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Cicero Diagnostics

“Infertility and Beyond! Cicero Diagnostics makes endometriosis easier to detect and helps resolve infertility issues even when IVF isn’t the answer”



Christopher Jackson
CEO & Founder

Cicero Diagnostics, Inc.
www.cicerodx.com

Contact:
Chris Jackson, President & CEO
Cicero Diagnostics, Inc.
800-795-5385
cjackson@cicerodx.com

Interview conducted by:
Lynn Fosse, Senior Editor
CEO CFO Magazine



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- Christopher Jackson

CEO CFO: *Mr. Jackson, what is the idea behind Cicero Diagnostics?*

Mr. Jackson: Our company is focused in the fertility sector of healthcare, providing new answers to help reproductive specialists and their patients better understand the potential causes of unexplained infertility, failed IVF and recurrent miscarriage. Despite all of the advances in reproductive medicine, 40-50% of women seeking advanced fertility help are still not able to become pregnant. Our testing service helps identify the underlying cause in the majority of these women. This new info allows for new treatment pathways and ultimately a new pathway to pregnancy.

CEO CFO: *How?*

Mr. Jackson: The ReceptivaDx™ test is based on the biomarker BCL6, a protein not normally found on the uterine lining at the time of conception. The marker was shown in studies to have 93% sensitivity and 96% specificity to be associated with endometriosis, a condition where endometrial tissue is found growing outside of the uterus. The inflammation we detect is a result of the body’s immune response to that endometriosis. Our data has shown this inflammation on the uterine lining is enough to block implantation and/or potentially cause a miscarriage during the first critical weeks of pregnancy. In one of our original studies, we found that if the marker was present, the chance for success in IVF was less than 12%. We then published if found and treated, chances for success increased to over 60%. That’s remarkable when you consider that average IVF success rates in the US are still 40-45% at most fertility centers.

CEOFCO: *Tell us more about the test?*

Mr. Jackson: We branded the test under the name ReceptivaDx™ after licensing the BCL6 marker from the University of North Carolina in the fall of 2016. The test is based on IHC analysis of an endometrial biopsy taken during the window of implantation, the same time an embryo would typically be transferred in the IVF process. Once our lab receives and processes the sample, a complete pathology analysis is performed, including interpretation of the BCL6 staining. Results are typically available in 5-6 business days.

CEOFCO: *Is endometriosis easy to identify?*

Mr. Jackson: Before our test, no. Endometriosis can still only be diagnosed definitively via laparoscopy, an expensive and invasive surgical procedure. It's a procedure usually reserved for women with severe abdominal or pelvic pain. In the area of infertility, laparoscopy, has almost completely disappeared. The reason for that? Well, the lack of insurance coverage and reduced training in the newer generation of reproductive specialists are the two biggest factors. But the biggest problem in women with unexplained infertility, failed IVF transfer history and recurrent pregnancy loss is that these women don't have the classic symptoms of endometriosis. Their infertility might be their only symptom. So, we looked for a non-invasive method to detect endometriosis in this group of patients and found the BCL6 marker to be a common denominator. Although we are not actually diagnosing endometriosis, we are able to detect the likely presence of endometriosis, which is great information instead of trying to convince a woman to undergo an invasive procedure without any physical symptoms and asking her to pay for it out pocket.

Our biggest hurdle was to convince the reproductive community that endometriosis was still a likely cause of infertility. The doctor wasn't suspecting it, the patient wasn't feeling it, yet there were no other plausible explanations. With so much focus on embryology and creating high quality embryos in the last 15-20 years, everyone stopped thinking about the uterine lining until recently. Success rates had been climbing with genetic testing of embryos and improved workups to rule out other male or female factors. Endometriosis was something that in the past was found routinely when they still scoped patients. When they stopped scoping, endometriosis just fell out of the picture and out of "newer thinking". ReceptivaDx testing gave providers a more affordable and accessible tool than laparoscopy to evaluate the uterine lining. Even better, we gave them a treatment pathway to pregnancy in their most challenging patients.

CEOFCO: *With your test, is it clear cut or are there some gradations? What are you able to identify?*

Mr. Jackson: To achieve such strong sensitivity and specificity numbers for endometriosis, we studied a group of women with unexplained infertility. The women agreed to have the ReceptivaDx™ biopsy and to also undergo laparoscopy. Of the 65 women that tested positive, 62 were confirmed to have visible endometriosis via laparoscopy. We also showed a false negative rate of less than 4%. This is where we felt comfortable to say, "This is a pretty good alternative to surgery," especially in women with no other signs or symptoms of endometriosis.

CEOFCO: *Is the infertility community aware?*

Mr. Jackson: They are! We have about three hundred centers across the country that are using ReceptivaDx™ and we also have centers in fifteen other countries that are accessing the test. It started off slow four years ago, but it really took off when providers at fertility centers found value in their most challenging patients, a group of women that had either exhausted their finances or simply didn't want to go through the whole physical and emotional process of an IVF cycle at the risk of not getting pregnant again.

CEOFCO: *If a doctor does the ReceptivaDx™ test, do they send the kit to you to process or is it done at local labs?*

Mr. Jackson: We have two testing laboratories in the US that are certified, licensed and experienced in this type of testing. Our labs review more endometrial biopsies for the fertility sector than any other lab in the US. We provide centers with collection kits at no-charge, so they have them on site ready for use. The endometrial biopsy is placed in a formalin vial and sent overnight via FedEx to one of our labs. Before staining for the BCL6 marker, a pathologist reviews the sample. The pathologist rules out other conditions such as infections, atypical cells or even cancer. The pathologist then orders the BCL6 stains. So, beyond the BCL6 marker searching for potential endometriosis, the fertility center and patient get a full pathology report, which is a value added proposition in itself and reduces the need and expense for a 2nd lab to be involved.

CEOFCO: *Once the doctors have the test back, would that be a decision maker for the woman to go forward or to not go forward? What is the full effect of what the results show?*

Mr. Jackson: In my original due diligence, the biggest question for me was "Ok, that's great that we found this marker as an alternative to surgery, but is there a treatment path?" There is nothing worse than identifying a problem for women trying to get pregnant, but not giving them a pathway to pregnancy once they did test positive for your test. So, working with the same clinical researchers that helped validate the BCL6 marker, we sought out to find an alternative treatment pathway instead of laparoscopy, that same expensive invasive procedure that had been used for years to ablate or excise lesions found while scoping.

As a result of those efforts, we found that hormone suppression therapy served as an effective alternative to doing surgery. The drug that was used in this study was LUPRON DEPOT ®. Although the therapy was not considered a cure for endometriosis, what it did was create a calming effect on the uterine lining that suppressed the inflammation long enough to achieve implantation and maintain the pregnancy. Women were on hormone suppression therapy for 60 days and then went right into an IVF protocol using a frozen embryo created after a prior egg retrieval.

LUPRON DEPOT was proven to be just as effective as surgery, both having over 52% percent "live birth" success rates on the very next IVF transfer attempt. You have to remember; this was a group of women that had already failed multiple times in the IVF setting and were ready to give up. Those success rates in the study were better than what most

fertility centers can boast in their normal over 35 population. That study really helped us grow the business and achieve success along with “buy-in” from the fertility community. Another very cool factor in the study...we were able to show that women who underwent treatment, either surgery or hormone suppression therapy, were five times less likely to miscarry than women who opted for no treatment. That was very important since recurrent miscarriage is a traumatic experience for women and their partners.

CEO CFO: *Where does cost come into play?*

Mr. Jackson: In the scope of infertility expenses, we are not that big of a deal. Our biopsy test is six hundred and ninety dollars. They obviously have to pay for a biopsy procedure in addition to that, but it’s still small in terms of cost to find out what your individual chances are for success when considering costly IVF procedures. Our providers also know their patients are voracious readers trying to understand IVF failure. In some cases, I know women that have challenged their doctor asking “Why didn’t you tell me about this test after the first IVF failure? Why did I have to wait for three failures and \$40,000 dollars to be spent before you even discussed it?” As a result, more centers are now performing our test sooner than later. Our social media programs also really helped our test get placed closer to the front end as opposed to the back end when we first introduced it four years ago.

CEO CFO: *Do you see a time when this would just be standard procedure at an early point?*

Mr. Jackson: We would like it to. We just received one million dollars in our second phase of an NIH grant. Therefore, we are doing a couple of things. We are looking at additional markers, but we are also looking and exploring to see if we can find different sample types that are less invasive. Experiencing an endometrial biopsy for a woman that is going through IVF is no big deal, but not exactly ideal when getting more women to get tested.

The bigger picture for us is to see if we can develop a test to detect the presence of endometriosis that is based on an easier sample to collect. We’re not there yet, but we are currently researching. If you think of a twenty year old that is not concerned with fertility, but very concerned why her periods are so heavy and painful, that’s who we want to help. What has been the norm in the past 20-30 years, were doctors telling that young women, “Well, that is your period, get used to it.” Left undiagnosed and untreated, that same young woman ten years later will likely have fertility issues. All of that scarring could have been prevented. Fertility treatments would not have been required. That young woman would have no idea they had endometriosis. Our long term goal and the reason we started this company wasn’t just to help the IVF community. It was to see if we could identify endometriosis earlier than the 7-10 years it typically takes now. In the process we help the 85% of women who can’t get pregnant that will never seek advanced fertility treatments and in the bigger picture, may help solve a problem that impacts over 176 million women worldwide.

CEO CFO: *What, if anything, has changed since more and more doctors are making use of the tests? Have you done tweaks long*

the way? Are there things you have learned over time about the testing?

Mr. Jackson: It's never easy to introduce and sell a new technology or service to an industry that is thriving just fine before you showed up. Everyone in the fertility sector of medicine for years had their focus almost exclusively on embryo quality. Then technology even allowed for genetic testing of the embryos. Success rates improved dramatically, historic highs. But the best centers were still only achieving 50-60% success rates. Now don't get me wrong, these success rates are indeed amazing, but from a business perspective, we saw the other side of the equation. Almost half of their patients were "unsatisfied customers", women still not getting pregnant. So, to sit down with folks enjoying dramatic success and significant increases in income, it wasn't always easy to find providers that would appreciate you coming in and letting them know, "You can do much better!" But our data helped them realize we were likely the next bridge to obtaining 75-80% overall success rates. So, when they realized we could help them achieve even greater success, folks began to listen and look at our data. So, the lesson we learned, like in any business, sometimes when things are going good for customers, they are less likely to adopt new processes or services. We had to have data. I never considered it lazy on their part to adopt new testing, in most cases the reproductive specialists weren't even noticing that half of their customers stopped coming back. They were just too busy with new patients coming in every week.

There are so many women out there that are just learning about our test and realizing they can learn more about why they can't get pregnant. The same thing applies to someone who is suffering multiple miscarriages. There is something happening on the uterine lining, it's not just genetic abnormalities causing these miscarriages. Most likely it's endometriosis. And in many of these situations no one has told them that was a possibility. For those starting to believe they weren't meant to have a baby, we believe we can help at least 60% of them achieve the dream of starting a family. That is the change we are making.

CEOCFO: Would you tell us a little more about your global reach? Are there areas where you are looking to be more involved with? How do you do that or are you focusing more on the US?

Mr. Jackson: Honestly, our goal was to focus more on the US. We just didn't have the bandwidth to conquer everywhere. I think because of the publications, Google searches and social media, our international business developed without much dedicated effort. We are very data driven and the publications are obviously appearing in journals that have reach outside of the US. But we are a lab service and have not put this in kit form. That means folks have to go through the process of getting a sample over to the US, which sometimes is a little bit harder than you think in terms of restrictions when sending biological samples. For right now we are focused on the US. We are also doing really well in Australia and the UK. The rest of the world market has been patient driven.

CEOCFO: Is there competition? Are there other ideas that you see as competing with yours or is this is really quite novel?

Mr. Jackson: In the fertility world, what we do is quite unique, and it will stay that way for some time. On a different level, outside of fertility, when it comes to being able to test for endometriosis, there is a lot of potential competition. Everyone is looking for a means of detecting endometriosis, but so far they have been unsuccessful. Obviously, it would be great if we could develop a blood or saliva test or something like that on the DNA level. As we speak, we are researching. I believe we have more data and experience than just about anyone else.

Endometriosis is probably one of the most misunderstood and misdiagnosed conditions that women experience. I think competition is always great when it comes to finding better technologies. I hope some advances start coming out and I'm confident we will be a part of that. As treatments are coming out now to help tame or reduce the symptoms of endometriosis, we need definitive markers to identify who would most benefit from treatment and to help insurance providers have a method for selecting who should qualify to be reimbursed for these treatments. Our company is getting closer and closer to understanding how endometriosis is triggered in the body and why it affects some women and not others. It's very exciting to be a part of.

CEOCFO: *You mentioned your NIH grant. Are you seeking additional funding, investment or partnerships?*

Mr. Jackson: At the time right now, no. We have the resources. We are profitable as a company, which is unusual for a startup in only its fourth year. But the NIH grant is allowing us to speed up the research, so that gave us the luxury of not looking for outside money. I think when it comes time where we are comfortable with the test that could and should be marketed to the OBGYN population directly, then I think we definitely will look for assistance or a partner at that time. It would make sense to do that. Right now, we are focused on validating everything we have done and developing the market in the IVF community. And we are achieving that with great success.

CEOCFO: *What, if anything, might people miss when they look at Cicero Diagnostics?*

Mr. Jackson: Most folks just don't know about us yet. Everyone has an interest in the fertility market. It's one of the most desirable sectors in healthcare. Today you see a lot of consolidation of practices via acquisition. But most people don't quite understand this space; they only know it's highly profitable. They know it's expanding and growing, but much harder to understand the companies that service this industry versus the fertility centers that see patients. We are a small company and we are not yet out there promoting ourselves. Mostly because we don't have to. There are lots of startups out there and they're raising crazy money before they even have a product. That's not us. Those other companies don't have the clinical data to back what they do. We believe that's what will help Cicero Diagnostics separate themselves from the pack when we start looking for partners. We provide data, we help doctors resolve issues for their most challenging patients and have outcome data to prove it. We have market share, proprietary technology, no long term debt, year after year consistent growth and the ability to stay out of the red. Not too many can say that.

We now have over three hundred sites accessing our testing services across the US. We now have five impactful publications with another one on the way. As mentioned before, we have been awarded a \$1.1M SBIR NIH Research Grant and are in Phase II of that research. That is simply unheard for a small company that started less than four years ago. Those are the things that people will eventually see about us, but we have not really gone out and sought and looked for help either. I think you have to do some shouting from the mountain top to be noticed and that just hasn't been our focus.

If anyone is looking at the fertility industry, they should realize this is the "Wild West of Medicine". There is more of a business approach in the fertility practices to the work performed compared to other medical disciplines. 80% or more of the industry is "self-pay" and doesn't involve insurance, write-offs or bad debt. It's a healthy place to be! We see centers that are all about the dollar and push IVF right away without offering other kinds of testing first. We see other centers that are truly approaching the patient with their best interests in mind and exhausting all methods before simply suggesting IVF is the best approach for them. We get to work with all of them, it just requires a unique approach on our part to understand what the motives are for each center as to how and why they will embrace our services. It's a very unique segment of healthcare. At the end of the day we love the fertility space. They are faster at accepting new technologies, less worried about insurance issues and ultimately want the patient to succeed as soon as possible. For patients and potential investors, there is no better place to see new technology being embraced at such a fast pace.



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