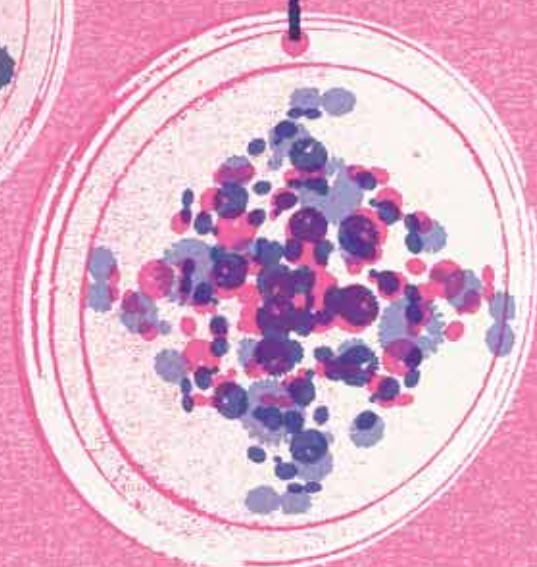
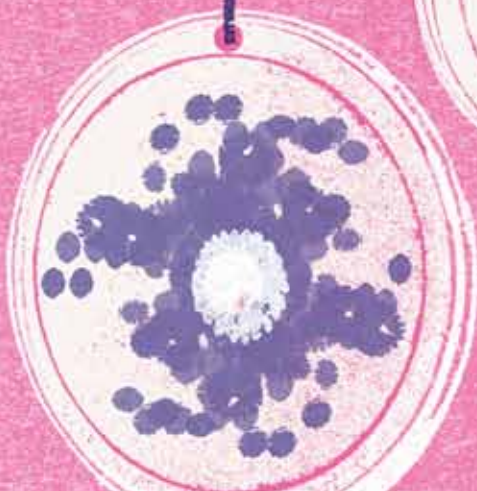
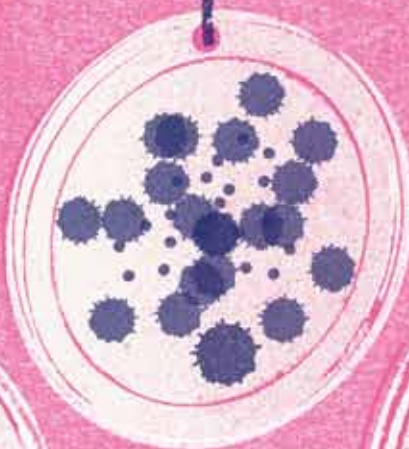


The Next Frontier

Magee is on a mission to improve prenatal genetic testing — and the peace of mind of parents-to-be.

— By Anna Dubrovsky



Every year, thousands of pregnant women and their partners come to a difficult crossroads.

Told they're at increased risk for having a baby with Down syndrome or another chromosomal disorder, the parents-to-be can elect amniocentesis or chorionic villus sampling (CVS). The prenatal tests are highly accurate at diagnosing some genetic abnormalities, but they pose a risk of miscarriage. Depending on the doctor's level of experience and other factors, the risk can be as high as 1 in 100 or as low as 1 in 1,000, as it is at Magee-Womens Hospital of UPMC.

"You're charged with making this decision about whether to expose your baby to clearly defined risk," says David Peters, PhD, whose lab is developing a safer, noninvasive alternative to amniocentesis and CVS. The former requires inserting a thin needle into the amniotic sac to remove a sample of fluid, while the latter involves taking a tissue sample from the placenta. Dr. Peters is endeavoring to prove that a simple blood test can be used to diagnose Down syndrome and other abnormalities early in pregnancy.

"Our preliminary data is very, very good," he says. It was good enough for the National Institutes of Health, which awarded him a \$2.8 million grant earlier this year. Dr. Peters, whose research in noninvasive prenatal testing has been funded by Magee-Womens Research Institute (MWRI) since 2007, will use the five-year grant to collect blood samples from 700 women in the first trimester of pregnancy and apply a new DNA sequencing method to look for extra or missing chromosomes. He expects his noninvasive approach to detect 95 percent of such fetal genetic abnormalities, with a false positive rate of just 1 percent. And the risk of miscarriage? Zilch.

"The overarching goal is to minimize the physical risk to the fetus and minimize the stress to the parents," says Dr. Peters, who is intimately familiar with the stress that can accompany amnio or CVS. He and his wife chose amnio when she was pregnant with their first child at 35 and their second child three years later because the risk of Down syndrome and other chromosomal disorders increases with the mother's age.

"We didn't have a bad outcome from our tests, but we did have a massive amount of anxiety. Minimizing that anxiety would be a major step in the right direction."

His isn't the only MWRI lab looking for ways to minimize the anxiety of parents-to-be. While Dr. Peters pursues an alternative to amnio and CVS, Aleksandar Rajkovic, MD, PhD, is stretching the limits of what we can learn from the procedures.

When a woman undergoes amnio or CVS, the fluid or tissue sample is usually sent to a lab for karyotyping, which involves staining and photographing the fetus's chromosomes, arranging them according to size and banding pattern, and examining them for abnormalities. Down syndrome, for example, is caused by three copies of chromosome 21 instead of the normal two. The problem with karyotyping, says Dr. Rajkovic, is that it doesn't detect smaller genetic changes — some of which cause major problems.

Consequently, many parents-to-be who seek amnio or CVS after receiving abnormal ultrasound results are left in the dark. "They want to know what's wrong with their baby, and more than 50 percent of the time, we cannot tell them," Dr. Rajkovic says. "They have to wait until the baby is born to figure out what's going on, which is a huge cause of anxiety."

When Dr. Rajkovic joined MWRI two years ago, he began using chromosomal microarray analysis, a new technology used to look for genetic abnormalities in children born with physical or mental disabilities, to examine samples obtained through amnio or CVS. Scientists isolate the baby's DNA, chop it into tiny pieces, label it with green fluorescent color, and combine it with DNA from a control group that's labeled with red fluorescent color. When they examine the combined samples,

matching DNA pieces appear yellow in color. If the baby is missing a critical part of its genome, the red of the control DNA predominates. "The beauty of this technology is that you don't need to know what you're looking for," Dr. Rajkovic says. "It's especially useful when you're scratching your head because you know there's a genetic problem with the baby, but you don't know what the problem is."

His hunch proved correct: chromosomal microarray analysis uncovers fetal genetic abnormalities missed by karyotyping. "We are able to find reasons for baby's problems in about 10 to 15 percent more cases than with karyotype alone," he says. "It improves our ability to explain to families why their baby is exhibiting anomalies on the ultrasound scan. Knowing the reason removes some of their anxiety."

Chromosomal microarray analysis has been offered to more than 100 women at Magee-Womens Hospital. Because it's not available at most hospitals, Magee's obstetrical geneticists see women from as far away as New York.

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Informed Decisions

Medicine has not advanced to the point where most genetic abnormalities can be corrected. But knowing about them has its advantages. Parents-to-be can make an informed decision about continuing or terminating the pregnancy. Those who choose to continue can prepare themselves — emotionally, medically, logistically, and financially — for the journey of raising a child with special needs.

Health care providers can prepare themselves for a potentially complicated birth and neonatal problems.

Not long ago, Dr. Rajkovic was asked to evaluate a fetus with a club foot and low amniotic fluid. Each problem is relatively minor, but the combination suggested a genetic abnormality. When the karyotype came back normal, the sample cells were sent to Dr. Rajkovic's lab for chromosomal microarray analysis. The test revealed that the baby carried a small chromosomal deletion called Prader-Willi syndrome, which causes a chronic feeling of hunger that can lead to life-threatening obesity. "It also causes babies to be hypotonic, meaning their muscular tone is very weak, and they have difficulty suckling," Dr. Rajkovic says. "Sometimes people think they have cerebral palsy or brain injury due to trauma during delivery. When the baby came to the NICU [neonatal intensive care unit] and it was hypotonic, the neonatologist didn't have to do a million-dollar workup to figure out why. We saved them from wasting time on trying to figure out what was going on because it was all explained by the fact that this baby had this particular deletion."

Alerting health care providers to genetic abnormalities is a simpler matter than alerting parents-to-be. "These things are not always easy for families to understand, and we spend a lot of time counseling them, explaining what's going to happen after birth and what problems the baby might have," he says.

Magee patients have access not only to world-class obstetrical geneticists like Dr. Rajkovic but also to an experienced team of genetic counselors. Michele Clemens, MS, supervisor of clinical services for the Department of Genetics, has been a genetic counselor for more than 30 years. In that time, ultrasound technology has gotten much better at identifying anomalies, new tests for genetic disorders have been developed, and methods of chromosome analysis have become increasingly sophisticated. "At Magee, we have always been on the forefront or to some degree ahead of the curve," she says.

What hasn't changed is the human factor. Genetic counselors provide critical support to patients before testing, explaining the various tests and the information that can be gained from them, as well as after testing, when emotions can run sky-high. Reactions to bad news are "all over the board," Ms. Clemens says.



"You have patients who are in denial and refuse to accept the result. You have patients who went through testing with the very specific intention of terminating the pregnancy if a problem is identified. And you have those patients in between who struggle with that decision. You even have couples who are discordant in their feelings about what to do. We're there to provide very accurate and clear information about the result, provide a variety of supportive services, and coordinate care if they decide to continue their pregnancy."

Obstetrical geneticists like Dr. Rajkovic envision a future where more and more of the problems caused by genetic abnormalities can be corrected or alleviated. "Diagnosing and understanding the pathologies is the first step," he says. "The question then becomes: can you devise interventions for families that do want to continue the pregnancy? That's the next frontier."

One thing is certain: Magee-Womens Hospital and its eponymous research institute will lead the way. ◆ ◆