you didn't have problems with baby number one, and that's one of the greatest fertility myths, is that if you didn't have problems having baby number one, then you should have an easy time having baby number two, and I think people spend too much time not getting tested because they believe that myth so with these tests, people can get their answers sooner so that they're not frustrated at home wondering why things aren't working.

Dr Beim: The other thing that I'll add is that some of the conditions and the risk factors that are genetic tests test for are things that get worse as you get older. So for example, we talked about the immunological issues. So we know from the autoimmune disorder world that sometimes age can contribute and that women can have issues that maybe are very subtle or undetectable. And maybe in your case, you were younger, and so whatever those subtle differences in your biology where were kind of patched over by the fact that you didn't have advancing maternal age as an additional factor, but then as you got older then maybe, that was like the extra straw that broke the camel's back, if you will, on a reproductive condition. And so I still think that even if you didn't have trouble getting pregnant with your first or your second, if you are struggling now, you are older now. It's still worthwhile to understand biologically under the hood what could be going on.

Dr Horsager: If I can just jump in there I think the one thing that's not well appreciated to is paternal age, a paternal age is an absolute factor and we certainly see epigenetic changes as a function of paternal age and these changes are definitely in regions that are important for fertility. So yeah, I have anything that's Dr Aimee and Dr Beim had said and I wholeheartedly agree with them. And this is represented also on the male side.

Shweta: Thank you so much for your answer. This is one question that just came up on the website and it says, what is your vision of in-vitro gametogenesis, do you see as possible in the future? And if yes, in how many years? There is a similar question – could you please give your opinion about the news from some days ago about oocytes grown in a lab by a UK team. So what is your vision about in-vitro gametogenesis is the question? Do you see it possible?

Dr Aimee: Yeah I mean I do see that's possible. That's that kind of what I said in 20 years, we won't have the need for egg donors, we would be able to take, let's say a skin cell and be able to convert it into a mature egg cell. So I do see that happening, but not for not anytime soon and as far as the story on being able to mature eggs in vitro, 3% of the eggs that they were, that they were able to turn into an abnormal mature eggs. So we're a long way off, but that study was extremely futuristic and that stuff excites me because if people don't realize it because eggs are actually extracted or ovarian strips taken from women who were undergoing a c-section. So they didn't even have to go through IVF. So I thought that was so, such a fun study to read.

Dr Beim: Yeah. And just to add to that, I did my PhD in egg biology effectively and I share Dr Aimee's excitement and I think we need to be investing so much more funding in the private sector and government funding into pushing this work forward. I know so many of the lead scientists in the field who have literally had to retire early or become cancer researchers because there's no funding for this research. And importantly that study was out of the UK. And so I think one, it's exciting and it's exactly why we should be doubling down on research. But two, I do hear sometimes from physicians that they worry when these really exciting stories gets so much press that then it discourage patients from taking advantage of the best opportunities that they have today to start their families. Maybe they are reluctant to move on to egg donation or to surrogacy and they see articles and they think, oh, I'll just wait until this new technology is ready for me and I think it's just really important with Dr Aimee said to point out that while this is very exciting, these are baby steps. And this is not something that I think will be solving somebody's fertility difficulties in the short term.

Shweta: Dr. Horsager would you like to comment?

Dr Horsager: Just a small comment too, and I agree that this stuff is pretty far out, but nevertheless it is very exciting. I think another area that's been very exciting is the CRISPR technology where you can actually do editing of the genome. But there's no evidence now that suggests that you can actually do editing of the Epi-genome, the DNA methylation as well. And so I think at a certain point you're trying to optimize your gametes for fertility, it might be that you could do the editing straight on the cells and they get them ready for optimal fertility.

Shweta: Alright. Thank you so much for all your answers and I guess it's time that we wrap up this session. We are already above our scheduled time, so thank you Dr Aimee, Dr Beim, Dr Horsager and Emily for your wonderful and very informative discussion and thank you for taking time out from your busy schedules to share all the knowledge with us today. It was a pleasure having you with us today and audience I thank you for your support and we look forward to having you all join us for our upcoming CureTalk on Endometriosis in March, the Endometriosis awareness month. And, if you would like to propose a talk for fertility or if you would like to be on one of the fertility talks, please email me at shweta@trialx.com . For more information on upcoming shows on CureTalks, please visit our website, curetalks.com. Thank you everyone.