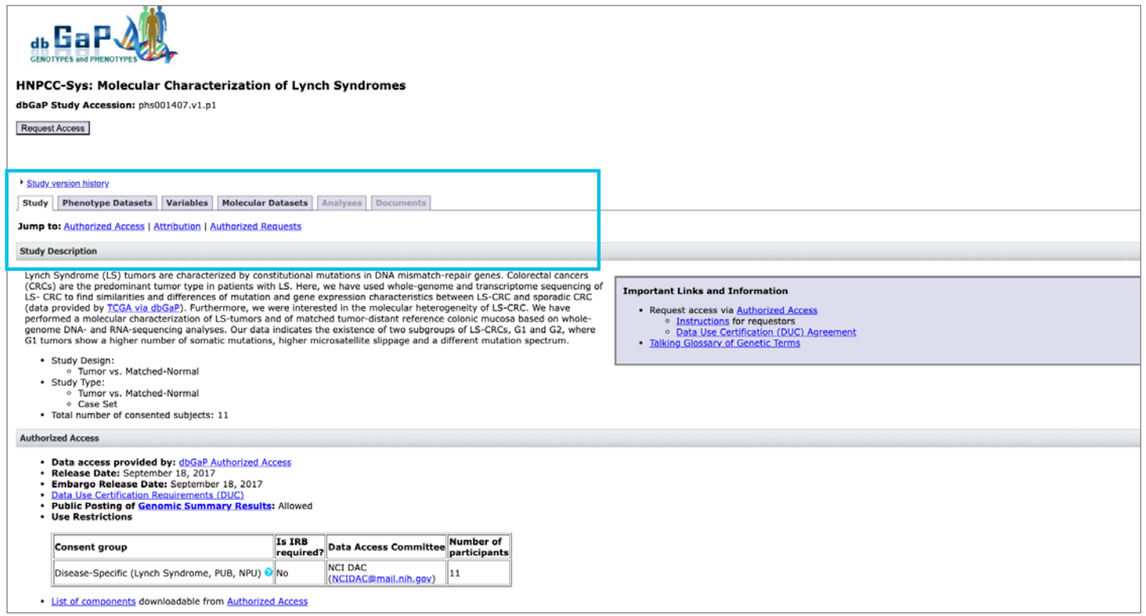
# Using NCBI Resources to streamline your genetic cases

## 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.



**HNPCC-Sys: Molecular Characterization of Lynch Syndromes**

**dbGaP Study Accession:** phs001407.v1.p1

Request Access

Study version history

Study | Phenotype Datasets | Variables | Molecular Datasets | Analyses | Documents

**Jump to:** Authorized Access | Attribution | Authorized Requests

**Study Description**

Lynch Syndrome (LS) tumors are characterized by constitutional mutations in DNA mismatch-repair genes. Colorectal cancers (CRCs) are the predominant tumor type in patients with LS. Here, we have used whole-genome and transcriptome sequencing of LS- CRC to find similarities and differences of mutation and gene expression characteristics between LS-CRC and sporadic CRC (data provided by TCGA via dbGaP). Furthermore, we were interested in the molecular heterogeneity of LS-CRC. We have performed a molecular characterization of LS-tumors and of matched tumor-distant reference colonic mucosa based on whole-genome DNA- and RNA-sequencing analyses. Our data indicates the existence of two subgroups of LS-CRCs, G1 and G2, where G1 tumors show a higher number of somatic mutations, higher microsatellite slippage and a different mutation spectrum.

- Study Design:
  - Tumor vs. Matched-Normal
- Study Type:
  - Tumor vs. Matched-Normal
  - Case Set
- Total number of consented subjects: 11

**Important Links and Information**

- Request access via Authorized Access
  - Instructions for requestors
  - Data Use Certification (DUC) Agreement
- Talking Glossary of Genetic Terms

**Authorized Access**

- **Data access provided by:** dbGaP Authorized Access
- **Release Date:** September 18, 2017
- **Embargo Release Date:** September 18, 2017
- Data Use Certification Requirements (DUC)
- **Public Posting of Genomic Summary Results:** Allowed
- **Use Restrictions**

| Consent group | Is IRB required? | Data Access Committee | Number of participants |
|---|---|---|---|
| Disease-Specific (Lynch Syndrome, PUB, NPU) | No | NCI DAC (NCIDAC@mail.nih.gov) | 11 |

- List of components downloadable from Authorized Access

View video on Lynch Syndrome




# Using NCBI Resources to streamline your genetic cases

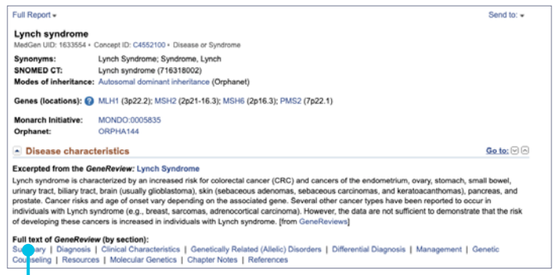

## Case Study

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:** Lynch Syndrome; Syndrome, Lynch
**SNOMED CT:** Lynch syndrome (716318002)
**Modes of inheritance:** Autosomal dominant inheritance (Orphanet)

**Genes (locations):** MLH1 (3p22.2); MSH2 (2p21-16.3); MSH6 (2p16.3); PMS2 (7p22.1)

**Monarch Initiative:** MONDO:0005835
**Orphanet:** ORPHA144

**Disease characteristics** Go to: ⊖ ⊕

**Excerpted from the *GeneReview*: Lynch Syndrome**

Lynch syndrome is characterized by an increased risk for colorectal cancer (CRC) and cancers of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin (sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas), pancreas, and prostate. Cancer risks and age of onset vary depending on the associated gene. Several other cancer types have been reported to occur in individuals with Lynch syndrome (e.g., breast, sarcomas, adrenocortical carcinoma). However, the data are not sufficient to demonstrate that the risk of developing these cancers is increased in individuals with Lynch syndrome. [from GeneReviews]

**Full text of *GeneReview* (by section):**

Summary | Diagnosis | Clinical Characteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | Chapter Notes | References

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.

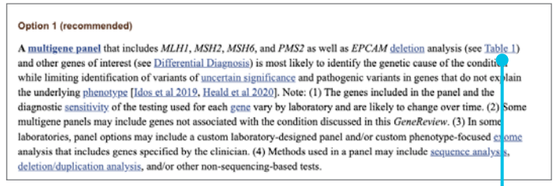
GeneReviews are actionable descriptions of genetic diseases created by experts. It covers diagnosis, management and genetic counseling.

**Full text of *GeneReview* (by section):**
Summary | Diagnosis | Clinical Characteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | Chapter Notes | References

## Step 2:

**Read more about Establishing a Diagnosis in the GeneReviews article. (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 uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype [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) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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.**

Molecular Genetic Testing Used in Lynch Syndrome

| Gene [1] | Proportion of Lynch Syndrome Attributed to Pathogenic Variants in Gene [2] | Proportion of Probands w/a Pathogenic Variant [3] Detectable by Method | |
|---|---|---|---|
| | | Sequence analysis [4, 5, 6] | Gene-targeted deletion/duplication 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] |


National Library of Medicine
National Center for Biotechnology Information

Follow us on Twitter @ncbi_clinical

Contact us at info@ncbi.nlm.nih.gov

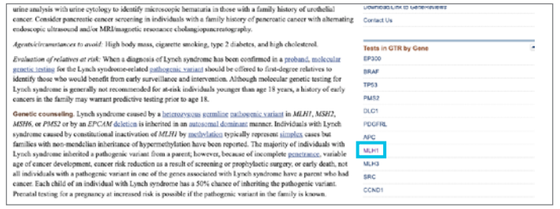
Visit us at ncbi.nlm.nih.gov/

# Using NCBI Resources to streamline your genetic cases

## Step 3:

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

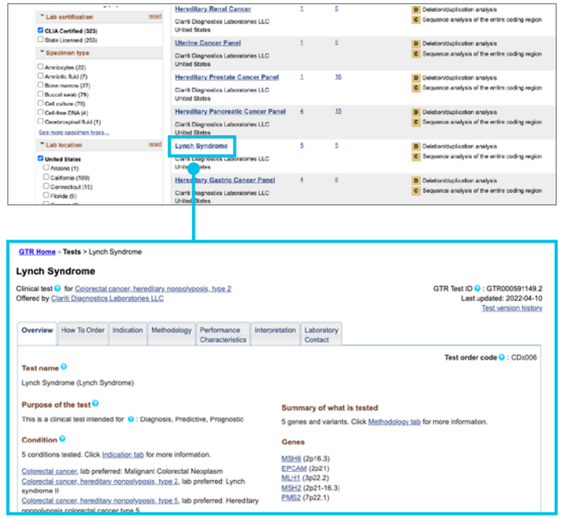
Click on the MLH1 link to see a list of genetic tests that include the MLH1 gene. You can see single gene tests and panels.




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.

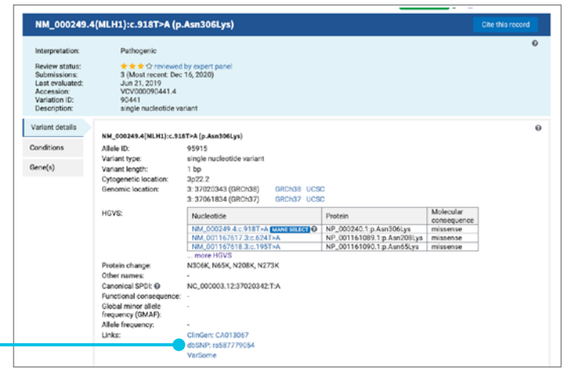



## Step 4:

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

The MLH1 p.Asn306Lys variant is interpreted as pathogenic in the ClinVar record. The record includes variant details such as location, variant descriptions, a link to dbSNP (rs587779054), submission data with descriptive comments, and citations.

MSH6 p.Tyr214Ter

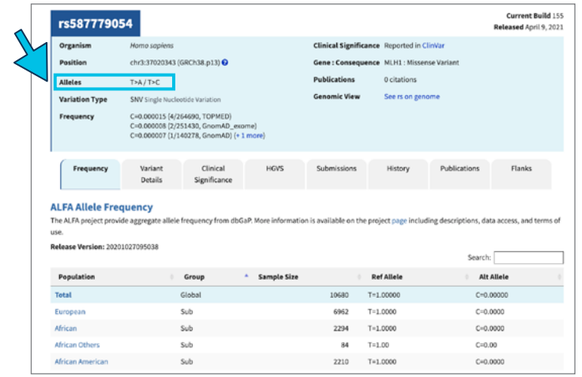



dbSNP: rs587779054

## Step 5:

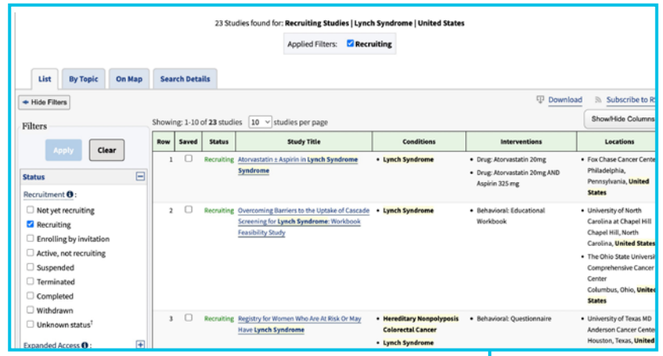
### Go to the dbSNP record (https://www.ncbi.nlm.nih.gov/snp/) to find relevant population frequency data for the variant.

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.




Your patient may be interested in participating in a clinical trial. There are currently 24 Lynch syndrome-related studies in the US recruiting patients.




# Using NCBI Resources to streamline your genetic cases

National Library of Medicine
National Center for Biotechnology Information
Follow us on Twitter @ncbi_clinical
Contact us at info@ncbi.nlm.nih.gov
Visit us at ncbi.nlm.nih.gov/