Lynch Syndrome

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FIGHT™ COLORECTAL CANCER

THE OHIO STATE UNIVERSITY
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Lynch Syndrome

Lynch syndrome designation is applied to patients with an identified germline pathogenic or likely pathogenic variant in a DNA mismatch repair gene (*MLH1, MSH2, MSH6, PMS2, EPCAM*)

Autosomal dominant genetic disorder

Carries increased risk for multiple cancers (more details on a later slide)

Very common condition

- Estimated to affect 1/279 people in the general population
- Most common cause of inherited colorectal cancer (accounts for 4%)
- Most common cause of inherited endometrial cancer (accounts for 3%)

Giardiello FM et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2014 Aug;80(2):197-220.

Win AK et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2017 Mar;26(3):404-412

Lynch Syndrome

Historical Background

First clinically described by Dr. Henry Lynch in 1966 and called "cancer family syndrome"

Was labelled "hereditary non-polyposis colorectal cancer" for a time to differentiate from familial adenomatous polyposis (FAP)

- This name was eventually abandoned to avoid confusion as patients often develop colon polyps and this is a multi-system cancer predisposition syndrome

Lynch syndrome was finalized as the preferred nomenclature in 2002

Giardiello FM et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2014 Aug;80(2):197-220.

Lynch Syndrome Cancer Risks (to age 80)

Cancer Type	*MLH1*	*MSH2 / EPCAM*	*MSH6*	*PMS2*	General Public
Colorectal Cancer	46-61%	33-52%	10-44%	8.7-20%	4.1%
Endometrial Cancer	34-54%	21-57%	16-49%	13-26%	3.1%
Ovarian	4-20%	8-38%	≤113%	1.3-3%	1.1%
Renal pelvis or Ureter	0.2-5%	2.2-28%	0.7-5.5%	≤1-3.7%	Not in SEER
Prostate	4.4-13.8%	3.9-23.8%	2.5-11.6%	4.6-11.6%	12.6%
Stomach	5-7%	0.2-9%	≤1-7.9%	Not Known	0.8%
Pancreatic	6.2%	0.5-1.6%	1.4-1.6%	≤1-1.6%	1.7%

NCCN Guidelines,Genetic/Familial High-Risk Assessment Colorectal,v2.2023

Lynch Syndrome
Cancer Risk

Carries an increased risk for multiple cancers as noted

- Risk variable per gene and surveillance recommendations increasingly specific between genes

Lynch Syndrome also carries a younger age of onset for cancer in comparison to the general population

Lynch Syndrome
Screening

Cancer resulting from Lynch syndrome has a feature called microsatellite instability (MSI)

- Easily tested by staining pathology specimens of tumor tissue with immunochemistry techniques or through direct microsatellite instability testing

This feature led to recommendations for universal screening of all colorectal cancers to increase Lynch syndrome identification as early as 2005

- This is widely endorsed by medical societies across the world, including the National Comprehensive Cancer Network, American Society for Clinical Oncology, American Gastroenterological Association and others

- This effort was expanded to also include all endometrial cancers as well as other cancer types

Lynch Syndrome
Genetic Testing I

Genetic testing for Lynch syndrome has been available since the 1990s

- The gene with a pathogenic variant is clearly indicated on all test results
- Imported directly into or scanned into the electronic medical record
- Would be specified in all or almost all clinical notes by relevant specialties
  - Oncology, GI, Gyn, Derm, etc

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SAMPLE REPORT

Ordered By Contact ID:405956 Org ID:249
Physician: Sample Doctor, A
Client: Sample Organization (00403)
Additional Authorized Recipient:
Counselor Sample, Genetic MS, CGC

Patient Name: **Last, First**
Accession #: **00-332049**
AP2 Order #: 205725
Birthdate: 01/01/1980
MRN #: ####
Indication: Diagnostic/Family History
Specimen #: 44-55-66
Specimen: Blood EDTA (Purple top)
Gender: F
Collected: 05/18/2018
Received: 05/19/2018

BRCA1/2 Analyses with CancerNext®

RESULTS

BRCA2 **Pathogenic Mutation: 5'UTR_EX10del**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **5'UTR_EX10del** pathogenic mutation in the *BRCA2* gene.
- This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
- **Risk estimate**: 45-84% lifetime risk of breast cancer and 11-18% lifetime risk of ovarian cancer (females only), at least a 6% lifetime risk of male breast cancer and 15% risk of prostate cancer by age 65 (males only), and increased lifetime pancreatic cancer risk.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (36 total): ***APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, PTEN, RAD51C, RAD51D, RECQL, SMAD4, SMARCA4, STK11*** **and** ***TP53*** **(sequencing and deletion/duplication);** ***HOXB13, POLD1*** **and** ***POLE*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only).**

From: Ambry Genetics, Sample Positive CancerNext report
https://www.ambrygen.com/file/material/view/1438/CancerNext%20v5.5_Positive%20BRCA2_07_14_2020.pdf

Lynch Syndrome

Genetic Testing II

Genetic testing for hereditary cancer syndromes is now standard practice

- National Comprehensive Cancer Network (NCCN) has recommended genetic testing for Lynch syndrome in patients with cancers having microsatellite instability or deficient mismatch repair immunohistochemistry for many years
- NCCN also now recommends testing for hereditary cancer syndromes for all patients with ovarian and pancreatic cancer and consideration in all patients with colorectal cancer

Germline genetic testing widely available and affordable

- Estimated that over 1 million genetic tests are done per year for cancer indications in the USA at this point
- Offered by multiple commercial laboratories that are CLIA-certified

Lynch Syndrome

Genetic testing for Lynch syndrome also allows for identification of this disorder prior to a cancer diagnosis

- Allows for implementation of screening procedures and imaging to prevent cancer

Early identification and ongoing clinical monitoring of Lynch syndrome patients is critical given the effectiveness of surveillance programs

- An early study of colonoscopy every 3 years achieved a 62% reduction in incidence of CRC and a 65% decrease in mortality

- If cancer develops, a Lynch syndrome diagnosis can guide treatments of cancer such as more extensive colectomy or earlier use of immunotherapy (immune checkpoint inhibitors)

Järvinen HJ et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000 May;118(5):829-34.

Lynch Syndrome
Surveillance

Surveillance recommendations vary slightly by gene for Lynch syndrome, but generally include:

- Colonoscopy every 1 -3 years starting at age 20 -25 or 30-35
- Consideration of endometrial screening at age 30
- Consideration of hysterectomy and oophorectomy (usually after age 40 and/or completion of childbearing)
- Upper endoscopy every 2 -4 years starting at age 30
- Pancreatic cancer screening in those with a family history

NCCN Guidelines,Fenetic/Familial High-Rish Assessment; Colorectal,v2.2023

Lynch Syndrome

Our application to create specific ICD10 coding for Lynch syndrome gathered broad support:

Medical Societies/ Organization	Patient Advocacy Organizations	Medical Experts
American Cancer Society American College of Gastroenterology American Society of Gastrointestinal Endoscopy Collaborative Group of the Americas on Inherited Gastrointestinal Cancer Lynch Syndrome Screening Network	Fight Colorectal Cancer Alive and Kick'n Catch It In Time Joan Rush (President of the Rush Foundation)	Prof. Heather Hampel, City of Hope CA Dr. Swati Patel, Univ Of Colorado Dr. Peter Stanich, The Ohio State Univ Dr. Jennifer Weiss, Univ of Wisco Robert Smith, PhD, ACS NCCRT Laura Makaroff, ACS NCCRT Michelle Springer, MS, CGC, Univ of Colorado Andrea Dwyer, Fight CRC and Univ of Colorado School of Public Health

Summary

Proposal for the new ICD-10-CM codes for Lynch syndrome

- Lynch syndrome is a common and high impact genetic syndrome
- Lynch syndrome is a well-established diagnosis based on widely available genetic testing
- A dedicated ICD-10-CM code would allow for better organization and implementation of clinical surveillance and treatments that are shown to have clear mortality benefit
- Dedicated ICD-10-CM codes would allow for a major step forward in research efforts including use of nation-wide data sets
- Our proposal has widespread support from medical organizations, patient advocacy organizations and medical experts