LYNCH SYNDROME PROGRAM

NEWSLETTER

November 2024

FALL 2024 EDITION

DIRECTOR'S Welcome

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

Jeffery and Cynthia King Assistant Professor of Lynch Syndrome Research

Assistant Professor of Medicine and Genetics

University of Pennsylvania Perelman School of Medicine

It's hard to believe the fall is here already, and I hope you all are well. In this season's newsletter, we recap our 3rd annual Lynch Syndrome Symposium, which had a record number of attendees! I am also thrilled to highlight that Penn genetic counselor, Jessica Long, has officially started as the Associate Director of Penn's Lynch Syndrome Program, and you can read more about her background and goals for the Program. Additionally, we profile Penn oncologist Dr. Parul Agarwal, as well as Dr. Alexander Huang, the recipient of the 2024 Borrelli Family Pilot Grant in Lynch Syndrome. This newsletter is filled with many other important updates, including new research findings. I hope you find it interesting and educational, and I look forward to seeing you at our upcoming Lynch Syndrome Program events.

UPCOMING EVENTS

Tuesday, November 19, 2024 | 5 pm – 6pm
Ethical and legal considerations in genetic evaluation for Lynch syndrome

Virtual
Featuring:
Jessica Ebrahimzadeh, MS, CGC
Moderated by:
Jessica Long, MS, CGC
PennMedicine.zoom.us/j/98267104170

Tuesday, March 17, 2025 | 10 am – 6pm
4th Annual Lynch Syndrome Symposium

In-Person and Virtual Event
Rubenstein Auditorium
Smilow Center for Translational Research
Penn Medicine
3400 Civic Center Blvd
Philadelphia, PA 19104
Med.upenn.edu/lynchsyndromesymposium

Note: Registration information for symposium to be available soon.

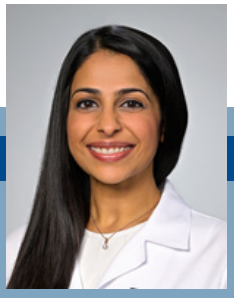
Penn Medicine

3rd Annual Lynch Syndrome Symposium Recap

The 3rd Annual Lynch Syndrome Symposium was held this year on March 11, 2024 and 600 people participated in-person or virtually! The symposium featured numerous engaging talks, including presentations on colorectal surgery considerations in Lynch syndrome as well as an update on the incredible progress on the use of immunotherapy for treatment of Lynch syndrome-associated cancers. The keynote address was delivered by Dr. Matthias Kloor from Heidelberg University in Germany. Dr. Kloor's in-depth and inspiring overview of the immune system's role in Lynch syndrome highlighted implications for cancer risk and prevention. The afternoon of the symposium was filled with cutting-edge research presentations spanning the spectrum of clinical to laboratory research. We also had another very dynamic multidisciplinary panel that answered a variety of questions from our attendees. Excitingly, this year we were able to offer continuing education units for the many genetic counselors in attendance at the symposium, which supports certification and licensure of these professionals. Much of the symposium's content is available online as recordings, so please visit our symposium website to learn more at: **www.med.upenn.edu/lynchsyndromesymposium.**

Jessica Long named Associate Director of the Penn Medicine's Lynch Syndrome Program

We are excited to announce that Jessica Long was named the Associate Director of Penn Medicine's Lynch Syndrome Program earlier this year! As Associate Director, Jessica will focus on the program's growing and incredibly important education and outreach efforts. Jessica has been a cancer genetic counselor since 2009 and joined Penn Medicine in 2012. She completed her undergraduate studies in molecular genetics with a minor in psychology, and then earned a Master's Degree in Human Genetics (Concentration in Genetic Counseling) from the University of Michigan. Jessica is passionate about helping individuals and families understand and adapt to genetic information and inherited cancer risk in ways that are meaningful to their life circumstances, and she enjoys helping educate genetic counselors and other health professionals to do the same. Jessica notes, "The awareness of hereditary cancer risk can empower people to take steps to proactively manage their health and to protect the health of their relatives." Jessica is grateful for the opportunity to support Penn Medicine's Lynch Syndrome Program in building a source of trusted information and scientific discovery related to Lynch syndrome, in addition to fostering communication and collaboration among healthcare providers, researchers, and individuals with Lynch syndrome.



PROVIDER SPOTLIGHT

Parul Agarwal, MD
Assistant Professor
of Clinical Medicine
Division of Hematology/Oncology
Perelman Center for Advanced Medicine

What are the most important roles an oncologist plays in the identification and/or management of Lynch syndrome? Oncologists play a critical role in identifying patients with Lynch Syndrome. We ensure the appropriate testing gets run on biopsy specimens to help identify patients with Lynch Syndrome. This allows us to refer patients for genetic testing and also guides our treatment options.

What areas are you currently working on to improve care for patients with Lynch syndrome? We are expanding the settings in which we offer immune-based treatments for patients with Lynch syndrome-associated cancers. We are finding that we may be able to avoid the side effects of surgery and radiation for certain cancers when we administer the right treatments. We are also optimizing how to use immunotherapy treatments in combination in order to maximize efficacy.

What motivates you to take care of patients with Lynch syndrome? The number of effective treatments for Lynch Syndrome associated cancers continues to expand. Some patients with advanced cancer can experience long-term responses with minimal toxicities from immune-based treatments. The opportunity to provide these treatments motivates me every day!

Establishment of the Jeffery and Cynthia King Professorship of Lynch Syndrome Research

The Jeffery and Cynthia King Professorship of Lynch Syndrome Research was established this year by Jeffery and Cynthia King as well as their daughter and son-in-law, Julie and Jason Borrelli. The King and Borrelli families are dedicated advocates for Lynch syndrome research, education, and awareness. Julie Borrelli is also the new Chair of the Abramson Cancer Center Director's Leadership Council.

This Professorship is the first of its kind at Penn in that it will provide support to the holder of the professorship that can be dedicated toward Lynch syndrome research. Bryson Katona, MD, PhD, a gastroenterologist at Penn and Director of Penn Medicine's Lynch Syndrome Program, was named the inaugural holder of the Jeffery and Cynthia King Professorship of Lynch Syndrome Research. "I am so incredibly humbled and honored to have been selected to serve as the inaugural holder of this Professorship. The support provided by the Jeffery and Cynthia King Professorship of Lynch Syndrome Research will be critical to furthering our program's research initiatives and priorities in Lynch syndrome, which we hope will ultimately improve the lives of individuals with Lynch syndrome," states Dr. Katona.

RESEARCHER SPOTLIGHT

Alexander Huang, MD
Assistant Professor of Medicine
Division of Hematology/Oncology
University of Pennsylvania
Perelman School of Medicine

Tell us about yourself.
I am a medical oncologist and an immunologist. When I was in medical school, I took a year off to see what research was like. During that year, I worked in a cancer vaccine lab, and I saw the hope that immunotherapy gave to patients, and this inspired me into a career of translational cancer immunology research.

How did you become interested in conducting research in Lynch syndrome? Honestly, I knew very little about Lynch Syndrome, and then John Wherry, co-Director of the Lynch Syndrome Program mentioned that I should think about research in Lynch Syndrome. As I read more about Lynch Syndrome and the role of the immune system, I found that there was so much opportunity for immunology research and the development of immunotherapy.

Lynch syndrome webinar series continues

The Penn Medicine Lynch Syndrome Program webinar series has featured multiple topics of interest to the Lynch syndrome community. Topics of recent webinars have included a webinar focused on strategies to discuss Lynch syndrome with children and family members, as well as a webinar focused on gynecologic care for individuals with Lynch syndrome. These webinars are held live, offering the opportunity for attendees to ask questions to the speakers. Additionally, these webinars are recorded and archived, and they can be accessed at any time on our program website: www.med.upenn.edu/lynchsyndromesymposium. Our next webinar will be held on Tuesday, November 19th at 5 pm ET, and will involve a discussion of ethical and legal considerations in genetic evaluation for Lynch syndrome, presented by Penn Medicine genetic counselor Jessica Ebrahimzadeh, MS, CGC (reference the link on page 1).

V Foundation grant awarded to Penn team to support Lynch syndrome research.

The V Foundation recently awarded a 4-year $800,000 grant to a Penn team of investigators to study the immune system in Lynch syndrome, specifically T cell responses. The study team is led by oncologist and principal investigator Alexander Huang, MD, along with co-principal investigators gastroenterologist Bryson Katona, MD, PhD, and biostatistician Mingyao Li, PhD. The title of the funded grant is "Molecular mechanisms of neoantigen immunosurveillance in Lynch Syndrome." Preliminary data for this grant was obtained through a Borrelli Family Lynch Syndrome Pilot Grant.

Congratulations on being the recipient of this year's Borrelli Family Pilot Grant in Lynch Syndrome. What type of research are you going to pursue with this award?
The questions that drive my research for my Pilot Grant and overall in Lynch Syndrome are: 1) Why does the immune system appear to be overactivated in Lynch patients, even before they have cancer, and 2) Why does the immune system fail in many cases to protect the patient from cancer. Answers to these questions will allow for us to develop ways to identify Lynch syndrome patients who are at the highest risk for cancer, and for us to introduce immunotherapies such as vaccines to protect them from cancer.

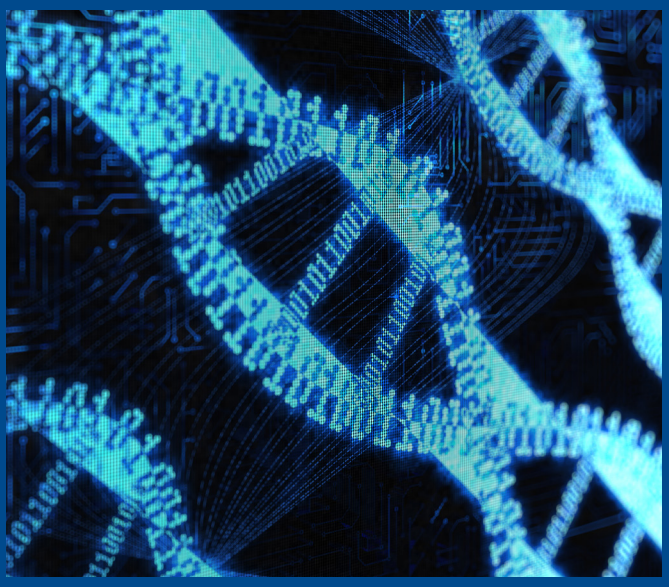
Genetic Counseling CORNER

UNDERSTANDING YOUR GENETIC TEST RESULTS & WHY IT MATTERS

Jessica Long, MS, CGC
Associate Director,
Lynch Syndrome Program
Penn Medicine

It's not uncommon to hear questions from people who've had genetic testing, such as "What do these letters and numbers on my test result mean?" or "Why do my relatives need my actual test report?" On first pass, the genes listed on a multi-gene panel test can look like alphabet soup. However, the genetic test results report provides essential information to genetic counselors and healthcare teams, such as which genes were evaluated, the methods used for testing, and the location and type of any changes identified in these genes, which are known as variants. Further, the test report provides information that helps assess whether a gene variant is classified as pathogenic (harmful), as benign (harmless) or as uncertain (due to limited evidence).

Importantly, we know that Lynch syndrome is caused by a pathogenic variant in one of five different genes, *MLH1, MSH2/EPCAM, MSH6,* and *PMS2*. As a reminder, these genes are called DNA mismatch repair genes, since their function in the body is to repair DNA damage that can otherwise cause cancer cells to form. For a family with Lynch syndrome, all relatives in the family with Lynch syndrome typically the same pathogenic variant in the same gene. In other words, since genes differ in many different ways, it's critical to know the specific gene and exact variant causing Lynch syndrome in a particular family. This then allows for highly informative, predictive genetic testing in at-risk relatives, who wish to learn whether or not they have inherited Lynch syndrome. Sometimes, a pathogenic variant in a gene may be difficult to detect depending on the type of genetic variant, other genetic variation in that person (called "polymorphisms") and/or available genetic testing technology. For this reason, genetic testing laboratories will typically request a copy of a family member's genetic test report, in order to ensure their ability to accurately detect a family's specific pathogenic variant in the gene. As an analogy, the genetic test result is like a roadmap: the "c." provides the location of the specific variant in the genetic code, while the "p." describes where in the protein this change in the genetic code alters an amino acid (which is like a protein "building block"). The family member's test report helps guide the laboratory staff in their genetic search to provide an accurate and informative test result.



SPREADING AWARENESS: NATIONAL HEREDITARY CANCER WEEK AND PREVIVOR DAY

For this year's National Hereditary Cancer week (September 29th to October 5th) and Previvor Day (October 2nd, 2024), our Lynch Syndrome Program held an outreach event in the lobby of Penn Medicine's Perelman Center for Advanced Medicine. National Hereditary Cancer week was established by Congress in 2010 to recognize and honor people impacted by all types of hereditary cancer. Previvor Day recognizes those who have not had a cancer diagnosis, but who have bravely taken steps to learn about their inherited cancer risk and make life-saving medical decisions. Penn Medicine staff, healthcare providers, researchers, patients and visitors stopped by our table to learn about the importance of family history and genetic risk assessment, and many learned for the first time about Lynch syndrome as the most common cause of hereditary colorectal cancer.

This was a wonderful opportunity to engage and familiarize people with the clinical, educational and research resources provided by Penn's Lynch Syndrome Program. We especially appreciated the chance to meet some of you in-person!

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 Therese Marmion **(tmarmion@upenn.edu)** in Penn's Development Office.

LYNCH SYNDROME RESEARCH UPDATES

1 **Low prevalence of gastric intestinal metaplasia and Helicobacter pylori on surveillance upper endoscopy in Lynch syndrome.** (Marya Pulaski et al., *Familial Cancer*, 2024) Upper gastrointestinal cancer screening is now recommended by the NCCN for individuals with Lynch syndrome. Current upper gastrointestinal cancer screening guidelines recommend empiric biopsies of the stomach to assess for the cancer-causing bacterial *Helicobacter pylori (H. pylori)* as well as for precancerous changes to the lining of the stomach, however there was only limited data assessing the frequency of these findings in individuals with Lynch syndrome. In this study, the results of empiric gastric biopsies in 165 consecutive patients with Lynch syndrome were analyzed. Of this cohort, 5.5% had gastric intestinal metaplasia and 3.6% had *H. pylori*. These findings indicate that individuals with Lynch syndrome may not be at increased risk of harboring these gastric cancer risk factors, however identification of these gastric cancer risk factors is important to allow for appropriate risk-reducing strategies, such as treating *H. pylori*. Together, these findings support inclusion of at least baseline gastric biopsies as a routine component of all standard surveillance upper endoscopies performed in Lynch syndrome.

2 **Universal testing of cutaneous sebaceous carcinoma: a missed opportunity in Lynch syndrome detection.** (Neil Rajan et al., *Lancet Oncology*, 2024) Current guidelines recommend universal mismatch repair immunohistochemistry (MMR IHC) staining of all colorectal and endometrial cancers in order to identify individuals who may have Lynch syndrome, as up to 5% of colorectal and endometrial cancers may be Lynch syndrome-related. As such, MMR IHC has become a powerful technique for identifying individuals who should undergo genetic testing for Lynch syndrome. In this manuscript, the authors highlight that sebaceous carcinomas of the skin may be another cancer where universal MMR IHC should be performed, as up to 20% of individuals with a sebaceous carcinoma will also have Lynch syndrome. This study was done in the UK and showed that less than a third of sebaceous carcinomas had MMR IHC performed, and only 5% of patients with a sebaceous carcinoma ultimately ended up having germline testing for Lynch syndrome.

3 **Genomic landscape of Lynch syndrome colorectal neoplasia identifies shared mutated neoantigens for immunoprevention.** (Ana Bolivar et al., *Gastroenterology*, 2024) Lynch syndrome-related cancers have loss of mismatch repair function, which leads to the development of lots of somatic mutations in Lynch syndrome tumors. These somatic mutations can lead to large numbers of neoantigens, which are abnormal proteins produced by cancer cells. These neoantigens can be recognized by the immune system, which may allow the immune system to eliminate these cancer cells. In this study, the authors demonstrate that a certain type of neoantigen (specifically shared frameshift neoantigens) is generated early on in Lynch syndrome colorectal cancers and precancerous lesions, and that these neoantigens can elicit an immune response by T cells. These common neoantigens may help facilitate future cancer prevention vaccine development.