

# The Center for Medical Genetics and Genomics: New Research and Clinical Advances

Originally founded as the Center for Medical Genetics in the early 2000s by W. Allen Hogge, MD, the renamed Center for Medical Genetics and Genomics has continued to expand its role and mission, providing a range of diagnostic screening and genetic counseling services as well as cutting-edge research for both some of the most common and the rarest of illnesses and conditions.

**Aleksandar Rajkovic, MD, PhD**, currently serves as medical director, as well as being a driving force in genetics and genomics research within the Department of Obstetrics and Gynecology and the Magee-Womens Research Institute. **Ed Smith, MS, MBA**, is the administrative director of the center with a background in genetic counseling. Along with Dr. Rajkovic and colleagues, Mr. Smith is responsible for the strategic planning and operations of the center and its day-to-day operations.

## Clinical Programs and New Screening Tests

The Center for Medical Genetics and Genomics encompasses a robust collection of services and testing for adults, and collaborates extensively on pediatric testing with labs and clinicians at Children's Hospital of Pittsburgh of UPMC. The center sees and counsels well over 4,000 adult patients each year and collaborates with many specialty areas throughout the UPMC system on patient screening and counseling, such as the Center for Innovative Fetal Intervention and the UPMC CancerCenter. The laboratories of the center perform testing for a full spectrum of conditions, including more than 3,600 molecular testing procedures, more than 7,000 pregnancy screening tests, and more than 17,000 cytogenetic tests each year.

Telemedicine programs are also in place and expanding, allowing the center to triage and reach patients for counseling services in outlying areas that would otherwise be burdensome for patients to travel from to the center's main location at Magee-Women's Hospital of UPMC in Pittsburgh.

## New Testing for Hereditary Cancers

Progress is something inherent in the work of the Center for Medical Genetics and Genomics. Research, testing protocols, patient counseling, and outreach all evolve and expand as the knowledge base unfolds over time and patient populations and their needs shift and grow. Adapting to and meeting these needs head-on is a hallmark of the center and its research and clinical staff.

In the next several months, the center will be launching a new hereditary cancer screening panel designed to answer genetic variant questions for patients with personal or familial histories of breast, ovarian, colorectal, and other cancers. Mr. Smith explains that the rationale for this hereditary cancer panel,

which screens and sequences 44 individual genes in one test, is to simplify the testing regimen for the patient and at the same time greatly expand the flexibility clinicians have in analyzing the patient's genetic profile. "With our patient population, we really wanted to develop a test that gives maximum flexibility. While we sequence 44 genes, a clinician may only be interested in 9 or 10, depending on the clinical applicability to the patient. Using software on the back-end, we are able to carve up the panel into a number of specific gene groupings that best address the clinical needs of our referring providers and their patients. We don't have to create a new test for each group, which leads to resource savings in time and cost, flexibility, and a consistent workflow," says Mr. Smith.

## Exome Sequencing

In the pipeline for a probable launch in the early part of 2018 is an exome sequencing panel that will concentrate on 5,000 of the approximate 19,000 to 20,000 genes in the human genome. This targeted sequence, also referred to as a medical exome, sequences the coding regions of these 5,000 genes, providing in one test a vast trove of personalized knowledge that can aid in both diagnosis and counseling. "This test concentrates on a battery of genes and coding regions of genes that clinicians have sufficient knowledge about, such that if something out of the ordinary is found they can investigate further," says Mr. Smith. The reason for only sequencing a portion of the genes with this test is that while an individual's entire genome can be sequenced, all 3 billion base pairs and roughly 19,000 to 20,000 genes, a large portion of this information is simply not understood at present. Therefore, this testing evaluates only those regions of genes for which the science sufficiently exists to allow interpretation and action in some way by the clinician.



**Aleksandar Rajkovic, MD, PhD**



*Dr. Rajkovic and colleagues in the lab discussing research findings.*

Mr. Smith explains that this new test will have particular value with the pediatric population as a way to possibly prevent or reduce the diagnostic odyssey for children with complex or multifactorial conditions of known or unknown origin. “Exome testing a child who has eluded diagnosis may help us find the genes or gene pairings that most likely explain the features of the illness. This will allow the clinicians to better understand how to manage and treat the individual, while at the same time reducing or preventing the idea of the diagnostic odyssey — of looking at individual suspected causes one at a time over many months or years,” says Mr. Smith.

## Cutting-Edge Research and New Grants

### Whole-Exome Sequencing

Dr. Rajkovic and his colleagues are active on numerous research fronts. One exciting area of exploration centers on how to better diagnose genetic disorders prenatally and postnatally. “We are looking at the utilization of cutting-edge technologies, such as whole genome sequencing in both prenatal and postnatal diagnosis. Clinically we are involved in this area, but we are also testing the utility of prenatal genome sequencing,” says Dr. Rajkovic. Because the information uncovered in whole genome sequencing is vast, Dr. Rajkovic and his colleagues are investigating how the information is returned to patients, and how much information related to the developing fetus is or should be shared. Some of their findings are discussed in their 2015 paper, “Prenatal Whole-Exome Sequencing: Parental Attitudes,” which surveyed a cohort of 186 individuals and their

preferences regarding knowing the results of fetal whole-exome sequencing. Among the findings were that 54 percent of individuals were interested in the screening for their fetus, and the majority of individuals would want to know about both treatable and nontreatable conditions uncovered in the screening. “We think that this will be a game changer in terms of helping us diagnose the diseases that individuals have prenatally,” says Dr. Rajkovic.

### Searching for Noninvasive Options

Dr. Rajkovic is also studying various ways to noninvasively diagnose genetic disease during pregnancy: “One area that shows promise is our current work at Magee in isolating — noninvasively — fetal cells from maternal blood and from the maternal cervix.” The research team’s hope is to eventually show that these noninvasive tests could replace some of the current invasive diagnostic procedures, such as chorionic villus sampling and amniocentesis.



**Ed Smith, MS, MBA**

### The MED12 Gene and Leiomyoma Formation

In July 2017, Dr. Rajkovic was awarded a new NIH RO1 grant<sup>2</sup> for a project examining MED12 Mechanisms of Uterine Leiomyoma Formation. Past research<sup>3</sup> by Dr. Rajkovic and colleagues at Magee has discovered that one particular gene — MED12 — has a significant responsibility in the formation of leiomyomas, or uterine fibroids. Their research has shown that mutations in the MED12 gene are not inherited but rather are actually seminally acquired by the uterus. Dr. Rajkovic’s research has uncovered that almost 70 percent of uterine fibroids have specific mutations in the MED12 gene. “Our research teams have published a number of papers on

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functional and anatomic motor levels at 2 years of age, stratified by mode of delivery and presence or absence of labor.” “In our study, we found no significant difference in the children delivered via C-section versus vaginally.” This has obvious implications for the mother and the baby. Avoiding a C-section if possible eliminates those inherent risks with the procedure and the implications to future pregnancies, allows for faster recovery, and affords for immediate mother-baby interaction.

“At Magee, our mission is to take care of women and their babies. Even in these rare cases where there may not be a good outcome, or intervention may not prove beneficial, we still have the capacity to help the mother. We always find a way to help her and the family through difficult times,” says Dr. Emery.

### References and Further Reading

- Emery SP, et al. North American Fetal Therapy Network: Intervention vs. Expectant Management for Stage 1 Twin-Twin Transfusion Syndrome. *Am J Obstet Gynecol.* 2016; 215(3): 346.e1-7.
- Emery SP, Greene S, Hogge WA. Fetal Therapy for Isolated Aqueductal Stenosis. *Fetal Diagn Ther.* 2015; 38(2): 81-85.
- Emery SP, Hogge WA, Hill LM. Accuracy of Prenatal Diagnosis of Isolated Aqueductal Stenosis. *Prenat Diagn.* 2015; 35(4): 319-324.



- Chen Y, Emery SP, Maxey AP, Gu X, Wagner WR, Chun Y. A Novel Low-Profile Ventriculoamniotic Shunt for Foetal Aqueductal Stenosis. *J Med Eng Technol.* 2016; 40(4): 186-198.
- Greene S, Lee SP, Deibert CP, Tempel ZJ, Zwagerman NT, Florio K, Bonfield CM, Emery SP. The Impact of Mode of Delivery on Infant Neurologic Outcomes in Myelomeningocele. *Am J Obstet Gynecol.* 2016; 215(4): 495.e1-495.e11.

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the role of MED12 in leiomyoma formation. With our new research into MED12 mutations driving fibroid formation, we theorize that in the future it may be possible to target this gene and its mutations with noninvasive treatment alternatives,” says Dr. Rajkovic.

### Ovarian Reserves and Premature Ovarian Insufficiency

Another current grant in progress seeks to understand and use an individual’s genetic profile as a biomarker for ovarian reserves. Understanding one’s reproductive capacity and duration is becoming more important in fertility and infertility as individuals postpone or delay pregnancy. These individuals would like to know whether they should be freezing their eggs, or whether they can wait and reproduce later. Research by Dr. Rajkovic has been using genome sequencing of individuals who experience early loss of fertility — premature ovarian insufficiency — to gain a better understanding of the basic biology and genetic underpinnings responsible for premature ovarian insufficiency.

Past and current research<sup>4-7</sup> by Dr. Rajkovic has identified a number of genes that play an important role in premature ovarian insufficiency. The current understanding is that the most important gene related to premature ovarian insufficiency is the MCM8 gene. This gene is involved in DNA damage response. When DNA becomes damaged, either by internal or external environmental factors, the body needs to repair that damage. The MCM8 gene appears to be critical in an individual’s ovarian reserves, and it plays a role in determining a women’s reproductive lifespan, explains Dr. Rajkovic.

### References and Further Reading

- Kalynchuk EJ, Althouse A, Parker LS, Saller DN Jr, Rajkovic A. Prenatal Whole-Exome Sequencing: Parental Attitudes. *Prenat Diagn.* 2015; 35(10): 1030-1036.
- MED12 Mechanisms of Uterine Leiomyoma Formation. NIH Award 1R01HD088629-01A1. Primary Investigator: Aleksandar Rajkovic.
- Mittal P, Shin YH, Yatsenko SA, Castro CA, Surti U, Rajkovic A. Med12 Gain-of-Function Mutation Causes Leiomyomas and Genomic Instability. *J Clin Invest.* 2015; 125(8): 3280-3284.
- Yatsenko SA, Rajkovic A. Reproductive Aging and MCM8/9. *Oncotarget.* 2015; 6(18): 15750-15751.
- Desai S, et al. MCM8 and MCM9 Nucleotide Variants in Women With Primary Ovarian Insufficiency. *J Clin Endocrinol Metab.* 2017; 102(2): 576-582.
- Genomic Basis of Premature Ovarian Insufficiency. NIH Award 4R01HD070647-05. Primary Investigator: Aleksandar Rajkovic.
- Transcriptional Regulation of Early Folliculogenesis. NIH Award 5R01HD044858-10. Primary Investigator: Aleksandar Rajkovic.

- Magee.UPMC.com
- Obgyn.Pitt.edu
- PittGenomics.org