Zane Cohen Centre for Digital Diseases

Sinai Health System

Familial Gastrointestinal Cancer Registy

NETWORK NEWSLETTER

Fall 201

A Message from the Director

We Build Knowledge To Improve Treatment

Dear friend,

I am most pleased to share with you the Fall 2017 edition of our Familial Gastrointestinal Cancer Registry Network Newsletter. At the Zane Cohen Centre for Digestive Diseases we are fortunate to have an outstanding multidisciplinary team of over 45 clinicians, geneticists, radiologists, genetic counsellors, information system specialists, psychologists, international fellows and students. This edition highlights some of the varied work coming from our team. Our centre's leadership was showcased this past May when we hosted a symposium on hereditary GI cancer, which was attended by healthcare providers from across the province.

In this issue, we are featuring information regarding hereditary stomach cancer, polyps and rectal bleeding in children, and some of the newer genes related to hereditary polyposis. We present to you research updates from the laboratory's Lynch syndrome genetic testing, the pancreatic cancer study and exciting new research into immunotherapy treatment.

Given the success of our 2015 Polyposis Education Night, generously supported by the Erika Heller Fund, we are proud to announce that we will be hosting our second Education Night for families with polyposis on November 7th, 2017. Additionally, we will be hosting our 7th Education Night for families with Lynch syndrome on November 1st, 2017, generously supported by Ann McLaughlin and Joe Aiello.

I do hope that you find the research updates informative, and the patient support material instructive. We very much look forward to your feedback. Please feel free to contact us to learn more about any opportunities for donations to support our work. Our work is centered on you and for the generations to come.

Dr. Zane Cohen
Director, Zane Cohen Centre

Kara Semotiuk
Genetic Counsellor

Evolution of Genetic Testing

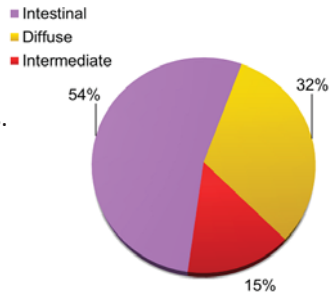
The field of genetics is advancing quickly. With new genes being discovered through research, and more efficient and cost-effective laboratory technologies being introduced, new genetic tests are becoming available. We are beginning to understand the clinical presentation of some new hereditary cancer and polyp syndromes, and to offer genetic testing for these conditions. For example, we are now testing for 2 relatively new genes called *POLE* and *POLD1*. Mutations in these genes have been reported in families with multiple adenomatous polyps, colorectal cancer and endometrial cancer. As well, the approach of genetic testing is changing with the introduction of new laboratory equipment and technologies. Labs are offering gene panel tests, meaning they can test a number of genes at once. This is in contrast to the traditional approach of more step-wise genetic testing.

While gene panels are not appropriate or indicated for everyone, they do offer a broader approach to genetic testing and might be useful for some people. We at the Familial Gastrointestinal Cancer Registry try our best to stay on top the latest genetic tests available to our patients. However, we are not able to go back to each patient or family every time a new test is introduced. Therefore, we rely on you to touch base with us periodically to see if you or your relatives might be eligible for updated genetic testing. If you have updates about your family history, or a strong family history of colorectal, endometrial or other gastrointestinal or genitourinary cancers, or multiple polyps, and your prior genetic testing was inconclusive (negative), please contact your genetic counsellor. We would be happy to review your case and see if further testing might be indicated. Please keep in mind that genetic testing is offered to people affected with multiple polyps or cancer themselves.

Melyssa Aronson
Sr Genetic Counsellor

Hereditary Stomach Cancer Q & A

The Zane Cohen Centre for Digestive Diseases specializes in hereditary stomach cancer. Here, Melyssa Aronson (Genetic Counsellor) answers some of the common questions about hereditary stomach cancer that are asked by families coming to our Centre.



Q. I have heard the term "diffuse gastric cancer". What does that mean?

A. Gastric is another word for stomach. Stomach cancers that arise from the epithelial cells (cells that line the stomach) are classified as adenocarcinomas. Adenocarcinoma can be further divided based on the way the adenocarcinoma grows and looks under a microscope. Diffuse-type adenocarcinoma accounts for 32% of the adenocarcinoma group and it is named because it grows diffusely, or widespread, often under the lining of the stomach.

Q. Are diffuse-type stomach cancer always related to a hereditary syndrome?

A. No, only 1-3% of all stomach cancer is related to a hereditary syndrome. Some features that may suggest the cancer is more likely to be related to a hereditary condition would be younger age of onset (under age 40), multiple relatives with stomach or breast cancer, stomach and breast cancer in the same individual or cleft lip/palate and diffuse-type stomach cancer. It is important to note that most cases of stomach cancer are NOT hereditary (including most cases of diffuse-type stomach cancer)

Q. Is it only diffuse-type stomach cancer that can be hereditary, or can other types of stomach cancer (such as intestinal-type) also be hereditary?

A. All types of stomach cancer can be hereditary and our suspicion is raised for reasons listed above, such as young age of diagnosis, multiple relatives with stomach or related cancers, multiple colon polyps or cancers in one person.

Q. If someone has a family history, or younger age of onset, what is the chance they will have a hereditary cancer syndrome?

A. Depending on how striking the family history is, or how young the patient is, we may highly suspect a hereditary cancer syndrome. However, the chance that we will find an answer through genetic testing is still pretty low in 2017. If someone has a high-risk family, there is a 10-20% chance we will identify the genetic condition in the family. The most common condition causing hereditary diffuse-type stomach cancer is Hereditary Diffuse Gastric Cancer Syndrome or HDGC. There are a few other conditions that have been linked to hereditary stomach cancer, such as Lynch syndrome and Familial Adenomatous Polyposis.

Q. If I had genetic testing and no mutations were found, does that mean my stomach cancer is NOT related to a hereditary syndrome?

A. No. If no mutation was found through genetic testing, it is possible that the current technology could not identify the mutation in your family, or perhaps the gene causing the cancer in your family has not yet been discovered. Testing continues to expand and improve, so if you had testing before 2016, you should contact your genetic counsellor to see if you qualify for additional testing.

Dr. Carol Durno
Pediatric Gastroenterologist

Is All Rectal Bleeding in Children and Adolescents Related to Polyps?

Some hereditary conditions, such as Juvenile Polyposis Syndrome and Familial Adenomatous Polyposis, can lead to polyps developing in children and adolescents, where other conditions, such as Lynch syndrome, rarely impact children. If a child or teen experiences rectal bleeding it is important to seek medical attention. In young patients with a family history of polyps or colon cancer it is important to report the bleeding to an expert, familiar with polyposis syndromes. A medical consultation will help determine whether further investigations are indicated. The history of the bleeding is often helpful to determine the most likely cause of the bleeding. Not all rectal bleeding is related to polyps. If the child experiences abdominal pain or feels faint or dizzy, or if there is significant bleeding (tablespoon or more), seeking immediate medical attention is recommended. Telehealth can also be contacted for management advice and guidance. Fissures are a common cause of rectal bleeding. A fissure is similar to a paper cut in the anus. Fissures can be related to hard bowel movements or large stools. Often anal pain accompanies the bleeding associated with fissures. Blood from a fissure is typically on the surface of the stool or the toilet paper. Stool softeners will often be suggested. It is important to know if the consistency of the stool has changed. If the stools are looser and more frequent compared to normal, an infectious gastroenteritis is a possible explanation. If mucus (white or clear material) is associated with the bleeding, infection should be considered. Stools are often sent for culture to identify an organism. Blood and mucus in the stool can be related to colitis (inflammation of the colon= large bowel). Causes of colitis include infection or inflammatory bowel disease. Young patients can develop rectal bleeding from a single polyp. A common cause of rectal bleeding is an isolated juvenile polyp. These polyps are very vascular so bleeding is common. The bleeding history is often bleeding for a few days and then it resolves and returns weeks or even months later. If your child has recurrent rectal bleeding it is best to be evaluated by a gastroenterologist. Blood tests are often performed when a patient has rectal bleeding to determine if the red blood cell count is decreasing. Occasionally, other imaging tests such as a Meckel's scan or air enema are performed to check for other causes of bleeding. A colonoscopy may be ordered to determine the cause of the bleeding. At colonoscopy it is possible to see colitis or polyps. If polyps are identified they can often be removed during the colonoscopy. The polyps are sent to pathology for review. Depending on the type of polyp and number of polyps, recommendations can be made as to ongoing management. Talk to your kids about rectal bleeding. Educate them to report any rectal bleeding so that professional guidance can be obtained.

Jordan Lerner-Ellis
Laboratory Director

Lynch Syndrome Genetic Testing at the Mount Sinai Hospital Laboratory

Around 3% of all colorectal cancers (CRC) occur due to Lynch Syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer), an inherited condition caused by a mutation in one of five known mismatch repair (MMR) genes: *MLH1, MSH2, MSH6, PMS2* or *EPCAM*. A mutation in a MMR gene impairs a cell's ability to fix DNA damage, leaving it more likely to become cancerous. People with Lynch Syndrome are at a higher risk of developing CRC, endometrial, and other cancers in their lifetime, and often at earlier ages. When an individual is known to have Lynch syndrome, targeted cancer screening can be started at younger ages, ideally preventing a cancer or catching it early. In 2001, Ontario's Ministry of Health and Long-Term Care started a genetic testing program for Lynch Syndrome. Since Lynch Syndrome is relatively rare, criteria were established to decide who should have MMR gene testing. The criteria include: 1) knowledge of a MMR gene mutation in a family, 2) cancer diagnosis with a high-risk family history (young age at diagnosis and/or multiple relatives with Lynch syndrome-associated cancers), or 3) microscopic features seen in the tumour suggestive of a MMR gene mutation (ie. missing one or more MMR gene proteins). Researchers at Mount Sinai Hospital recently published an article in the journal *Cancer*, which describes how many new individuals were found to have Lynch Syndrome based on these criteria. As of 2015, Mount Sinai Hospital's Advanced Molecular Diagnostics lab has performed MMR gene testing for over 1400 people and identified almost 600 of them to have Lynch Syndrome. When a relative had a MMR gene mutation, roughly half of the immediate family members (49.9%, 298 of 597) were found to have the same mutation, as would typically be expected knowing the inheritance pattern of Lynch syndrome. Of individuals with cancer and a high-risk family history, 17.6% (34 of 193) were found to have a mutation. For individuals diagnosed with a tumour that was missing one or more MMR gene proteins, 37.9% (251 of 662) were found to have a mutation. The most commonly missing MMR gene protein in the tested population was *MSH2*, and they had the highest rates of MMR gene mutations, 51.5% (115 of 229). Overall, this study found that the Ministry of Health criteria successfully identified individuals with Lynch syndrome. Once a family is identified to have a MMR gene mutation, predictive testing for an individual's unaffected relatives can determine which other family members would benefit from preventative screening and surgical interventions, and which family members are at general population cancer risk. In a public healthcare system, testing for at-risk relatives in families with Lynch syndrome is both cost-effective and life-saving.

We invite you to partner with us
www.zanecohencentre.com/donate

Dr. Steven Gallinger
HPB Surgeon

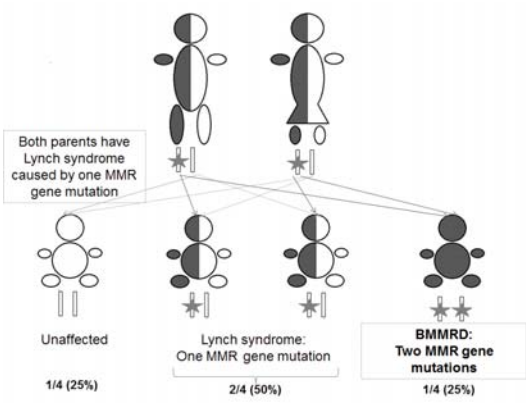
Ontario Pancreas Cancer Study

Pancreatic adenocarcinoma (PA), the most common type of pancreas cancer, is the fourth leading cause of cancer related deaths worldwide and remains one of the most fatal malignancies with minimal improvements in survival rates over the last few decades. Dr. Steven Gallinger is the Principal Investigator of the Ontario Pancreas Cancer Study (OPCS) at Mount Sinai Hospital and the University Health Network. The objectives of the OPCS are to identify and characterize causes of pancreas cancer, including genetic, environmental, and lifestyle factors, as well as explore treatment options available to patients with this disease. The OPCS is a large registry with overall aims to help us better understand risk factors, patterns of inheritance, and discover possible genetic and biochemical markers of pancreas cancer. In addition, we are interested in evaluating pancreas cancer screening techniques with the hope that, in the future, the disease may be detected at an early stage. Eligible participants include those living in Ontario with a recent diagnosis of pancreas cancer. The first stage of the study involves obtaining information about family history, treatment, and personal history/lifestyle from a questionnaire package that is provided to participants. The second stage of the study involves collecting blood (or saliva), medical records, and any available tissue samples from previous biopsies or surgeries (if applicable). These samples are used to investigate potential sources of genetic risk of pancreas cancer. If there is a family history of cancer, genetic counsellors can provide information and make referrals for further genetic assessment and possibly genetic testing and cancer screening, when appropriate. We are now in our 15th year and have recruited over 2200 participants since 2003. We are fortunate to have an outstanding team of researchers, genetic counsellors and clinicians to collaborate together on multiple national and international research projects.

Dr. Uri Taborri
Haematologist-
Oncologist

Immunotherapy Treatment of the Childhood Cancer Condition BMMRD

Bi-allelic mismatch repair deficiency syndrome (BMMRD) is a rare condition which occurs when a person inherits faulty DNA repair genes from both of their parents. The mismatch repair (MMR) genes are the same genes that cause Lynch syndrome. Having one MMR gene mutation causes Lynch syndrome, and having a mutation in each copy of a MMR gene causes BMMRD (see diagram for BMMRD inheritance). When DNA is copied, a mismatch can occur if the wrong combination of DNA building blocks is put together. The MMR pathway works to correct mistakes, or mutations, made in this process. Since someone with BMMRD has defects in the MMR genes involved in this pathway, they cannot correct these errors like most people can. Consequently, they accumulate mutations in their DNA that may lead to the development of childhood cancers, including those affecting the brain, gastrointestinal system and blood. Our group, centered in Toronto, established the International BMMRD Consortium (IBMMRDC) to learn more about the treatment and management of BMMRD. This is a global collaboration involving physicians, genetic counsellors and researchers from more than 30 countries who study biological and clinical data collected from over 100 affected patients and their families. Although there is currently no known cure for BMMRD, research carried out by the consortium has shown that the tumours found in BMMRD patients have a very high number of errors in their DNA compared to other childhood cancers, and are thus termed 'hypermutant'. Because the DNA in these hypermutant cancers is so damaged, researchers believe that they may be sensitive to treatment with immune checkpoint inhibition (ICI), which works by priming the patient's own immune system to tackle the cancer. Our immune system distinguishes between cells that belong to our body and those which are considered 'foreign,' such as bacterial cells.



Inheritance of BMMRD

Unfortunately, the immune system does not always identify cancer cells as 'foreign', as many cancer cells have evolved ways to hide from the immune system. However, tumours with a lot of DNA mutations are more likely to look 'foreign' and activate the immune system. ICI drugs, such as Nivolumab, target the immune system and give it a boost, increasing the chance that it will be able to attack cancers in BMMRD patients. We were the first to show that BMMRD cancers can disappear when treated with ICI (Bouffet et el. Journal of Clinical Oncology 2016). Currently, more than 20 patients registered with the IBMMRDC have been treated with ICI. Initial results are very encouraging, and significant tumor shrinkage has been observed in brain, gastrointestinal and other cancers. This suggests that ICI may be a very promising approach for treating cancers in patients with BMMRD. To further investigate the use of ICI in treating BMMRD, an international clinical trial recently opened at the Hospital for Sick Children, with involvement across four continents. Over several years, this trial will assess the effectiveness of ICI in children with BMMRD (between ages 1-18 years) with recurrent or progressive MMR deficient cancers. To learn more about hypermutant tumours and the IBMMRDC, please visit our website at https://www.sickkids.ca/MMRD/index.html

FGICR UPDATES

Zane Cohen Centre Hosts Hereditary GI Cancer Symposium

Keynote Speaker Dr. Patrick Lynch, with Dr. Zane Cohen

The leadership of the Zane Cohen Centre (ZCC) was showcased at the Hereditary Gastrointestinal (GI) Cancer Symposium, when genetic counsellors, physicians, pathologists and molecular geneticists gathered for a provincial symposium hosted by the ZCC. Nearly 150 clinicians attended from across the province, and were provided with an update on hereditary GI cancer syndromes and the current state of tumour and germline testing within Ontario. The symposium also created working groups to establish an Ontario-wide consensus on genetic testing algorithms and the use of cancer gene panels for hereditary GI cancer syndromes. Recommendations from the working groups will be presented to Cancer Care Ontario. The symposium's keynote speaker was Dr. Patrick Lynch, a gastroenterologist at MD Anderson in Texas. Dr. Lynch presented on the evolving tools to work up the most common hereditary colorectal cancer syndrome, known as Lynch syndrome, which was named after his father. An expert in hereditary cancer syndromes, he has a busy practice following these patients, he is well published in this area, he serves on many boards to establish guidelines for testing and surveillance in these conditions, and has also headed up important drug trials to try and prevent polyps in FAP and Lynch syndrome. Informative presentations were given throughout the day by Dr. Sav Brar on hereditary stomach cancer, Dr. Sarah Ferguson on endometrial cancer in Lynch syndrome, Dr. Uri Tabori on novel therapies (immunotherapy), Dr. Robert Gryfe on new polyposis conditions, Melyssa Aronson on an update for provincial testing criteria, Dr. Nancy Baxter on an update on population-based tumour testing and Dr. Aaron Pollett on a review of governmental processes for hereditary cancer protocols. Held on May 26, 2017 at the Hyatt Regency Toronto, this event was made possible thanks to a generous donation from the Erika Heller Fund.

Lynch Syndrome Education Night

Lynch syndrome is a rare genetic condition that greatly increases the risk to develop cancer, primarily colorectal and endometrial cancer. At one time, it was thought that all colorectal cancer followed a similar pathway to becoming cancerous, but we now know that this is not the case. While most lectures on colorectal cancer refer to the general population, talks for families with Lynch syndrome should be tailored to the research on risk, screening, and treatment of cancers in these families. It was for that reason that an education night just for families with Lynch syndrome was created. We began hosting this night in 2003 and over the years, have invited surgeons, gastroenterologists, gynecologists, pathologists, family physicians, dermatologists and psychologists to update our families on the latest research and understanding of this syndrome. We also invited individuals with Lynch syndrome to share their stories, which were always greatly appreciated by the audience. **We will be hosting the 7th Biennial Lynch Syndrome Education Night on November 1, 2017**. If your family has Lynch syndrome, you should have received a special flyer with details on the speakers for this night, along with the time. If you have not received a flyer and are interested in attending, please feel free to contact us at 416-586-4800 ext. 5112 and we can add you to the mailing list designed for this evening. More information can be found at zanecohencentre.com/event/lynch

Education Night for Families with Familial Polyposis: A Special Thank You to the Erika Heller Fund

There are two main types of familial polyposis: Familial Adenomatous Polyposis (FAP) and *MUTYH*-Associated Polyposis (MAP). Both are rare genetic conditions that cause multiple polyps (mainly adenomas) in the colon and rectum, starting from as young as childhood. There is a high risk for the polyps to turn into colorectal cancer, if not removed. There is also a milder form of FAP called Attenuated FAP, where fewer polyps develop, and at later ages. FAP and MAP are passed down differently in families, and therefore risks to relatives will vary. In 2015 we hosted our first education night for families with FAP, Attenuated FAP and MAP to address issues specific to these conditions. This evening was a huge success, made possible by generous support from the Erika Heller Fund. **The next Familial Polyposis Education Night will be held on Tuesday November 7, 2017**. If your family has FAP, Attenuated FAP or MAP, you should have received a special flyer with details on the speakers for this night, along with the time. If you have not received a flyer and are interested in attending, please contact us at 416-586-4800 ext. 5112 and we can add you to the mailing list designed for this evening. For more information, or to RSVP, please visit: zanecohencentre.com/event/polyposis

Staff of the Zane Cohen Centre thank you for your continued support

Laura Winter
Genetic Counsellor

Peer Support Program

The FGICR is committed to offering support to families with hereditary gastrointestinal cancer and polyposis syndromes. An important part of this support is our ability to connect people who share the same hereditary conditions. For decades, individuals and families involved in the FGICR have found it very helpful to connect through the Peer Support Program (aka Buddy System), and have benefited from sharing experiences with each other. Research studies have proven peer support programs to have social and emotional benefits.
As these hereditary conditions can be rare, we are so appreciative of the men, women and children who have volunteered to provide support to their peers over the years. This program matches people based on diagnosis and other factors. Matches are made on request, and have been particularly helpful at the time of a new diagnosis, around the time of a surgery, and when parents have concerns about their children.
In an effort to formalize the Peer Support System, we are asking if you are willing to be included as a potential match to please complete a form online at www.zanecohencentre.com/fgicr/peer, or to complete a paper participation form. You may be contacted if you are matched with someone in need of support. As someone with personal experience with a hereditary cancer syndrome, you are uniquely qualified to help someone like you.
Thank you for your participation.

Zane Cohen Centre for Digestive Diseases
Sinai Health System

We Invite You to Partner With Us ...
... as we "join the dots more quickly" to bring new knowledge into practice for better care for patients and their families.

There are many ways to support our work. These include gifts of cash, stocks or existing insurance policies.

Legacy gifts to the Zane Cohen Centre can also be designated in a will.

To donate online: www.zanecohencentre.ca/donate
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