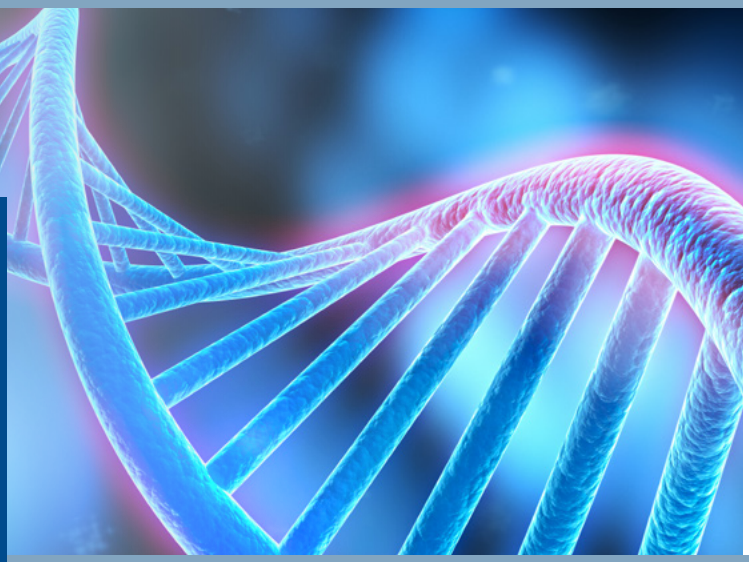
LYNCH SYNDROME PROGRAM

NEWSLETTER

November 2022

FALL 2022 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

Greetings all! I am very excited about this inaugural newsletter for Penn Medicine's Lynch Syndrome Program. This newsletter highlights many important happenings in the Lynch syndrome field, and I hope that it will serve as valuable source of information for both patients and providers in the Lynch syndrome community. In this issue we highlight our 2022 Lynch Syndrome Symposium and some of the incredible faculty who are focusing on the care of Lynch syndrome patients and research in the field here at Penn. We also discuss recent changes to upper gastrointestinal cancer surveillance, provide an update on our ongoing β-hydroxybutyrate (BHB) study, and much more. I hope you enjoy this newsletter, and please mark your calendars for the 2023 Lynch Syndrome Symposium, on March 22nd, 2023. I hope to see you there!

2023 UPCOMING EVENTS

March 22, 2023 – 2nd Annual Lynch Syndrome Symposium
Rubenstein Auditorium
Smilow Center for Translational Research
Penn Medicine
3400 Civic Center Blvd
Philadelphia, PA 19104

Date TBD – Patient-focused webinar: Resistant starch: What is it, where do I get it, and how may it potentially benefit Lynch syndrome?
Virtual

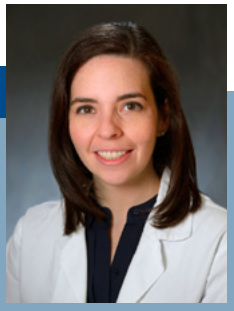
Date TBD – Provider-focused webinar: Identification and collaborative management of Lynch syndrome in clinical practice
Virtual

Penn Medicine

2022 LYNCH SYNDROME SYMPOSIUM RECAP

Penn's inaugural Lynch Syndrome Symposium, held on March 24th, 2022, was a great success with close to 300 attendees who joined either in-person or virtually. The morning of the symposium was dedicated to patient care, with talks on Lynch syndrome cancer risks, colorectal cancer prevention, and cancer screening outside of the colon in Lynch syndrome. The morning was capped off by an engaging panel discussion with a multidisciplinary group of Lynch syndrome experts, followed by lunchtime breakout sessions with expert faculty. Our keynote speaker was Dr. Luis Diaz, who gave a compelling talk highlighting advances in immunotherapy in Lynch syndrome. The afternoon consisted of a Lynch Syndrome Research Symposium, where speakers from across Penn gave talks about their ongoing research, ranging from laboratory science research to clinical science research such as using the electronic health record to promote cancer screenings in Lynch syndrome. All of the recorded talks from the symposium are available on the symposium website **www.med.upenn.edu/lynchsyndromesymposium/**

PROVIDER SPOTLIGHT



Elizabeth Clement, MD
Assistant Professor of Clinical Obstetrics and Gynecology

Department of Obstetrics and Gynecology

University of Pennsylvania Perelman School of Medicine

Tell us about yourself.
I'm a general obstetrician-gynecologist with a strong interest in preventative health care for all.

What motivates you to take care of patients with Lynch syndrome? My patients with Lynch syndrome have the ability to take concrete, actionable steps to keep themselves and family members healthy by participating in recommended screening. I feel like I can make a difference for an individual patient by helping them make proactive choices and decisions.

What are the most important roles that a gynecologist plays in the management of Lynch syndrome?
I spend time speaking with my patients about reproductive options (including in-vitro fertilization with preimplantation genetic diagnosis to select for embryos that are not affected by Lynch Syndrome - an option that some patients are very interested in and others less so), surveillance for gynecologic cancers, and discussion of timing for risk reducing surgery.
I also then manage hormone replacement therapy and sexual dysfunction for my patients who have undergone premature surgical menopause due to their risk reducing surgery.

What areas are you currently working on to improve care for patients with Lynch syndrome? I have been working with Dr. Katona to do combined endometrial biopsies at the time of colonoscopy so that patients can have that procedure done when they're asleep to avoid the discomfort of the office procedure when possible! Our patients thus far have really appreciated this.

β-HYDROXYBUTYRATE (BHB) STUDY

Exciting work from Dr. Maayan Levy's lab at Penn showed that a ketogenic diet can suppress colorectal cancer growth and progression. Additionally, Dr. Levy's lab showed that the single metabolite β-hydroxybutyrate (BHB) was found to mirror the effects of a ketogenic diet, and alone BHB could suppress colorectal cancer. Through support of Penn's Abramson Cancer Center, Drs. Maayan Levy and Bryson Katona launched an early phase study investigating the role of BHB supplements in colorectal cancer prevention. This study is being conducted in patients with Lynch syndrome, and has already accrued more than half of its target number of participants. **More information on this trial can be found here at Clinicaltrials.gov**. Stay tuned for further updates from this study, and if successful this study will hopefully lead to a larger scale study that may one day provide a dietary method for colorectal cancer risk reduction in Lynch syndrome.

CHANGES TO UPPER GASTROINTESTINAL CANCER SURVEILLANCE

Guidelines from the National Comprehensive Cancer Network (NCCN), including guidelines pertaining to the surveillance of patients with Lynch syndrome, are some of the most trusted and frequently utilized guidelines in clinical practice. This year the NCCN made a major change in recommendations for upper gastrointestinal cancer surveillance in Lynch syndrome. Specifically, the NCCN now recommends upper endoscopy in all patients with Lynch syndrome due to a pathogenic variant in *MLH1, MSH2/EPCAM,* or *MSH6* starting between age 30-40 years old and repeating surveillance every 2-4 years. Furthermore, NCCN states that upper endoscopy should also be considered in *PMS2* carriers. These changes substantially strengthen the recommendation for upper gastrointestinal cancer surveillance in Lynch syndrome. The changes were enacted due to increasing data showing that upper endoscopy identifies upper gastrointestinal tract cancers, such as gastric cancer and duodenal cancer, at early stages. Recent work from Penn's Lynch Syndrome Program provided critical evidence to move this change can be found in these two journals: AACR and MDPI.

RESEARCHER SPOTLIGHT

Maayan Levy, PhD
Assistant Professor
Department of Microbiology
University of Pennsylvania Perelman School of Medicine

Tell us about yourself.
I'm a first-generation scientist from Israel, and I moved to the United States four years ago to pursue the unconventional career path of early independence by starting my own research group after completing my PhD. In my lab we study the interface between the host and its microbiome in the gastrointestinal tract, with a particular focus on diet- and microbiome-derived metabolites. I am also the mother of two young children (aged 1 and 4) who make my days (and nights) very busy.

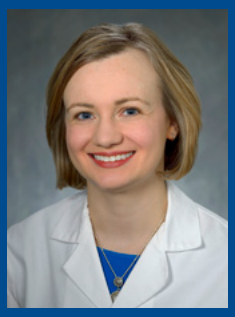
How did you become interested in conducting research in Lynch syndrome? We have recently discovered a new approach for the prevention and treatment of colorectal cancer. We identified a diet-induced metabolite-receptor-transcription factor pathway that decelerates epithelial proliferation and thereby counteracts the development of tumors in the large intestine. Dietary and other lifestyle strategies that delay or even prevent the onset of colorectal cancer are very relevant in Lynch syndrome, where effective lifestyle measures are highly sought after.

Congratulations on being the inaugural recipient of the Borrelli Family Pilot Grant in Lynch syndrome. What type of research are you going to pursue with this award?
The Borrelli Family Pilot Grant in Lynch syndrome enables us to take the first step toward translation of our basic research findings to humans. Our discovery of a diet-induced metabolite signaling pathway that suppresses colorectal tumor growth has inspired a clinical trial to assess whether the same pathway could be used to counteract colorectal cancer development in individuals with Lynch syndrome.

What do you see as some of the most important questions in Lynch syndrome that need answering in the future?
One of the most pressing questions to individuals with Lynch syndrome is what they can do in their daily lives to minimize their likelihood of developing cancer. Prevention via dietary strategies is an attractive approach that might reduce the frequency of surveillance colonoscopies and decelerate the growth of existing polyps. Furthermore, I believe that using individual metabolites as standalone interventions or in combination with more conventional modalities is even more promising with respect to feasibility and efficiency. We call this approach "metabotherapy" and hope that our project funded by the Borrelli Family Pilot Grant will serve as a stepping-stone for many more efforts in this new area.

Genetic Counseling CORNER

TALKING TO YOUR FAMILY ABOUT LYNCH SYNDROME



Jessica Long, MS, CGC
Genetic Counselor
Division of Hematology and Oncology
Penn Medicine

Discussing cancer and genetic risk in a family can be challenging. It's not uncommon to hear concerns for causing worry in relatives and parental guilt about passing on a genetic condition such as Lynch syndrome. These concerns are layered over existing family dynamics and communication styles, as well as cultural background, religious beliefs and a family's experiences with cancer, caregiving and healthcare in general. As a genetic counselor, I find it's important to help people reframe genetic risk information, in terms of thinking about genetic testing for Lynch syndrome as a way to better identify who in a family is at-risk (or not), in order to provide the necessary tools to reduce or manage cancer risk. In short, although difficult, these discussions could be life-saving!

WHEN AND HOW TO START THE CONVERSATION

After a new diagnosis of Lynch syndrome, a person may need time to adjust to the news before feeling ready to share with relatives. It may be helpful to discuss first with a trusted support person (a spouse, a friend) who is not themselves at-risk (i.e., not biologically related). If additional support is needed, connecting with your genetic counselor, a mental health provider, or a peer support person via an advocacy organization (resources below) may be helpful.

When talking with family members, consider sharing how learning about Lynch syndrome can allow for personalized, proactive medical care. Cancer risks are higher in Lynch syndrome, but there are steps a person can take to reduce those risks and help protect one's health. Simply put, genetic testing for Lynch syndrome can help determine when and how often a person should have a colonoscopy, which has been shown to help lower odds for colon cancer or to help detect colon cancer at earlier, more treatable stages. Additionally, for people with cancer, an oncologist may advise certain treatments if a diagnosis of Lynch syndrome is known, since these options may be more effective.

It's also natural that these conversations may take time and may need to occur more than once. Learning about and managing a new genetic diagnosis is a process, and it's different for each person and family depending on their own experiences with cancer.

If a family member isn't ready to pursue genetic testing – that's ok! But if they are at-risk for Lynch syndrome, it would be recommended they meet with a genetics professional to learn more. They may be advised to start closer monitoring for cancer (e.g. colonoscopy) until they decide to pursue genetic testing. Often, many people ultimately decide to have genetic testing to confirm whether they have Lynch syndrome, since this allows a person to avoid unnecessary colonoscopies if genetic testing can show they did not inherit the condition.

WHEN TO TEST CHILDREN

Multiple professional societies advise waiting until after age 18 to pursue genetic testing for adult-onset conditions (i.e., if the child's medical care will not be impacted by the genetic condition). That said, genetic counselors are still happy to speak with a family if questions arise that can be addressed.

Genetic testing for Lynch syndrome will impact medical care when decisions about colonoscopy need to occur. Currently, people with pathogenic variants in *MLH1, MSH2* and *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 in time.

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Some young adults wish to pursue genetic counseling and testing sooner, in order to know the information for the future or for family planning purposes.
Very rarely, a childhood condition called Constitutional Mismatch Repair Deficiency Syndrome (CMMRD) can arise if both parents have Lynch syndrome due to a pathogenic variant in the same gene. Meeting with a genetic counselor when considering a pregnancy can help determine if this is a concern. Other young adults may prefer to defer genetic testing for Lynch syndrome while they focus on school, new jobs and relationships, later returning for genetic testing when it's time to decide if a colonoscopy is needed.

WHERE TO FIND HELP AND SUPPORT

Penn Medicine:
https://www.pennmedicine.org/GICancerGenetics

AliveAndKickn:
http://aliveandkickn.org/

KinTalk:
http://kintalk.org/

ConnectMyVariant:
http://ConnectMyVariant.org

Imerman's Angels:
https://imermanangels.org/

FORCE Peer to Peer Navigation Program:
https://www.facingourrisk.org/get-support/PNP/index.php

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 Christian Hyde **(hydec@upenn.edu)** in Penn's Development Office.

LYNCH SYNDROME RESEARCH UPDATES

1 **Resistant starch has a protective effect against non-colorectal cancers in Lynch syndrome.**
(John C. Mathers et. al., Cancer Prevention Research, 2022). This study followed patients treated in the CAPP-2 trial, which was aimed at determining the effects of aspirin and resistant starch on cancer prevention in Lynch syndrome. When examining the data on resistant starch (where study participants were randomized to 30 grams of resistant starch daily or placebo for up to 4 years), the authors found that those patients in the resistance starch group had almost 50% fewer cancers outside of the colon. However, there was no difference in incidence of colorectal cancer. This study raises the intriguing possibility that resistant starch may decrease the risk of cancers outside of the colon in Lynch syndrome.

2 **There is substantial variation in colorectal cancer risk amongst families with Lynch syndrome.** (The International Mismatch Repair Consortium, Lancet, 2021). This study utilized 5255 families with Lynch syndrome across 15 countries. The authors showed that there were substantial familial risk factors that led to large variations in colorectal cancer risk amongst families carrying variants in the same gene. These large variations were even noted amongst families carrying the exact same variant (c.942+3A>T) in the *MSH2* gene. This study highlights that there are important risk modifiers of colorectal cancer risk in Lynch syndrome that can lead to substantially different risks of colorectal cancer amongst different families.

3 **Pancreatic cancer surveillance leads to down-staging of pancreatic cancer and prolonged long-term survival.**
(Mohamad Dbouk, et. al., Journal of Clinical Oncology, 2022) The CAPS5 study is a NCI-funded study of pancreatic cancer surveillance in high-risk individuals being run at 8 US centers, including the University of Pennsylvania. A recent report from the CAPS5 study showed that amongst high-risk patients undergoing pancreatic cancer surveillance with either MRI and endoscopic ultrasound, pancreatic cancers were found at earlier stages, with only 5% being stage 4, compared to pancreatic cancers found outside of surveillance where > 80% were stage 4. Patients with pancreatic cancers found during surveillance also had significantly prolonged five-year survival. While at this time pancreatic cancer surveillance is only recommended for patients with Lynch syndrome with a first or second degree family member with pancreatic cancer, this study shows that close monitoring of pancreases of these high-risk individuals is likely beneficial.