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How Not to Introduce Laboratory Tests to Clinical Practice: Preimplantation Genetic Testing for Aneuploidy

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Guest: Dr. Norbert Gleicher from the Center for Human Reproduction in New York and the Foundation for Reproductive Medicine.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Even with the very best laboratory tests, 100 percent accuracy unfortunately is seldom achievable, and the value of testing must be carefully weighed on the potential outcomes. In reproductive endocrinology, a test that has come under recent scrutiny is pre-implantation genetic testing for aneuploidy or PGT-A, which was formerly called pre-implantation genetic screening, or PGS.

Based on claims of better live birth and reduced miscarriage rates, utilization of PGT-A in association with in vitro fertilization has increased in the United States over the past 20 years. However, there is some doubt that this testing meets expectations. An opinion piece on PGT-A testing with the provocative title, "How Not to Introduce Laboratory Tests to Clinical Practice," appears in the April 2022 issue of *Clinical Chemistry*. Its senior author, Dr. Norbert Gleicher, is the Medical Director and Chief Scientist at the Center for Human Reproduction in New York, as well as President of the not-for-profit Foundation for Reproductive Medicine. He also holds an appointment as a guest investigator at Rockefeller University and a professor at the Medical University of Vienna. So, doctor, many physicians remain confused about the clinical utility of PGT-A in association with in vitro fertilization. What is the test supposed to do and how well does it do it?

Norbert Gleicher: What a great question. Many physicians being confused is probably an understatement. This is a test which is meant to determine whether an embryo is chromosomally normal or not so that chromosomally abnormal embryos can be excluded from transferring them into the uterus, into the womb of the mother. And it is a test that has been in use for over 20 years, but in recent years has gained a lot of traction, but is completely worthless. And indeed, in our opinion, here at the Center for Human Reproduction, harms a significant portion of women.

Bob Barrett: What data were observations made you reach your conclusions on the test utility, or lack thereof?

Norbert Gleicher: It's not only me or my colleagues reaching that conclusion. It's kind of an interesting picture. In science and in medicine, there are a lot of smart people with a lot of great ideas. But ideas are not fact, and generally, the rule is, if you generate the hypothesis and you want to convince your colleagues, you have to convince them. In other words, you have to produce the data to show that your hypothesis works, your treatment works.

When it comes to the 20-plus year history of PGT-A, that was turned on its head. The proponents of PGT-A, which I have to acknowledge when I heard it for the first time also sounded genius, but the proponents of PGT-A, were never able to demonstrate that it really did what they promised it would do, which is to improve IVF outcomes. And every time, it was up to the opponents of PGT-A to prove that the proponents had been wrong in whatever they tried to demonstrate. And every time the opponent succeeded in demonstrating that the proponents had been wrong in whatever they tried to demonstrate, and every time the opponent succeeded in demonstrating that, the proponent moved the goal post and changed the methodology and said, "Oh, this time it will work," and we have gone through four generations.

We are now in the fourth generation of PGT-A for all of these reasons and to this day, there is not really a single study that has shown that PGT-A really works, that it does anything. And there's more and more evidence that it hurts particularly women who have few eggs and few embryos and cannot afford to lose embryos for wrong reasons. It obviously costs a lot of additional money and, finally, it also harms people because it sends a lot of especially older women again into egg donation because they are made to believe that they no longer can get pregnant with their own eggs.

Bob Barrett: Well, as you said, PGT-A in its various formats have been in clinical use for over 20 years. What took so long to come to these conclusions?

Norbert Gleicher: Well, it's one of those things where an idea sounds too good to be true.

The concept that you can diagnose embryos that are chromosomally abnormal, which we know in many cases will either not implant or be miscarried, is obviously a genius idea, if it works. But to make the claim that you can biopsy an embryo and take five cells of that embryo, and with those five cells determine the fate of the whole embryo, what the whole embryo is like, that turned out to be naive. I mean, we all

believed it in the beginning when it was proposed, but the more we learned about the biology of early embryos, of implantation-stage embryos, the more it became apparent that this was really a house built on no basis, that biologically the whole concept didn't work. But in the meanwhile, there has been a big industry built around this test and there are enormous economic interests linked to it. So, it became harder and harder to argue against it, but especially now, I think the tide is turning, and we are not alone in this, in criticizing the testing of embryos.

The FDA just issued yesterday a warning about early pregnancy testing [this interview was recorded on April 20, 2022. The FDA guidance mentioned here is from April 19, 2022: "FDA Warns of Risks Associated with Non-Invasive Prenatal Screening Tests" https://www.fda.gov/news-events/press-announcements/fda-warns-risks-associated-non-invasive-prenatal-screening-tests], which is basically built on the same technology or similar technology, where the FDA now came out with a statement saying that this test, in early pregnancy, produces a significant rate of false positive results that can lead to wrong decisions, like having pregnancies aborted that are really not chromosomally abnormal. And in my opinion and my colleagues' opinion, this problem is even much, much larger in conjunction with PGT-A because it is fortunately very, very rare that women will have an abortion because of a false positive early pregnancy test. On the other hand, we are throwing out thousands of embryos every day for no good reason, and they have significant pregnancy potential.

We just published a paper in *Human Reproduction* where we showed in our first 50 couples who transferred their so-called abnormal embryos to us, in which we transferred, that we could get them still a very decent birthrate. So, this took time because we did not know as much as we know now about early embryology when all of this started but the more we have learned, the more obvious it became why this grandiose idea, in the end, really doesn't work.

Bob Barrett: What about the use of this testing in other countries? Can we learn anything from their practices?

Norbert Gleicher: Yeah, it was not too long ago, a paper comparing the U.S. to the U.K., and the U.K. probably does one-fifth of the number of tests that are done in the U.S. In the U.S., most recent data suggests that over half of all IVF cycles use PGT-A. In the U.K., it's less than 5 percent, and I think that says it all.

Bob Barrett: Are there any wider repercussions to your work on this subject?

Norbert Gleicher: Yeah. There are, and actually our paper in *Nature Medicine* addressed those. That came out last month. We wrote an opinion piece there, where we addressed this whole concept of genetic testing in reproductive medicine, which mostly involves chromosomal testing, but now, also paradoxically, goes into a field that is called polygenic risk assessments. Some companies and some IVF centers have indeed started offering this polygenic risk scoring of embryos, which is not looking like PGT-A for chromosomal abnormalities, but here, the alleged usefulness of this is preventing the transfer of embryos that have polygenic risks.

Now, polygenic risks can be diseases but can also be blue eyes or particular abilities. Those are highly complex calculations, which just have entered adult medicine as experimental procedures, and to use it in embryos is insanity.

And the British Genetics Society actually just came out with a statement that using polygenic risk assessments in human embryos in association with IVF is completely unproven and unethical. I mean, those were their words, written words, but yet those tests are also already offered. So, the piece we wrote in *Nature Medicine* really addressed three separate areas: one--PGT-A, two--the kind of early prenatal testing that the FDA just criticized and warned about, and third--this polygenic risk testing, and the genetic testing industry is making a lot of money and wants to make more money, and really is selling, to a large degree, a product that cannot deliver, for biological reasons, cannot deliver what it promises it does.

Bob Barrett: So, are there any alternatives to PGT-A and testing embryos chromosomally?

Norbert Gleicher: No, and frankly, we don't need an alternative because as we also learned in the recent years, embryos have an innate capability to self-correct themselves. So, even assuming for a moment the test, the PGT-A test, is normal – I mean, is correct and is technically well done, just because those few cells that are being biopsied are chromosomally abnormal doesn't mean that the whole embryo is chromosomally abnormal or that it cannot get rid of whatever amount of chromosomal abnormality it has at that moment. Indeed, the time where we are doing the testing, where we are getting the embryo biopsy, the pre-implantation stage, that is where human embryos routinely are abnormal. In over 80 percent of cases, they have chromosomal abnormalities. It's normal to be abnormal. And most of these embryos, or at least many of these embryos, self-correct downstream, and end up being completely normal. So, what's the purpose of doing a test when downstream that embryo can still self-correct?

Bob Barrett: Well, finally, what words of advice do you have for IVF physicians and couples seeking specialty treatment for infertility regarding these tests?

Norbert Gleicher: Again, I want to be very careful, and I always tell students and whoever wants to listen to me that we never can say in medicine that something is 100 percent or zero percent. Biology always works in ranges, and that applies here too. I don't want to say that there is absolutely no clinical purpose ever to do a PGT-A test and try to determine the chromosomal makeup of an embryo. What I can say is that there are very few indications. If there is for example an indication or a reason to determine whether an embryo is female or male, that's great. If you want to do that, that will be accurate, and that's good. PGT-M, meaning the search for single gene diseases, is a great thing. I mean, absolutely in favor of. But the testing for chromosomal abnormalities makes biologically no sense, and therefore I can't find a lot of indications except, what in the recent times a few papers have said, which is that this should be reserved for clinical studies, for experimental protocols. There's no reason why not, study, do it? That should have been done before it's introduced into clinical practice, not after. But maybe it will show us something, but at the present time, I as I sit here, I cannot see a clinical situation where I would recommend a patient to have her embryos tested except in those few exceptions I mentioned before.

Bob Barrett: That was Dr. Norbert Gleicher, the Medical Director and Chief Scientist of the Center for Human Reproduction in New York, as well as President of the not-for-profit Foundation for Reproductive Medicine. His opinion piece on pre-implantation genetic testing for aneuploidy appears in the April 2022 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.