

# Establishing Connectivity and Clinical Decision Support Rules for Patients Carrying MLH1, MSH2, MSH6, and PMS2 (Lynch Syndrome) Variants

## An Implementation Guide

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CSER EHR Working Group

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## Introduction

The goal of this guide is to specify how system developers and healthcare organizations can implement clinical decision support (CDS) that produces patient specific alerts for Lynch Syndrome. Specifically, the CDS is designed to remind clinicians when Lynch Syndrome patients are due for colonoscopies given the evidence that such practices improve morbidity and mortality of patients. It begins with a proposed standardized process for transmitting the data needed to underlie the CDS and then follows with a recommendation for how the CDS rules could be implemented.

This guide was produced by the CSER (Clinical Sequencing Exploratory Research) Electronic Health Record (EHR) Working Group part of a NIH sponsored consortium of institutions working to evaluate expanded use of genetic sequencing in clinical medicine (Green et al., 2016). The working group's mission is to understand and facilitate cross-site collaboration to improve genomic data integration into electronic health (medical) record (EHR), development of genomic-aware CDS, and linkage to variant databases/knowledge bases. The members of the EHR working group include geneticists, laboratory diagnosticians, medical informatics specialist from institutions across the US. We developed this guide following the work of the [DIGITize](#) (Displaying and Integrating Genetic Information Through the EHR) Action Collaborative, an ad hoc multi-stakeholder effort associated with the Roundtable on Genomics and Precision Health at the National Academies of Sciences, Engineering, and Medicine.<sup>1</sup> The goal of DIGITize is to increase support for clinical genomics within the EHR ecosystem by creating implementation guides for standardized clinical decision support.

This guide uses Lynch Syndrome (also referred to as hereditary non-polyposis colon cancer) as a use case in genomic CDS to describe how this CDS functionality could improve clinical care for hereditary cancer risk management. We selected Lynch Syndrome as our example use case because it is one of the more common cancer risk syndromes, it affects both men and women and there are interventions with established clinical utility (i.e., surveillance colonoscopy). This is a situation where

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<sup>1</sup> This implementation guide was developed with some of the participants of DIGITize, an ad hoc activity associated with the Roundtable on Genomics and Precision Health at the National Academies of Sciences, Engineering, and Medicine (the National Academies). This guide does not necessarily represent the views of any one organization, the Roundtable, or the National Academies and has not been subjected to the review procedures of, nor is it a report or product of, the National Academies.

implementation of CDS stands to improve care if it reinforces guideline concordant colonoscopy.

The underlying genetic basis of Lynch syndrome was first reported over 20 years ago and genetic testing for alterations in the genes associated with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and certain deletions in *EPCAM*) is widely available. Germline testing of individuals who meet established criteria (e.g. individuals who have a strong family history of colorectal cancer (CRC), particularly early-onset disease, or other Lynch-related cancers) is guideline endorsed (Cite NCCN guidelines, ACG, Bethesda, Amsterdam). Furthermore, a systematic attempt to identify cancer patients who have Lynch syndrome through somatic (tumor) mismatch repair testing (i.e., immunohistochemistry (IHC) testing for the *MLH1/MSH2/MSH6/PMS2* proteins and/or microsatellite instability (MSI) testing), with subsequent genetic risk evaluation and germline testing for appropriate individuals, is now guideline endorsed for all newly diagnosed colorectal cancer patients (PMID 24853227, 25220566, 26602911). Identification of individuals with Lynch Syndrome is critical given the high lifetime risk of colorectal cancer often with onset of disease prior to initiation of surveillance as recommended by population screening guidelines, the established clinical utility of early and frequent surveillance by colonoscopy, the elevated risk of non-colorectal cancer Lynch-related malignancies and possibility for additional risk-reducing interventions, and the potential implications for family members (Giardiello et al., 2014; NCCN, 2017).

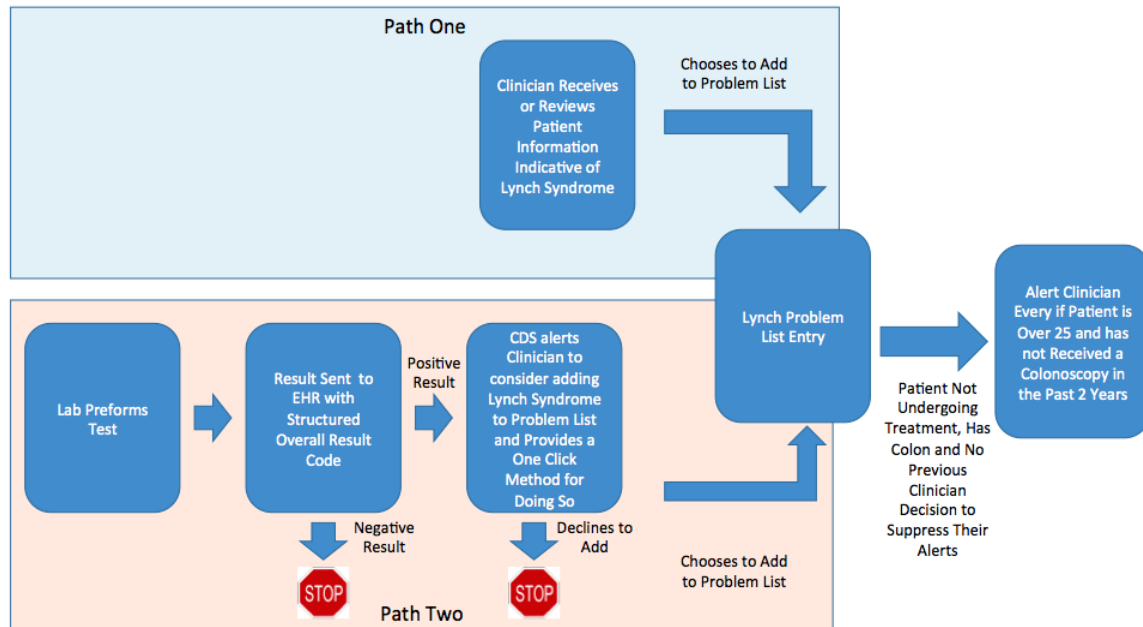
### Lynch syndrome and colonoscopy screening

Although the exact recommendations (for example with regard to timing interval or age of first colonoscopy) for colorectal risk management in individuals who have Lynch Syndrome vary slightly by organization and gene, there is a general consensus that regular colonoscopy screening should begin at an early adult age. For example, the American College of Gastroenterology recommends that individuals with Lynch Syndrome undergo surveillance colonoscopy screening every 1-2 years, beginning between the age of 20-25 years (Giardiello et al., 2014). Data from Europe has demonstrated that Lynch syndrome colonoscopy screening significantly reduced the morbidity and mortality of individuals who underwent systematic surveillance (Forsberg et al., 2015). Despite the promise of genomic testing and the use of risk reducing strategies in Lynch Syndrome, there are several critical gaps in care delivery. Studies suggest that Lynch testing use in some US health care settings may be suboptimal (Beamer et al., 2012; Gray et al., 2017). Even more relevant to this guide, there are a paucity of data on Lynch Syndrome patient's compliance with surveillance colonoscopy screening or on provider's recommendations for colonoscopy for patients with Lynch Syndrome. Furthermore, to our knowledge, there have been few systematic information-technology-based attempts to improve the implementation of Lynch syndrome surveillance colonoscopy use across healthcare settings. This guide is intended to provide the needed documentation required to implement a CDS mechanism for Lynch Syndrome colonoscopy use. Current guidelines are written for clinicians and allow flexibility in the context of patient care (Giardiello et al., 2014; NCCN, 2017).

Machine structured CDS could provide a reminder to clinicians. This working group concluded that automated CDS alerts should be least intrusive and follow the most lenient interpretation of recommended action. CDS could be implemented to warn the clinician in the following situations:

- “An order for colonoscopy is suggested by national guidelines for a patient who has genetic results that are diagnostic for Lynch syndrome, is over 25 and has not had a colonoscopy in the last 2 years.”

Implementing institutions could use the framework provided in this guide to instantiate more frequent screening guidance if their internal policies differ from the above guidance (for example, triggering if a colonoscopy is missed in one year). This guide describes two pathways which implementing institutions may choose to create CDS for Lynch colonoscopy screening recommendations. These two pathways are summarized in the workflow diagram below.



In addition to their being two pathways there are also two forms of CDS depicted in this diagram. The bottom pathway involves CDS promoting the the provider to add Lynch Syndrome to the problem lists when genetic tests indicate doing so may be warranted. The top pathway involves the clinician placing Lynch Syndrome on the problem list without such a prompt. Then both pathways converge to enable a form of CDS that alerts relevant clinicians when a colonoscopy for a patient may be recommended.

## Updating the problem list

The “Lynch Syndrome Positive” observation result is defined as a key observation that drives American College of Gastroenterology and NCCN guidelines

recommendations. This observation is created by a physician based on clinical history and results from a testing laboratory of a single heterozygous pathogenic or likely-pathogenic variant identified in the genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or the promoter deletion of *EPCAM* (which results in silencing of *MSH2*).

## SNOMED compatible standard Problem List Codes for physician coding of Lynch syndrome

The diagnosis of Lynch syndrome is a clinical diagnosis that is closely tied to a genetic laboratory finding. Though many individuals have already been diagnosed with Lynch syndrome, many testing laboratories do not uniformly implement clinical interfaces with hospital EHRs. Even when an interface is present, it is possible that data for all historically tested patients may not be available. Because of these obstacles we recommend the use of the problem list to flag patients with a Lynch syndrome diagnosis for CDS to support colonoscopy screening by the use of the problem list.

It is beyond the scope of this guide to define how this problem list entry should be specified at each institution. A future version of this guide could be built to specify a uniform SNOMED that could be used for this purpose. Within the scope of this guide we instead specify the high level logic that recommend be implemented based on the representation chosen by each site.

## Establishing the Problem List Activated Clinical Decision Support

### *Trigger Condition*

Monthly process that runs and checks all patients with:  
Lynch Syndrome – Positive on problem list

### *Queries to be Run on Trigger Condition*

Query 1: Determine whether the patient has had a colonoscopy in the last two years:

This requires determining what SNOMED codes are used to represent colonoscopies with a site's EHR. Then a query can be run to determine whether there are any entries within the patient record containing these SNOMED observation codes with a date of entry within the last two years

Query 2: Determine if there is a non-overridden record of a clinician choosing to suppress this alert:

This requires implementing functionality to track these specific alert overrides and then querying to see if any of these overrides are present. Our working group felt this functionality would be important to reduce alert fatigue.

Query 3: Determine if the any conditions exist that should suppress the alert:

Query to see if the patient is less than 25 years old (or above the cutoff age the institution chooses) or if the patient has had their colon removed.

### *Check 1: Determine if the System Should Intervene*

If no records are returned in any of the above queries an intervention should trigger. This intervention could take the form of an alert. An alert should have at least two parts:

- 1) A high level concise description of the issue in a format similar to the interaction alert.
- 2) A more detailed description potentially based on the NCCN and ACG guidelines, for example, could state: "Colonoscopy is recommended every 1-2 years for patients with Lynch Syndrome. Colonoscopy testing does not appear to have been ordered for this patient in the last 2 years."

Implementers who have the ability to detect if a colonoscopy has been ordered but not yet completed may choose to tailor the detailed message above to provide this information.

Each institution must determine whether its clinicians should be allowed to acknowledge the alert and continue without taking action. Some implementers may want to consider facilitating or automating the colonoscopy ordering process if evidence of colonoscopy result is not available in the record and the clinician does not indicate that they have access to the colonoscopy result through another source.

In making this decision, it is important to consider how situations where a patient has previously discussed colonoscopy frequency with clinicians should be handled. Alerts may be overridden if a colonoscopy has been performed at an outside institution, if a previous colectomy has not been documented in the EHR system, or for many other reasons.

## **Establishing CDS to Prompt Providers to Enter Lynch Syndrome into the Problem List**

Laboratories that generate genetic test results often run different information systems than the providers who receive the test results. Therefore it is important that there be a standardized method for transmitting information between different systems. Structured data transmission from laboratory information systems (LIS) to the EHR environment could facilitate improved Lynch syndrome screening by allowing CDS that assists clinicians in adding appropriate Lynch syndrome diagnoses to the problem list (See path two in workflow diagram) .

There are large bodies of literature and public databases (ClinVar, ClinGen, LOVD, InSight) that address classifying variants, discussion of variant classification is an active field and is outside the scope of this implementation guide. We recommend sites work with laboratories to establish a mechanism for classifying Lynch Syndrome results at the test level as POSITIVE (defined as a pathogenic or likely pathogenic variant in a disease gene), NEGATIVE, or INCONCLUSIVE for Lynch syndrome in a tested subject. No further observation results are required from the testing laboratory in order to fulfill the CDS rules for the use case surrounding structured reporting of Lynch syndrome in the problem list. However, structured transmission of variant information could be required for other purposes. For example, it may be important to update the test level results as new information emerges on previous reported variants. Implementing this logic could require additional test level information.

One approach to enabling this high level test transmission would be to use a specific LOINC code. The writers of this guide do not believe there is an existing LOINC code that is appropriate. A new code could be created based on 35379-7 that has updated information on Lynch syndrome (such as defining answer lists that codify the acceptable result terms for clinical decision support, and updating gene lists). Absent a standard code, laboratories and providers should work together to establish an interface that consistently transfers the high level test results.

## **Clinical Decision Support Logic for Promoting Physicians to Add Lynch Syndrome to the Problem List**

### *Trigger Condition*

Viewing of a screen showing a Lynch Syndrome Genetic Test

### *Queries to be Run on Trigger Condition*

Query 1:

All records within the patient record containing the LOINC or other observation code used to the indication to represent Lynch Syndrome Overall Test Results that have an Overall Test Result: POSITIVE

Query 2: Determine if there is a non-overridden record of a clinician choosing to suppress this alert:

This requires implementing functionality to track these specific alert overrides and then querying to see if any of these overrides are present. Our working group felt this functionality would be important to reduce alert fatigue.

Query 3: Determine if Lynch Syndrome is already on the problem list

Query the problem list to determine if there are any entries that conform to the representation the institution uses to represent Lynch syndrome

### *Check 1: Determine if the System Should Intervene*

If the first query result contains at least one record with a positive result and the second and third queries return no records, an intervention should trigger. This intervention could take the form of an alert. An alert should have at least two parts:

- 1) A high level concise description of the issue in a format similar to the interaction alert.
- 2) A more detailed description potentially based on the NCCN and ACG guidelines such as, "Based on a positive laboratory results guidelines suggest that Lynch syndrome diagnosis should be added to the problem list."



Each institution must determine whether its clinicians should be allowed to acknowledge the alert and continue without adding Lynch Syndrome to the problem list.

### A Note Regarding Scope and Future Direction

This guide does not cover the transmission of structured data describing specific genetic variants or positions or regions assayed in diagnostic test. These transfers are not required to implement the use cases outlined and there are potentially thousands of different pathogenic variants in these four genes and thus specifying a variant list is likely to miss many patients with Lynch syndrome. However, we believe these transmissions will be important to many future use cases, particularly disorders that result from a limited number of pathogenic variants. As capability to transmit structured variant data into the EHR is implemented, it may make sense to update the recommendations we have made here. We also have not standardized uniform coding strategies that could make this CDS more transferable across sites. Users of this guide should be aware that this future work could involve deprecating the structures and strategies proposed below. Our current goal is to build momentum for the exchange of genetic data, provide recommendations for using these data in CDS, and gather information to help guide future standards and recommendations. To help achieve this goal, we've outlined proposed logic we believe will reduce barriers to entry for organizations interested in implementing CDS for Lynch syndrome. This guide is not intended to be a complete long-term solution but rather a mechanism for getting started.

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