Using NCBI Resources to streamline your genetic cases



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For Follow-up:

Search dbGaP (https://www.ncbi.nlm.nih.gov/gap/) to find human Lynch Syndrome studies to further research.

dbGaP houses studies that provide access to some demographic, clinical and molecular data. While this data is provided at no cost, due to the nature of the patient-level data full access requires an application to an NIH Data Access Committee.

For more information see the dbGaP website.





Your patient is a 40-year-old mother of two presenting with changes in bathroom habits, bleeding, and abdominal pain. She has a medical history of colonic polyps. Her family history reveals that her maternal grandmother, mother and uncle had several forms of cancers including colon, breast, and endometrium. You suspect Lynch Syndrome.

Use NCBI resources to gather information useful for diagnosing your patient's disorder.

Step 1:

Look up Lynch Syndrome in MedGen (https://www.ncbi.nlm.nih.gov/ medgen/) to learn more about the disorder.

Full Report •		Send to: •
Lynch syndrome MedGen UID: 1633554 •	Concept ID: C4552100 + Disease or Syndrome	
Synonyms: SNOMED CT: Modes of inheritance	Lynch Syndrome; Syndrome, Lynch Lynch syndrome (716318002) : Autosomal dominant Inheritance (Orphanet)	
Genes (locations): 🔞	MLH1 (3p22.2); MSH2 (2p21-16.3); MSH6 (2p16.3); PMS2 (7p22.1)	
Monarch Initiative: Orphanet:	MONDO:0005835 ORPHA144	
 Disease charac 	teristics	Go to: 🖂 🔿
ynch syndrome is char arinary tract, biliary trac	racterized by an increased risk for colorectal cancer (CRC) and cancers of the endometrium, it, brain (usually glioblastoma), skin (sebaceous adenomas, sebaceous carcinomas, and kera	ovary, stomach, small bowel, toacanthomas), pancreas, and
Lynch syndrome is chai arinary tract, billary trac prostate. Cancer risks i ndividuals with Lynch s of developing these car Full text of GeneRevic Sugary Diagnosis Courseling Resource	racterized by an increased risk for colorectal cancer (CRC) and cancers of the endormatrium, It brain (usually diobatanin), akin (behancous adenous, sebaceous cancinomas, and kern and age of onset vary depending on the associated gene. Several other cancer types have be synchrome (e.g., breass, surcomas, advencedited generon). However, the data are not suffic noers is increased in individuals with Lynch syndrome. [from GeneReviews] bry (by section): [Jinical Characteristics Genesically Related (Allelic) Disorders Differential Diagnosis rs Molecular Genetics Chapter Notes References	overy, storach, small bowel, toacanthomes), puncreas, and en reported to occur in lient to demonstrate that the risk Management Genetic

Case Study



(https://www.ncbi.nlm.nih.gov/books/NBK1116/)

Go to the section, Establishing the Diagnosis.

Option 1 (recommended

A multigene panel that includes MLH1, MSH2, MSH6, and PMS2 as well as EPCAM deletion analysis (see Table 1) and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of <u>uncertain significance</u> and pathogenic variants in genes that do not ex the underlying <u>phenotype</u> [Idos et al 2019, Heald et al 2020]. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2 multigene panels may include genes not associated with the condition discussed in this GeneReview. (3) In som laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused en analysis that includes genes specified by the elinician. (4) Methods used in a panel may include sequence deletion/duplication analysis, and/or other non-sequencing-based tests.



View video on Lynch Syndrome

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MedGen displays clinical genetics information from authoritative sources. You can find disease descriptions from OMIM and GeneReviews, clinical features from HPO, Professional Guidelines from medical societies and Recent clinical studies and Recent systematic reviews in PubMed.

GeneReviews are actionable descriptions of genetic diseases created by experts. It covers diagnosis, management and genetic counseling.

acteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Genetics | Chapter Notes | References

Read more about Establishing a Diagnosis in the GeneReviews article.

In Establishing the Diagnosis, it states that a multi-gene panel including 4 mismatch repair genes, plus EPCAM, is most likely to identify the genetic cause of the condition. In addition, DNA methylation analysis of the MLH1 promoter region is recommended.

Table 1.

Come 1	Proportion of Lynch Syndrome Attributed to	Proportion of Probands Detectable by Method	w/a Pathogenic Variant ³
Gene '	Pathogenic Variants in Gene ²	Sequence analysis ^{4, 5, 6}	Gene-targeted <u>deletion</u> / <u>duplication</u> analysis ^{5, 6, 7}
MLH1 ⁸	15%-40%	80%-90%	10%-20%
MSH2	20%-40%	60%-80%	20%-40%
MSH6	12%-35%	90%-100%	0%-10%
PMS2 9, 10	5%-25%	45%-80% ⁹	20%-55% 9
EPCAM 11	<10%	None reported	100% 12

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Step 3:

Click a link to find a genetic test in the NIH Genetic Testing Registry (GTR). (https://www.ncbi.nlm.nih.gov/gtr/)

Click on the MLH1 link to see a list of genetic tests that include the MLH1 gene. You can see single gene tests and panels.

urine analysis with urine cyclology to identify microscopic hemataria in those with a family history of urothelial eancer. Consider parcentic enner servering in individuals with a family history of parcentic eancer with alternating endoccopic ultrasound and/c MRI/magnetic resource cholamochanoureratoremphy.	Contact Us	
Agraticircumstances to avoid: High body mass, eignette anoking, type 2 diabetes, and high chelesterol. Evaluation of relatives at risk: When a diagnosis of Lynch syndrome has been confirmed in a proband, melecular	Tests in GTR by Gene EP300	
genetic instange for the Lynch syndheome-related guiltogenic virtual should be offered to first-deprese relatives to identify those who would benefit from early surveillance and intervention. Although molecular genetic iterating for Lynch syndhome is generally not recommended for at-takk individuals younger than age 18 years, a history of early cancers in the family may variant endecitive statistic more role to an 81.	BRAF TP53 PM52	
Genetic counseling. Lynch syndrome caused by a <u>heteropropen</u> semilar pathogenic variant in <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , or <i>PMS2</i> or by an <i>EPCMV</i> deletion is inherited in an autosemul dominane manner. Individuals with Lynch the inherited and the inherited of the MLH1 was understand dominane.	DLC1 PDGFRL	
Syndrome classes by constraintion in indications or orientity by <u>indications</u> operating types in <u>intigic</u> , cases but families with non-meddition indications of hypermethylation have been reported. The single cases but Lynch syndrome inherited a pathagenic variant from a parent, however, because of incomplete <u>generance</u> , variable are of cancer development, ensure risk reduction as a result of screening or procebased: surgery or early death, not	APC MUH1 MUH3	
all individuals with a pathogenic variant in one of the genes associated with lynch practome have a parent who had cancer. Each child of an individual with Lynch nyndrome has a 50% chance of inheriting the puthogenic variant. Prestatil testing for a pregnarcy at increased risk is possible if the pathogenic variant in the family is known.	SRC CCND1	

Check the boxes on the le to filter on your desired parameters. For example, if you want CLIA certified labs in the United States.

Click on the title of an interesting test from the list to learn about the test's purpose, methodology, clinical and analytic validity, clinical utility, and how to order it.

GTR includes clinical and research tests for Mendelian disorders,
somatic phenotypes, drug responses, complex diseases and
infectious diseases.

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Step 4:

Search ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) with information from test results to learn about the patient's variant.



Step 5:

population frequency data for the variant.

The dbSNP report provides allele frequencies from several sources, including our ALFA project, the Allele Frequency Aggregator, which provides population frequencies for millions of variants in dbGaP, the NCBI database of Genotypes and Phenotypes.

Step 6:

Find relevant Clinical Trials (https://clinicaltrials.gov/) for Lynch Syndrome with a Link from the MedGen record.

List By Topic On Map	Search	Details	23 Stur	tiles found for: Recruiting Studies Lynck	a Syndrome United States			Your patie clinical tr related st	ent may be interested in partici ial. There are currently 24 Lynch tudies in the US recruiting patie	pating in a syndrom nts.
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Go to the dbSNP record (https://www.ncbi.nlm.nih.gov/snp/) to find relevant

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