Stage I: Rule-Out Dashboard

Incidental Findings in Adults

GENE/GENE PANEL: ***MLH1/MSH2/MSH6/PMS2/EPCAM***	**DISORDER:** Lynch Syndrome
HGNC ID: *7127, 7325, 7329, 9122, 11529*	**OMIM ID:** 609310, 120435, 614350, 614337, 613244

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	**Patient Management**
☒	☐	**Surveillance or Screening**
☒	☐	**Family Management**
☒	☐	**Circumstances to Avoid**

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☒ **YES** ☐ **NO**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Summary Report

Incidental Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: ***MLH1/MSH2/MSH6/PMS2/EPCAM*** **DISORDER:** Lynch Syndrome			
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		Currently in the US, roughly 1,154,000 people are living with CRC while 600,000 women are living with endometrial cancer. LS is the most common heritable CRC and accounts for 1-5% of all CRC cases and 2% of all endometrial cancer cases.	(1-6)
Signif/Burden of Condition	**Clinical Features** (Signs/symptoms)	LS is characterized by an increased risk of CRC and other cancers including endometrial, ovarian, and gastric. Cancers typically develop at an early age and individuals may develop multiple cancers. The majority (>90%) of LS-associated CRC tumors show microsatellite instability indicating the malfunction or loss of mismatch repair gene products.	(1-3;5-8)
	Natural History (Important subgroups & survival/recovery)	The average age at diagnosis is 44-61 years for CRC, 48-62 years for endometrial cancer, 42 years for ovarian cancer, and later for other LS-associated cancers. The most common LS-associated cancer is CRC, which is not associated with polyposis and typically arises from a single colorectal lesion, advances more rapidly from adenoma to carcinoma than sporadic CRC, and is most common on the right side of the colon. The lifetime risk of cancer varies with the gene mutated and sex, with males having a higher risk of developing CRC compared to females. Recurrence of CRC is common. However, patients with LS-associated CRC and endometrial cancer have improved survival compared to patients with sporadic tumors.	(2;3;6-8)
2. How effective are interventions for preventing the harm?			
Patient Management		Prophylactic hysterectomy and salpingo-oophorectomy have been shown to reduce the risk to develop endometrial and ovarian cancer associated with LS, and should be discussed as an option to mutation carriers once child-bearing is complete and after age 35-40. A retrospective study showed an absence of gynecological cancers among women who underwent prophylactic hysterectomy and/or bilateral salpingo-oophorectomy, compared to 33% and 5% incidence of endometrial and ovarian cancer, respectively, among women who did not have surgery. **(Tier 2)** Regular aspirin significantly reduces LS cancer incidence. Evidence from a randomized controlled trial indicated regular aspirin reduced the incidence of CRC and other LS-associated cancers by 60%. **(Tier 2)** Health professionals should be aware of potential psychosocial problems associated with genetic testing and surveillance, and patients experiencing psychological distress should be offered referral to a clinical psychologist. **(Tier 2)**	(2;5-9) (2;5;6;10) (5)
Surveillance		Regular colonoscopic surveillance has been shown to lead to significant reduction of LS CRC incidence, detection of CRC cases at an earlier stage, and reduction in CRC-associated mortality. Individuals with LS should undergo colonoscopy every 1-3 years starting at age 20-25 years. Five out of six studies found a significantly reduced incidence rate of CRC with surveillance (OR estimates ranged from 0.11 to 0.35), while the sixth study reporting an OR of 0.93 was not significant. Two out of four studies have shown a significant reduction in CRC-related mortality with surveillance (OR estimates range from 0.04 to 0.17), while three of the four studies reported no mortality in the study arm with surveillance. **(Tier 1)** Transvaginal ultrasound with endometrial biopsy may detect cancers and premalignant lesions of the endometrium, though interval endometrial carcinomas still occur and no subsequent improvement in survival has been demonstrated. **(Tier 1)** Individuals with LS should undergo esophagogastroduodenoscopy to screen for gastric cancer, though the age to start screening and the frequencies varies across recommendations, from age 30-25 to age 50 and from twice a year to every 2-3 years,	(7;11) (7)

	respectively. However, there was no evidence provided that this surveillance reduces mortality. **(Tier 2)** To screen for cancers of the urinary tract, individuals with LS should undergo urinalysis on an annual basis beginning at age 25-35 years. **(Tier 2)**	(6;8;12;13) (6;8)
Family Management	Relatives of individuals with LS should have genetic testing to identify non-carriers who can then be released from additional screening. **(Tier 2)** First degree relatives of individuals with LS who have not undergone genetic testing are recommended to undergo colonoscopy every 18 months starting at age 25 years **(Tier 2)** and esophagogastroduodenoscopy twice yearly starting at age 50 **(Tier 2).**	(10;12) (12) (12)
Circumstances to Avoid	Smoking and high BMI are associated with an increased risk of adenomas and CRC in LS, thus patients are advised to stay within the normal weight range and refrain from cigarette smoking. **(Tier 2)**	(5)

Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

GENE/GENE PANEL: ***MLH1/MSH2/MSH6/PMS2/EPCAM*** **DISORDER:** Lynch Syndrome		
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	Autosomal dominant	
Prevalence of Genetic Mutations	LS has an estimated prevalence of 1/440 in the general population. **(Tier 3)** By definition, cases of Lynch Syndrome are due to a defect in one of the mismatch repair genes. **(Tier 3)**	(3) (2)
Penetrance OR Relative Risk (include high risk racial or ethnic subgroups)	Cumulative risks of cancer in LS by age 70: colorectal =25-70% , endometrial =30-70%, gastric=1-9%, small bowel=1-4%, biliary tract=1-2%, pancreas=1-4%, urinary tract =2-8%, upper urinary tract=6%, bladder=2-16%, ovarian=6-14%, brain =3.5%, prostate=9-30%, breast=5-14%. Risk may vary by MMR gene. Carriers of EPCAM deletions have a similar risk of CRC but a lower risk of endometrial cancer (12% by age 70). **(Tier 3)**	(5)
	Males have a roughly 2.1- to 2.3-fold risk of prostate cancer. **(Tier 1)**	(14)
Expressivity	Information in variable expressivity was not available.	
4. What is the nature of the intervention?		
Nature of Intervention	Endoscopic surveillance can be burdensome for individuals. **(Tier 2)** In addition, colonoscopy is associated with risks, including pain, nausea, bleeding, perforation, and death. **(Tier 3)**	(7) (1)
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	LS-associated CRC has a lower average age of onset and advances at a more rapid rate compared to sporadic CRC and an increased risk of endometrial cancer **(Tier 4)**, making it likely that these patients would escape detection using surveillance recommendations for average risk populations as screening for CRC is recommended in older populations and endometrial cancer screening is not recommended for the general population at all.	(7)

Stage II: Summary Report

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Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
MLH1 *MSH2* *MSH6* *PMS2*	Colorectal cancer/Surveillance	2	3A*	3A	2	10AA
	Endometrial cancer/Surveillance	2	3A*	1A	2	8AA
	Endometrial cancer/Risk reducing surgery	2	3A*	3B	1	9AB

*Scores where the tier of evidence recommendation of the Working Group differs from the evidence level tier in the Summary Report

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/

Date of Search (MM.DD.YYYY): 04.03.2014

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