LYNCH SYNDROME PROGRAM

NEWSLETTER

October 2023

FALL 2023 EDITION

DIRECTOR'S Welcome

Bryson Katona, MD, PhD
Director, Penn Medicine's Lynch Syndrome Program

Assistant Professor of Medicine Division of Gastroenterology and Hepatology

University of Pennsylvania Perelman School of Medicine

Hello all, I hope that everyone has had a wonderful summer! 2023 has been off to an exciting start with our 2nd Annual Lynch Syndrome Symposium in the spring followed by our first Lynch syndrome-focused webinar. We highlight both of these events in this issue of our Lynch Syndrome Program Newsletter. We also profile Dr. Emily Chu and Dr. Ken Cadwell and their work in Lynch syndrome, as well as provide some important research updates. Additionally, in this issue's Genetic Counseling Corner, Arravinth Anantharajah MS, CGC discusses family planning with Lynch syndrome. I hope you all enjoy this issue of our Lynch Syndrome Newsletter, and I hope to see you at one of our upcoming events.

UPCOMING EVENTS

November 13, 2023 | 5 pm
Talking Lynch syndrome: Strategies for discussing Lynch syndrome with your children and family
Virtual
Featuring:
Jessica Long, MS, CGC—Penn Medicine
Sarah Baldino, MS, CGC—CHOP
Mary Egan Clark, MS, CGC—CHOP

March 11, 2024 | 10 am to 6 pm
3rd Annual Lynch Syndrome Symposium
Rubenstein Auditorium
Smilow Center for Translational Research
Penn Medicine
3400 Civic Center Blvd
Philadelphia, PA 19104

Note: Registration information for these events to be available soon.

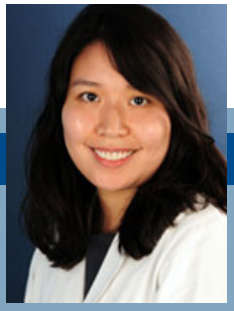
Penn Medicine

2ND ANNUAL LYNCH SYNDROME SYMPOSIUM RECAP

The 2nd annual Lynch Syndrome Symposium was held this year on March 22, which was also Lynch Syndrome Awareness Day. We had more than 300 registrants for the symposium, with a fantastic group of attendees both in-person and virtually. The patient-focused talks in the morning included breakout sessions focused on both women's and men's health, and there was also a riveting hour-long multidisciplinary panel discussion that answered numerous questions from attendees. The discussion would have kept going if time permitted! After multiple lunch breakout sessions, our Borrelli Family Keynote Talk was delivered by Dr. Eduardo Vilar Sanchez from MD Anderson Cancer Center. The talk was focused on opportunities for vaccine development in Lynch syndrome. The afternoon was research focused with talks ranging from exploring the impact of psychological stress on colorectal cancer in Lynch syndrome, to outcomes of genetic testing amongst all individuals with colorectal cancer, to the results of universally performed gastric biopsies in patients with Lynch syndrome who are undergoing upper endoscopy. Much of the content from the symposium is available as recordings online, so please visit our symposium website to learn more. **www.med.upenn.edu/lynchsyndromesymposium**

INSPIRING PATIENT STORIES ABOUT LYNCH SYNDROME

Everyone diagnosed with Lynch syndrome has their own personal story, and each of these stories is undoubtedly different and unique. We are honored to be able to share two inspirational stories, from Joel and Pamela, about their own journeys with Lynch syndrome. These stories can be found on the **Gastrointestinal Cancer Genetics Program** website.



PROVIDER SPOTLIGHT

Emily Chu, MD, PhD
Associate Professor
Dermatology & Pathology and Laboratory Medicine

Department of Dermatology

Hospital of the University of Pennsylvania

Tell us about yourself.
I am a dermatologist and dermatopathologist, specializing in the diagnosis and treatment of melanoma and genetic conditions affecting the skin (including Lynch syndrome).

What motivates you to take care of patients with Lynch syndrome? Since Lynch syndrome patients may have a variety of health concerns, it is gratifying to be able to help at least in the domain of their skin health.

What are the most important roles that a dermatologist plays in the management of Lynch syndrome?
One of the most important things a dermatologist can do for Lynch syndrome patients is to help make the appropriate diagnosis and guide treatment of any Lynch-related skin lesions, which include sebaceous tumors and squamous cell carcinomas. Many of the sebaceous tumors are benign, but some show more concerning changes under the microscope and necessitate surgery to ensure removal. Since I am a dermatopathologist also, the microscopic diagnosis of sebaceous tumors is of particular interest to me, since it is not always straightforward.

What do you see as exciting future directions for the care of patients with Lynch syndrome? We are learning more about molecular markers of Lynch-related skin lesions, which may ultimately make it easier to make diagnoses and may even impact treatment approaches.

FIRST LYNCH SYNDROME WEBINAR FOCUSES ON RESISTANT STARCH

We were excited to host our first Lynch syndrome-focused patient educational webinar this spring focused on the use of resistant starch in Lynch syndrome. Entitled "Resistant Starch: What is it, where do I get it, and how may it potentially benefit Lynch syndrome?," this webinar was moderated by Dr. Bryson Katona and featured a presentation by two of our star dieticians within Penn's Division of Gastroenterology and Hepatology, Jessica Griffin and Laura Dickens. This webinar provided an overview of recent data showing that resistant starch may decrease risk of certain cancers, explained what resistant starch is, and also explored ways to increase one's intake of resistant starch. This webinar will be available on our future new Lynch Syndrome Program webpage (which is under development). Additionally, Jessica Griffin and Laura Dickens put together an informational handout about resistant starch that will also be found at the Program website and will be attached to the end of this newsletter. We hope to see you at our next webinar this fall, which will focus on strategies for discussing Lynch syndrome with your children and families.

FLU SHOT SEASON – STUDYING IMMUNE HEALTH IN LYNCH SYNDROME

Our **L**ynch syndrome **I**mmune **P**rofiling **P**roject (LIP2) study, frequently referred to as the "LIP2 study," is a longitudinal study being run by Drs. Bryson Katona and John Wherry. This study has a goal of characterizing the immune profile in peripheral blood of individuals with Lynch syndrome and also determining the immune response to vaccinations in individuals with Lynch syndrome. More than 250 individuals with Lynch syndrome have already enrolled in LIP2. With flu vaccine season approaching, this study aims to collect blood samples before and after a flu vaccine. If you might be interested in participating in this portion of LIP2, please contact the study research coordinator, Michaela Dungan, at Michaela.Dungan@Pennmedicine.upenn.edu.

RESEARCHER SPOTLIGHT

Ken Cadwell, PhD
T. Grier Miller Professor of Medicine

Division of Gastroenterology and Hepatology, Department of Medicine

University of Pennsylvania Perelman School of Medicine

Tell us about yourself.
I am a father of two school-age kids. I recently moved to Philly from New York because I was attracted by the incredible research community at Penn. My lab investigates how a balanced immune response is achieved in the gut.

How did you become interested in conducting research in Lynch syndrome?
The problems underlying colorectal cancer, which is more frequent in Lynch syndrome patients, resemble those associated with another disorder that my lab studies called inflammatory bowel disease. In both cases, an overactive immune response causes collateral damage to the gut.

Congratulations on being one of the recipients of this year's Borrelli Family Pilot Grant in Lynch Syndrome. What type of research are you going to pursue with this award?
We would like to develop and apply an advanced technique for comprehensively profiling intestinal tissue at single cell resolution to identify the immune and gut signatures of Lynch syndrome. We hope to use this information to infer the molecular underpinning of colorectal cancer susceptibility. This project is only possible thanks to the generous funding provided by the Borrelli Family Pilot Grant in Lynch Syndrome.

What do you see as some of the most important questions in Lynch syndrome that need answering in the future?
In contrast to our understanding of genetic susceptibility, how the immune environment of the gut contributes to cancer in Lynch syndrome is obscure and merits further study.

Genetic Counseling CORNER

FAMILY PLANNING WITH LYNCH SYNDROME

Arravinth Anantharajah, MS, CGC
Genetic Counselor
Division of Hematology and Oncology
Penn Medicine

Our genetic make-up aside, the experience of starting a family can look vastly different from one person to the next. For some, family planning is simply an aisle at the convenience store. For others, preparing for new life is a carefully calculated process. No matter the approach, having Lynch syndrome poses unique challenges to future parents. The possibility of a child inheriting Lynch syndrome from a parent is a common source of guilt. Questions such as "Am I doing the right thing?" or "Should I have biological children?" are frequent. Where definitive answers are hard to come by, I find it especially important to be able to provide individuals with strategies to address their feelings. Placing a focus on making an informed decision, rather than fixating on a specific outcome, can be a helpful way to make a decision that is best for you and your family.

COMMUNICATING WHAT IS IMPORTANT TO YOU

Our personal values can help us determine our priorities when it comes to starting a family. In some cases, the desire to have a genetically related child can helpfully inform family planning. In other cases, the desire to have |a child without a specific genetic condition may guide decision-making. These desires are entirely personal and there are no right or wrong answers. Communicating these desires to your partner and/or healthcare providers can be a useful step in facilitating a discussion about family planning with Lynch syndrome.

DOES MY PARTNER NEED GENETIC TESTING BEFORE WE HAVE A CHILD?

Constitutional Mismatch Repair Deficiency Syndrome (CMMRD) is a rare condition that can occur when both biological parents have Lynch syndrome due to a pathogenic variant in the same gene. Though rare, CMMRD is a life-threatening condition. As such, some partners opt for their own genetic testing to rule out the possibility of CMMRD in children. If your partner does not have a personal or family history of colon or uterine cancer, the risk of having a child with CMMRD is very low. Meeting with a genetic counselor when considering pregnancy can help clarify these risks.

WHAT KINDS OF TECHNOLOGY ARE AVAILABLE TO ASSIST WITH HAVING CHILDREN?

Multiple technologies exist to help individuals and/or couples achieve pregnancy. Assisted reproductive technology (ART) is a general term used to describe fertility treatments that involve the handling of sperm and or eggs to achieve pregnancy. ART methods vary by cost, ability to screen for genetic conditions, and ability to have a genetically related child. One example of ART is in-vitro fertilization (IVF). IVF is the process by which an egg is fertilized by sperm in a laboratory (outside the body). The fertilized egg (or embryo) is then transferred to the uterus.

IVF can be performed in combination with a type of genetic testing called pre-implantation genetic testing for monogenic (single-gene) disorders, also called PGT-M. PGT-M is a genetic test performed on embryos to assess for genetic conditions such as Lynch syndrome. PGT-M can be used to transfer embryos that do not carry the pathogenic variant that causes Lynch syndrome in a family.

IS PRE-IMPLANTATION GENETIC TESTING (PGT-M) AVAILABLE FOR EVERYONE WITH LYNCH SYNDROME?

Unfortunately, PGT-M is not available for every family. This is because PGT-M involves the development of a custom test by the performing laboratory. This type of testing is completed by performing a biopsy on an embryo while it is still outside the body. Because only small amounts of DNA are available for testing, the laboratory will request additional information to help interpret the results. For example, they may request a DNA sample from a relative. This is usually obtained from a grandparent or sibling of the expected child. Ideally, this relative will carry the same pathogenic variant that is being tested for. PGT-M may be possible without a

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sample from a relative. The ability to have PGT-M varies based on the availability of embryos, relatives, and the type of pathogenic variant in the family.

Managing expectations throughout the IVF process is important. For many individuals, more than one IVF cycle is needed. This can be a financially costly procedure and may not be the right fit for all families. Furthermore, transfer of an embryo into the uterus does not guarantee pregnancy. Between test development, request of additional samples, and embryo transfer, achieving pregnancy via IVF is a process that requires time and resources.

WHAT IF I DECIDE TO CONCEIVE WITHOUT ASSISTED REPRODUCTIVE TECHNOLOGY (ART)?

For many couples, conceiving without ART is the best fit for their family. In these cases, it is important for at-risk children to be tested to determine their medical management recommendations (i.e. when to start colonoscopy). A genetics provider can assist in determining the appropriate age for testing your child. In general, professional societies advise to wait until adulthood to test for Lynch syndrome. An adult may wait until the age at which colonoscopy is recommended or earlier. Currently, people with pathogenic variants in *MLH1, MSH2,* or *EPCAM* are advised to start colonoscopy screening between the ages of 20-25. For people with *MSH6* or *PMS2* pathogenic variants, current recommendations include colonoscopy starting at 30-35. It is important to check in with your genetics provider periodically, as these recommendations may change over time and may be personalized based on the family history of cancer.

GIVING BACK

We are indebted to our incredible donors, whose generosity has allowed our Lynch Syndrome Program to grow and has enabled our research program to expand. We would like to specifically thank:

Jason and Julie Borrelli
Jeffery and Cynthia King
Scott and Suzi Lustgarten

If you are interested in supporting Penn's Lynch Syndrome Program, please contact Katie Dewees Detzel (kdewees@upenn.edu) in Penn's Development Office.

LYNCH SYNDROME RESEARCH UPDATES

1 **Multigene panel genetic testing has a high yield of clinically actionable variants in patients with colorectal cancer.** (Sarah E. Coughlin et. al., JCO Precision Oncology, 2022). In this study, performed through a collaboration between investigators at the University of Pennsylvania and Invitae, the genetic testing results of more than 34,000 patients with colorectal cancer were analyzed. This is the largest study of genetic testing results in patients with colorectal cancer-to-date, and also has the most diversity amongst the patients analyzed. This study demonstrated that 9.1% of all colorectal cancer patients had a genetic mutation found in a gene that increases colorectal cancer risk (including 5.7% with Lynch syndrome) and additionally 3.1% of patients had a genetic mutation in a non-colorectal cancer gene that is associated with increased cancer risk. Together, this data provides the largest and most diverse outcomes from genetic testing in patients with colorectal cancer and provides support for expanding criteria for genetic testing in colorectal cancer to allow more patients to undergo genetic testing and hopefully to also encourage insurance companies to provide coverage for this testing.

2 **MMR deficient rectal cancer has complete response to immunotherapy.** (Andrea Cercek et. al., New England Journal of Medicine, 2022). Treatment of rectal cancer often involves initial chemotherapy and radiation followed by surgical resection. In this phase 2 study, twelve patients with mismatch repair-deficient rectal cancer (some of whom had Lynch syndrome) were treated with only a single agent immunotherapy regimen (dostarlimab), without radiation and without surgery. All twelve patients (100%) in the study had a complete response of their tumor, with no residual tumor noted on subsequent imaging studies. Longer term follow-up studies are needed to assess the length of this response, but these initial results are incredibly promising. This exciting data demonstrates patients with Lynch syndrome who develop rectal cancer may be able to undergo definitive treatment with immunotherapy alone and potentially avoid for surgery for their rectal cancer.

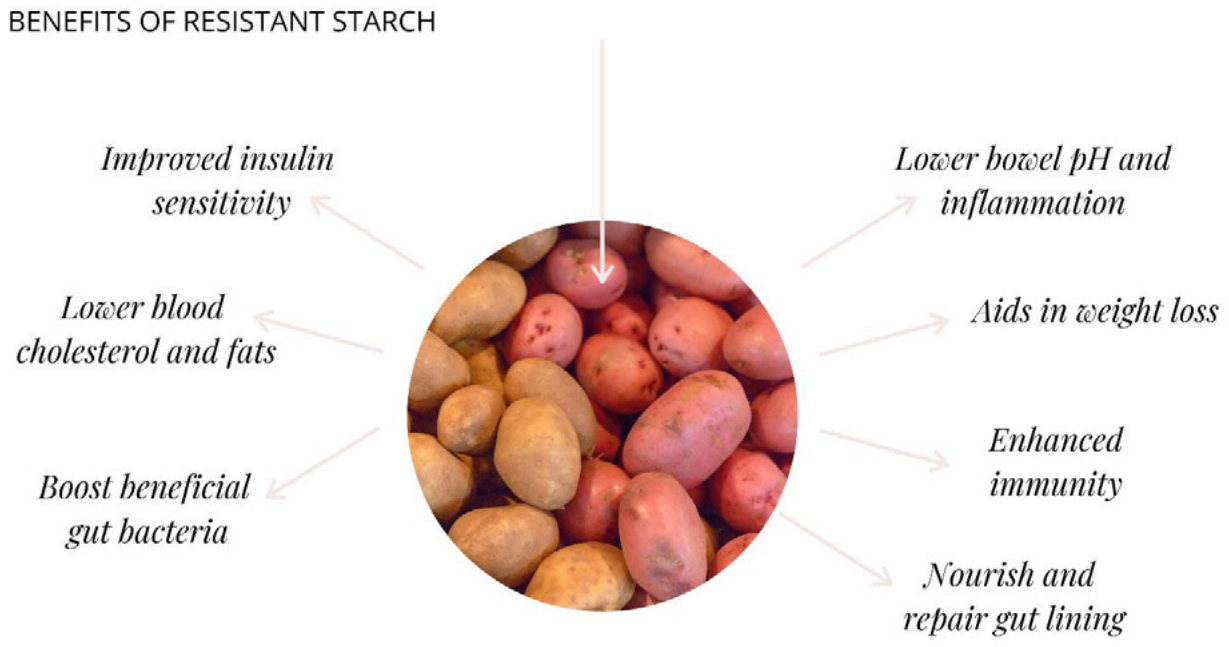
3 **Endoscopic screening detects upper gastrointestinal cancers and other important findings in Lynch syndrome.** (Shyam Vedantam et. al., Gastrointestinal Endoscopy, 2023). This study was a meta-analysis that looked at nine different studies evaluating the use of upper endoscopy in Lynch syndrome. Included in the studies analyzed were 2,356 patients with Lynch syndrome who underwent more than 7,000 upper endoscopies. The study concluded upper gastrointestinal tract screening with upper endoscopy led to detection of upper gastrointestinal tract cancers, precancerous lesions and other important findings that are clinically actionable. Together, these findings support the use of regular upper endoscopy as part of a comprehensive cancer risk management plan in Lynch syndrome.

Jessica Griffin, MA RD LDN
Clinical Dietitian Specialist
Gastroenterology & Hepatology

Penn Medicine
University of Pennsylvania Health System

RESISTANT STARCH

WHAT IS IT?
• Starches are one of the main forms of dietary carbohydrates • Resistant starch (RS) is a type of starch that's "resistant" to digestion—your body can't break it down • This type of starch is similar to dietary fiber because it can't be fully digested, and acts like a prebiotic as good gut bacteria feed on RS, producing a short-chain fatty acid, butyrate, through a fermentation process • Butyrate is one of the most important SCFAs for gut health. It provides a host of benefits including fuel for intestinal cells and assistance in maintaining integrity of the gut lining



https://pranathrive.com/what-is-resistant-starch/

R E S I S T A N T S T A R C H

HOW TO INCORPORATE IT?
• Meal prep a batch of rice at the beginning of the week. Cooling it will allow RS to develop, and reheating doesn't decrease the amount of RS • Overnight oats: mix rolled oats with milk, yogurt, fruit and a healthy fat such as peanut butter and let soak, enjoy in the morning • Blend green bananas or plantains into smoothies. If you can't use them before they ripen, freeze them • Incorporate more beans & legumes into your meals *Aim for gradual inclusion: Since it acts similarly to fiber in the body, you could experience minor gas and bloating if you eat higher levels of RS. Gradually incorporating sources, along with adequate hydration, may help to prevent GI distress

https://pranathrive.com/what-is-resistant-starch/