

Center for Clinical Genetics and Genomics Newsletter

January 2017



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MESSAGE FROM THE DIRECTOR

The inaugural issue of the CCGG newsletter will inform referring providers with clinical, educational and research activities in the Center. The Center consists of physicians, Genetic Counselors, laboratory directors and laboratory personnel that strive to provide diagnostic and risk assessment services at UPMC and beyond. We hope to address topics that are of interest to the referring providers and their patients. Please contact us with specific topic or issues that you would like to see discussed in this newsletter. Your suggestions are welcome and I can be reached at rajkovic@upmc.edu. You may also want to visit our recent website for additional information regarding genetic services across UPMC: <http://pittgenomics.org/>

Dr. Aleksandar Rajkovic

NONINVASIVE FETAL DNA TESTING IN CURRENT OBSTETRICAL PRACTICE

Cell free DNA (cfDNA) from maternal plasma can be analyzed to screen for the common forms of Trisomy 21, Trisomy 13, Trisomy 18, and sex chromosome aneuploidies. Such testing is called Noninvasive Fetal DNA Testing or Non-Invasive Prenatal Testing (NIPT). There are several private companies offering NIPT, each with its own commercial name. At the present time there are not data to suggest that one commercial test is superior to others.

Test Your NIPT Knowledge! True or False?

NIPT can be used as a primary screening test in women at increased risk of aneuploidy. *True!*

This includes pregnant women of advanced maternal age (≥ 35 yo), those with abnormal 1st trimester or second trimester maternal serum screening results or abnormal ultrasound findings that indicate increased risk for Trisomy 21 or 18, or a previous pregnancy with trisomy 21, 13 or 18.

NIPT can be used as a primary screening test in pregnant women with low risk for aneuploidy. *True!*

While initial studies and the American College of Obstetrics & Gynecology (ACOG) recommendations suggested NIPT was most appropriate for high risk populations, NIPT has now been validated in general population. ACOG Practice Bulletin #163 (May 2016) reviews screening tests for the general population and suggests that "No one screening test is superior to other screening tests in all test characteristics."

Some medical conditions may affect NIPT accuracy. *True!*

NIPT results may not be accurate in patients diagnosed with cancer or with the history of organ transplant due to possible existence of non-maternal DNA in plasma. Furthermore, NIPT results should be interpreted with caution in obese pregnant women or in multiple gestations, egg donation and vanishing twin cases.

NIPT is a diagnostic test. *False!*

NIPT can have both false positives and false negatives. While positive results are highly suggestive of aneuploidy, the positive predictive value of a given result depends upon the chromosome involved and patient specific data. Additionally, NIPT does NOT detect all aneuploidies, triploidy, other structural chromosomal abnormalities/ genomic imbalances that can cause birth defects and intellectual disability.



Dr. Devereux N. Saller is currently the Director of Clinical Genetic Services at the Center for Clinical Genetics & Genomics and the Medical Director, Pregnancy Screening Laboratory at the Magee-Womens Hospital of UPMC.

OUR TEAM

Aleksandar Rajkovic MD PhD



-Director of Reproductive Genetics, Department of Obstetrics, Gynecology and Reproductive Sciences

- Program Director of the Medical Genetic Residency/Fellowship

- Professor of Obstetrics, Gynecology and Reproductive Sciences, Pathology and Human Genetics

- Marcus Allen Hogge Chair in Reproductive Sciences

Edward Smith MSc MBA



Director, Laboratory Services.
Center for Genetics & Genomics

Pre and Post-test Counseling is optional. *False!*

It is critical that all patients understand the risks, benefits and limitations of NIPT. Thorough genetic counseling, by health care providers or Certified Genetic Counsellors at the Center for Clinical Genetics and Genomics, followed by offering of diagnostic tests (CVS or amniocentesis) in the setting of a positive NIPT result are essential.

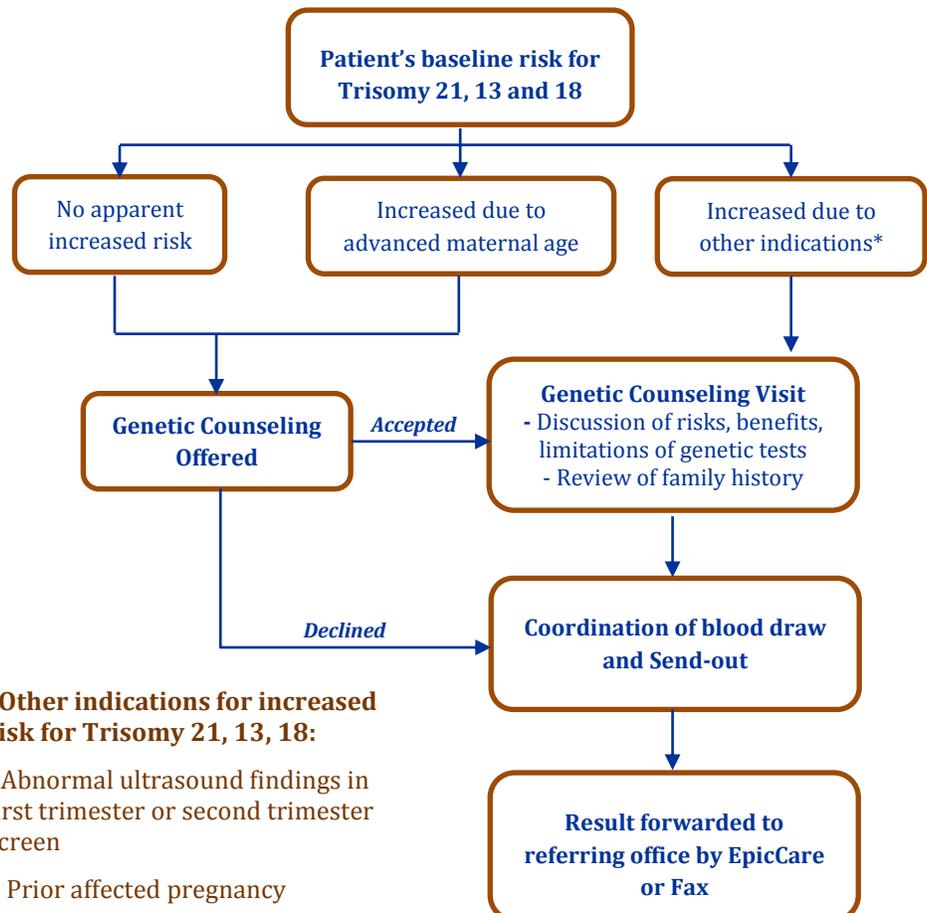
NIPT can be more expensive than traditional screening tests. *True!*

Traditional screening tests (1st trimester screen or 2nd trimester maternal serum screen) are often covered by health insurance. NIPT is usually covered for high risk individuals. However, it may not be covered for individuals without known risk for aneuploidy. It is important for physician or counselor to discuss financial obligations that client may incur.

NIPT is not readily available and is difficult to coordinate. *False!*

NIPT is widely available and can easily be coordinated by health care providers or by referring patients to our Center. Our Certified Genetic Counsellors stand ready to provide both pre- and post-test genetic counseling for women interested in NIPT and other screening and diagnostic tests. The algorithm below highlights our NIPT process. To refer a patient or for more information, please call 1- 800-454-8155.

Algorithm for patients referred for cell free DNA coordinated via Genetics



OUR TEAM

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CANCER GENETICS PROGRAM: IDENTIFYING AND SUPPORTING PATIENTS WITH HEREDITARY CANCER PREDISPOSITIONS

Approximately 5-10% of cancer is associated with an inherited cancer predisposition syndrome. Individuals with a cancer predisposition have higher chance of developing cancer, and the cancer(s) tend to occur at an earlier age. Genetic evaluation can help determine whether an individual or family is likely to have a hereditary cancer syndrome.

The Cancer Genetics Program – a joint Program of UPMC Cancer Centers and Magee-Womens Hospital– has been providing risk assessment and education for individuals and their families for over 20 years. The Program officially joined the Department of Reproductive Genetics in early 2016. In addition to providing genetic counseling and genetic testing, the Cancer Genetics Program also offers a comprehensive cancer risk assessment that takes into account family history along with personal cancer-specific risk profiles, including environmental and lifestyle factors. Dr. Aleksandar Rajkovic, Medical Director of the Department of Reproductive Genetics explains: "Understanding the individual cancer risks is important, as it allows us to take the proper actions to mitigate these risks and help prevent cancer from developing, and to implement surveillance strategies to detect cancer at early stages."

Who Should Be Tested?

While majority of patients at the Cancer Genetics Program are referred by physicians, individuals with concerns about their personal or family history of cancer can make an appointment themselves. "We encourage people who are concerned about the possibility of familial cancer predisposition to contact us to inquire whether they may benefit from cancer risk assessment or genetic counseling," says Darcy Thull, a Genetic Counselor with the Program.



Risk Management Recommendations

Individuals who are at risk of developing cancers due to a cancer predisposition syndrome are recommended to follow high-risk cancer surveillance and management, which might include intensive screening, risk-reducing surgery/medications, and lifestyle modifications. Individuals who are not identified to have a hereditary cancer predisposition, but who are at increased risk of developing certain types of cancers due to a combination of factors, also benefit from risk management recommendations.

Genetic Cancer Expert Joins Program

Dr. Puong Mai was recently recruited to lead the Cancer Genetics Program at Magee-Womens Hospital. Prior to joining Magee, Dr. Mai was at the Clinical Genetics Branch of the Division of Cancer Epidemiology and Genetics, National Cancer Institute. After her medical oncology fellowship at the University of Texas Health Science Center in San Antonio in 2004, Dr. Mai completed a 2-year training program in Clinical Cancer Genetics at the City of Hope National Medical Center where she focused on cancer risk assessment and management as well as genetic counseling related to hereditary cancer predisposition syndromes. Another of Dr. Mai's interests is in understanding the psychological and social impact having a hereditary cancer syndrome has on the individual as well as the family. Dr. Mai is excited about the Program's future: "The goals of Cancer Genetics Program are to obtain a better understanding of the various hereditary cancer syndromes, to better predict individual cancer risks associated with these syndromes, to provide risk-appropriate management recommendations that will lead to reduction of cancer risk and detection of cancers at their earliest stages, and to provide support to individuals and families with a hereditary cancer syndrome."



OUR TEAM

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Daniel Bellissimo PhD

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Denise Pollett PhD

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COLLABORATIONS ON GENETIC DISORDERS: HHT GENETIC TESTS

Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic disorder that affects about one in 5000 people, characterized by improper connections between arteries and veins thus forming telangiectasias or arteriovenous malformations. Complications of HHT result from such abnormal connection and include nosebleeds, hemorrhages in gastrointestinal tract, lungs, or brain, resulting in anemia, poor oxygenation and stroke.

HHT is an autosomal dominant genetic disease involving the *ENG*, *ACVRL1*, *GDF2* or *SMAD4* genes. Thus, a genetic diagnosis is highly recommended for all related family members of HHT patients. An early diagnosis, follow-up care, and long-term monitoring can help prevent the complications of HHT. So far, more than 600 different mutations have been found in HHT families including single base-pair changes to major deletions of multiple exons. Yet up to 10% of patients do not receive molecular diagnosis which may be attributed to the presence of deletions/duplications or mutations in other unknown genes.

The HHT Center of Excellence of UPMC and the University of Pittsburgh consists of clinicians, laboratory specialists, genetic counselors, and researchers. The Center aims to provide patients with the highest quality of care and to push the boundaries of current knowledge to find even better strategies for managing HHT complications. Our genetic experts at the UPMC Center of Genetics and Genomics have contributed to the HHT Center by designing and validating a high resolution microarray assay that can detect intermediate size deletions and duplications in four known HHT genes and 5 additional genes *RASA1*, *BMPR2*, *CAV1*, *CCM1/KRIT1*, *CCM2* which are associated with capillary malformations. For more information or to refer a patient, please call the HHT Center of Excellence: 412-648-6161.

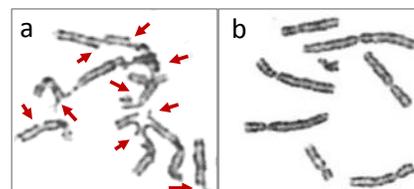
RESEARCH: DNA DAMAGE AND PREMATURE OVARIAN INSUFFICIENCY

Inherited defects in DNA repair are genetic conditions characterized by hypersensitivity to DNA damage. Double-strand breaks can induce chromosomal rearrangements such as translocations, deletions and duplications. Such genomic aberrations may trigger permanent cell cycle arrest and, ultimately, cell death or malignancy. Hereditary defects in DNA repair processes lead to syndromic recessive conditions such as Fanconi anemia and ataxia-telangiectasia. Remarkably, most patients susceptible to chromosome breakage and genome instability also present with early gonadal dysfunction.

Premature ovarian insufficiency (POI) affects 1-4% of women and is defined by irregular menses with low serum estradiol and menopausal range gonadotrophin levels in women <40 years of age. Women with POI are susceptible to early onset osteoporosis, cardiovascular disease, neurocognitive disorder and increased overall mortality.

Genetic specialists at our Center recently performed research in patients/families presenting with POI and discovered mutations in *MCM8* or *MCM9* genes which are integral to DSB repair process (Desai *et al.* 2016, AlAsiri *et al.* 2015, Wood-Trageser *et al.* 2014).

To establish a new clinical test for proper assessment of our POI patients, we initiated a translational study to evaluate DNA breakage susceptibility in the peripheral blood lymphocytes of girls and women between the ages of 14-40 diagnosed with POI. The study is directed by Dr. Aleksandar Rajkovic to utilize latest research findings into innovative clinical service to patients and their families. For details regarding the study and enrollment process, please contact: Dr Sunita Katari, M.D., kataris@upmc.edu, Pager: 412-917-0030.



Chromosome breakage (red arrows) in a patient with primary amenorrhea (a) as compared to a normal chromosomal appearance in unaffected woman. (b).

OUR TEAM

Special Congratulations to our wonderful staff at the Center for Clinical Genetics & Genomics on their career milestones:

JOHN UHRMACHER, 40 YRS.

ANDREW BEDNAR, 15 YRS.

LORETTA MCCUNE, 15 YRS.

JANICE OKELLO, 10 YRS.

Thank you!
We are so proud of you!

NEWS

The Center for Genetics and Genomics has launched a new website with complete updated information on clinics, laboratories and services. Details of our research projects and educational programs are also found at the Center website:

<http://pittgenomics.org/>

MEET THE GENETIC STAFF!

PREGNANCY SCREENING LABORATORY

Standing, left to right: Dianna Kendra and Luanne Fraer; Sitting: Kirsten Stewart.



CLINICAL GENOMICS LABORATORY

This small group of "Lab Rats" (as we call ourselves) exemplifies every quality of a great team. The degree of trust, respect, comfort and confidence that they possess in one another is rare and exceptional. Because of this, they see our common goal of providing world-class patient care with complete clarity. They truly know what this means. They are uncompromising on quality and safety, and are committed to continual improvement. They don't back down on what they believe in. They simplify. They get things done. They embrace and support one another. They share, cheer for one another, and celebrate diversity and success. They aren't afraid of challenge and their eyes are wide open. There is never more than a fleeting moment of surprise; nothing gets by this group. They handle every situation together with poise and ease, and leave no one stranded. But most importantly, they genuinely care for one another. This small team of most wonderful individuals is the best that I've had the pleasure of working with. They make my job easy, each and every day, and it is a pleasure and an honor to work with them (Denise Pollett, Lab Supervisor).



*Back row, left to right:
John Uhrmacher,
Scott Stiffler, Dr. Alex
Yatsenko, Dr. Dan
Bellissimo, Matt Filip;
Front row, left to right:
Denise Pollett, Kelly
Donahue, Heather
Bakos, Evan Powell.
Not Present: Emily
Spindler*