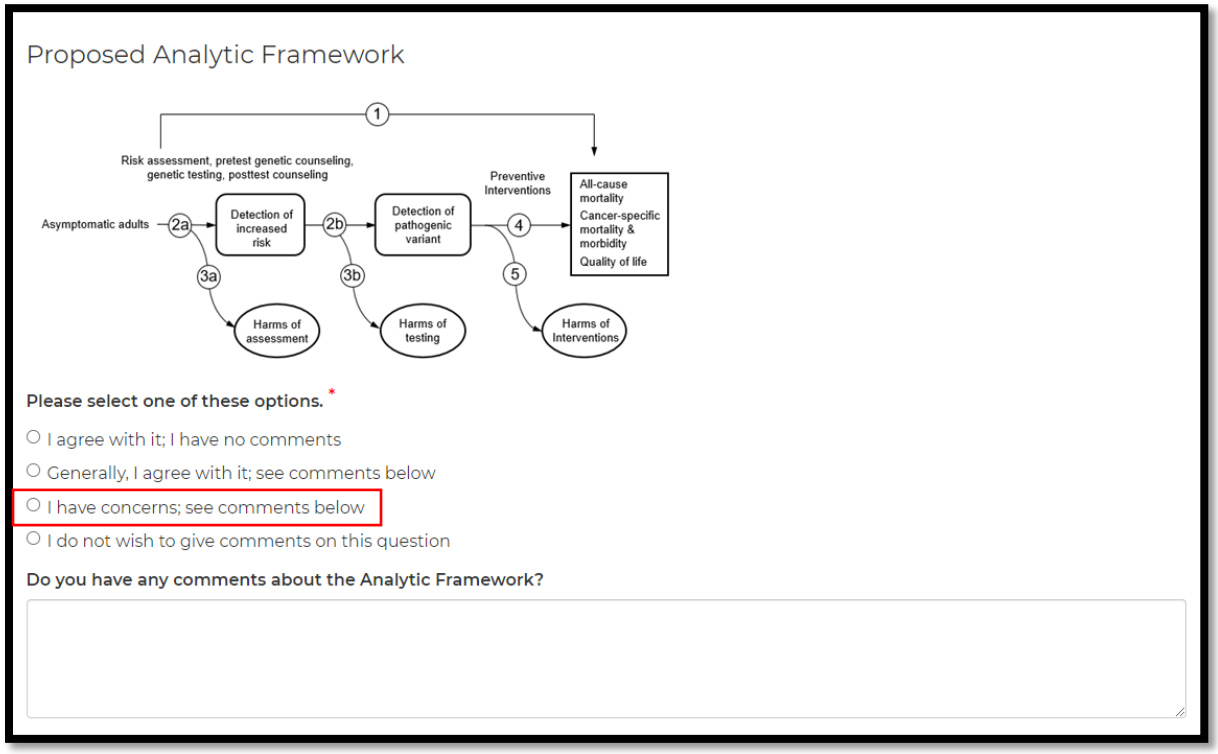
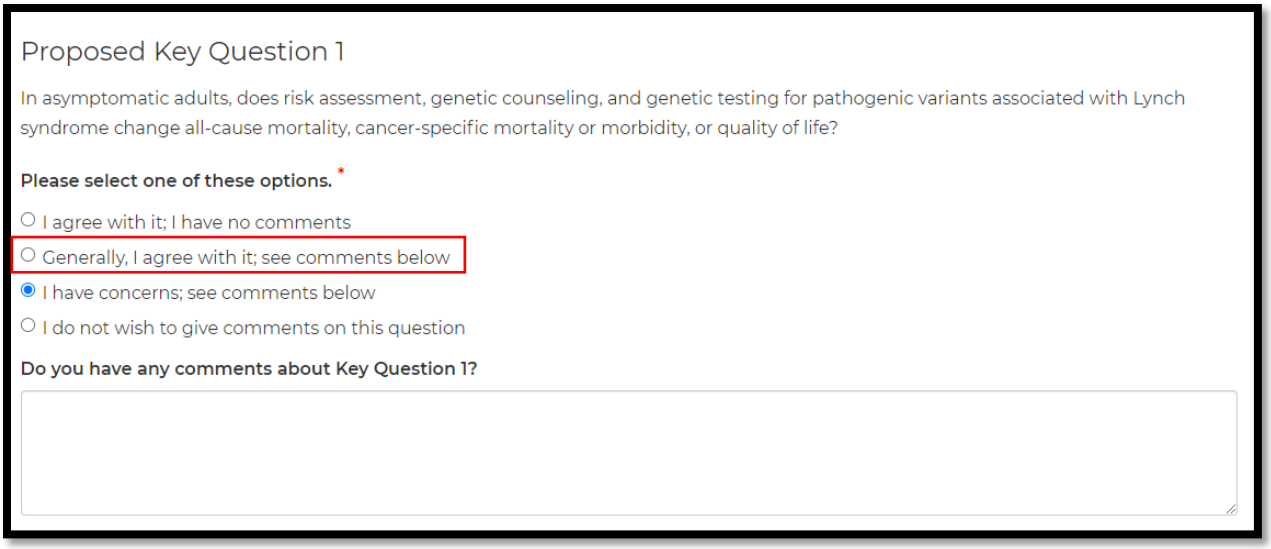
ACMG Response to USPSTF Draft Research Plan titled “Lynch Syndrome-Related Cancer in Adults: Risk Assessment, Genetic Counseling, and Genetic Testing”

https://www.uspreventiveservicestaskforce.org/uspstf/document/draft-research-plan/lynch-syndrome-related-cancer-adults-risk-assessment-genetic-counseling-testing

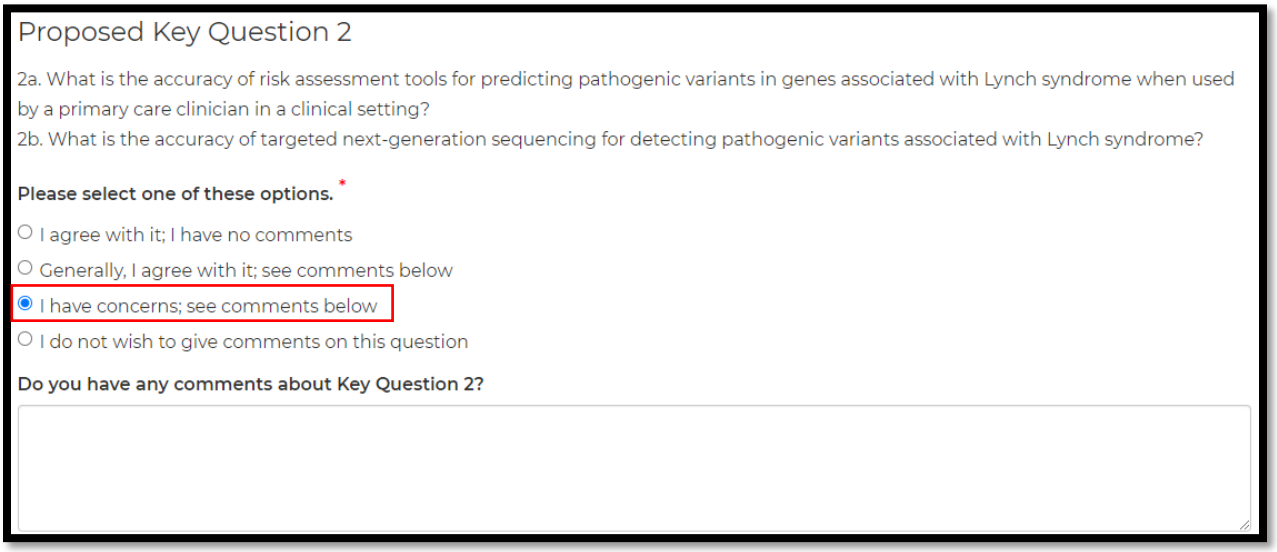
Submitted March 1, 2023 through the USPSTF webform



- Pretest and post-test genetic counseling isn’t a measure of efficacy of testing and intervention. It may be a success modifier but shouldn’t be a primary endpoint.
- Outcome of all-cause mortality is a long-term outcome and is not specific to Lynch syndrome.
- Cancer-specific mortality and morbidity is non-specific. Measures such as cancer stage at detection, recurrences, and intensity of treatments required are more meaningful.
- Harms of assessment, testing, interventions – should exclude non-medical constructs, such as potential for genetic discrimination in life-, long-term care, and disability insurance, since these are legal, not medical constructs. The potential harm is the policy, not the intervention, and the policy can be changed.
- Harms are ascertained at each step, which is artificial since some harm risk can be tolerated at one step if the benefits of all the steps taken together are large.



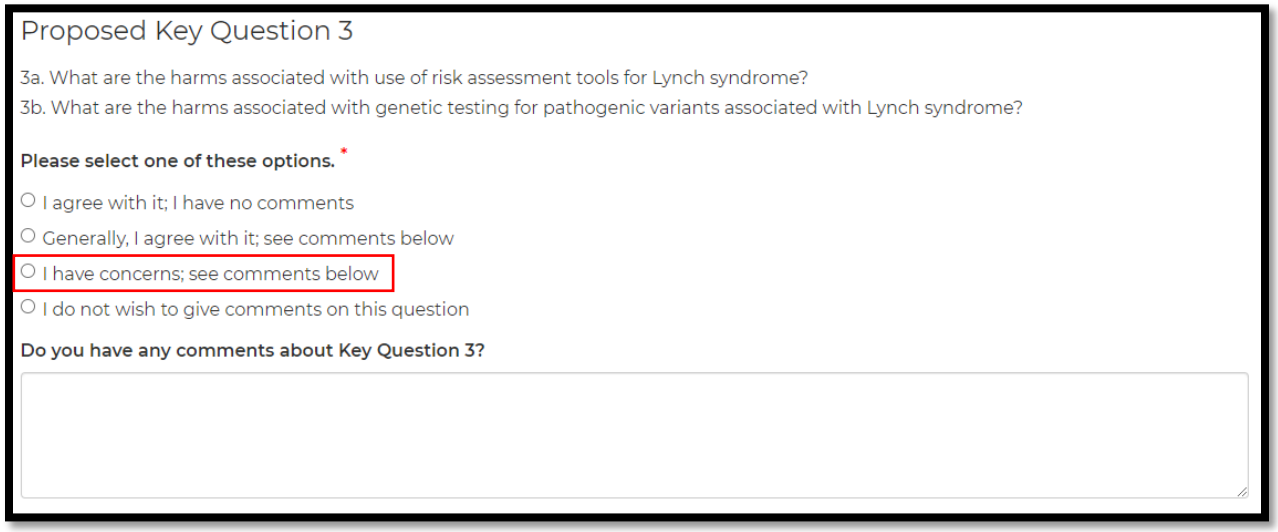
- Pre- and post-test genetic counseling must be evaluated separately. These 4 components (pre-test genetic counseling, post-test genetic counseling, risk assessment, and genetic testing) are all worthwhile for exploring for effectiveness but must be looked at individually.
- Pre-test genetic counseling is valuable and highly encouraged but should not preclude someone from getting testing. Experiences in genomic population health screening suggests the information could be delivered through a variety of modalities. A better question would be whether a care navigator would help get recommended screenings done (compliance) rather than whether genetic counseling (understanding) was done or understood.



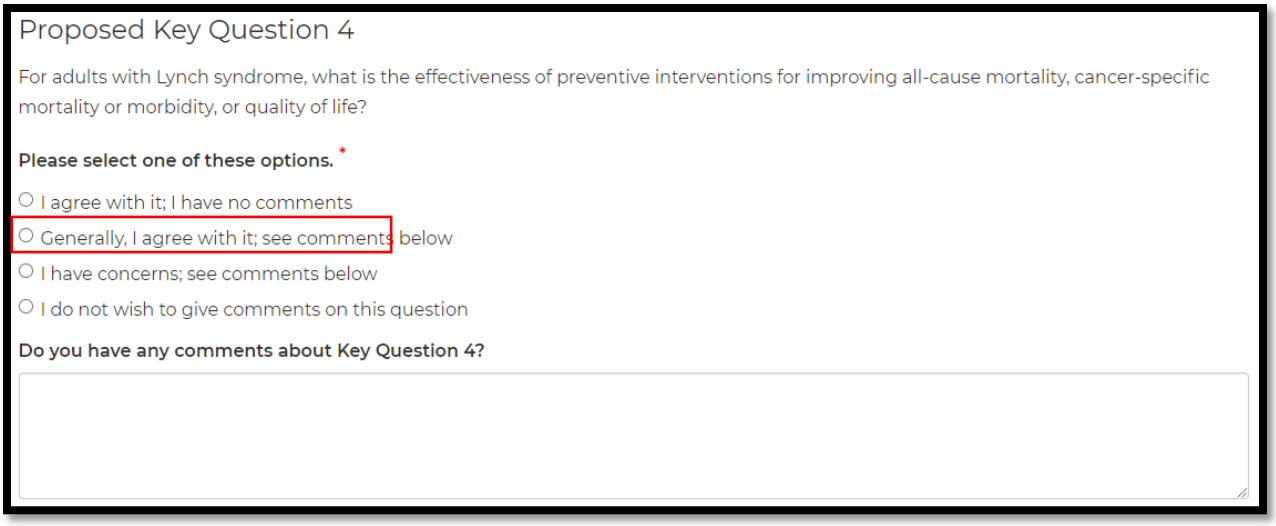
- 2a. We presume the risk assessment is a pre-test determination of family history (like PREMM5). The evaluation should also include a comparison of using risk assessment before genetic testing vs NOT using risk assessment before genetic testing (the comparison listed is no screening which is one good comparison but I would argue is not the only comparison)… the PREMM5 is basically a family history tool but we know from BRCA testing that about 50% of those with a pathogenic

variant do not have a significant family history. Unless the study considers a comparator of testing regardless of a PREMM5 score or other such enrichment screen, we don't have the data on whether or not family history should really be a requirement.

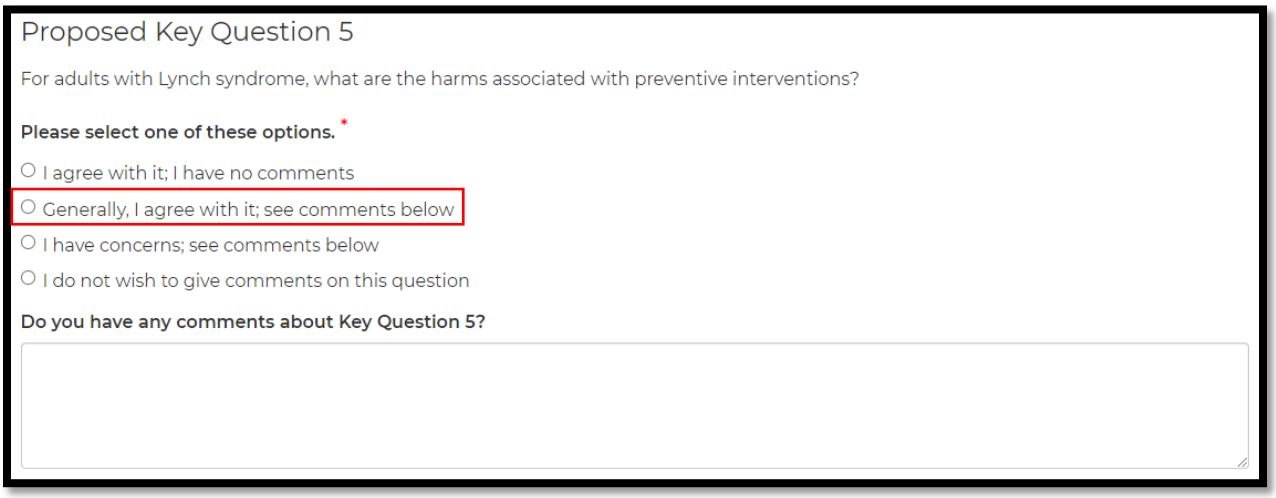
- 2b. This is a narrowing down of capabilities of the technology overall, which has been well established in the literature. It would be better to ask whether there is any reason to believe that NGS applied to Lynch syndrome genes is any less accurate than when it is applied to any other genes.



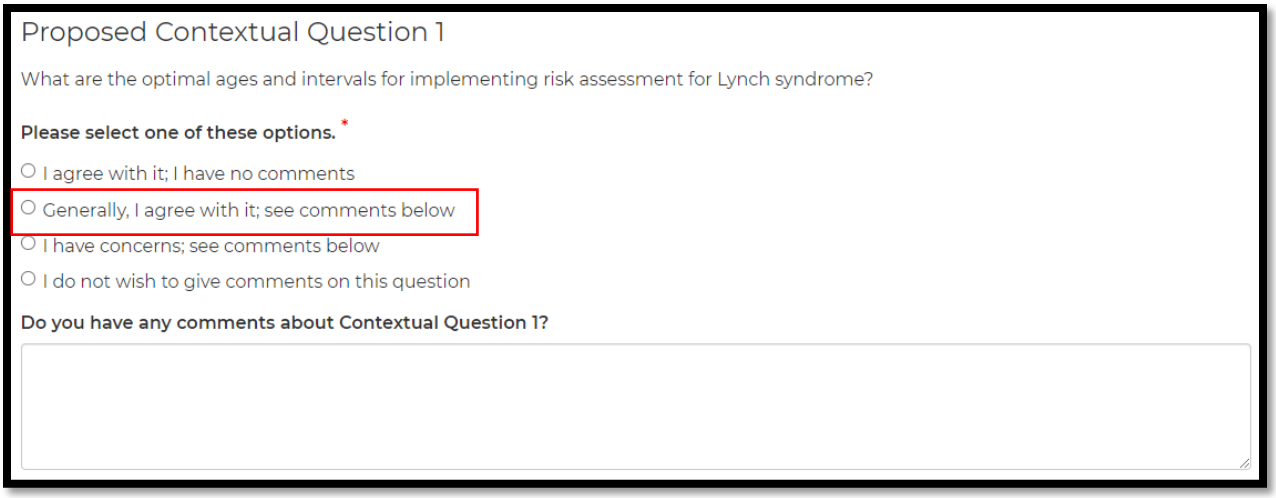
- 3a. Is this referring to harms from taking a family history? What about, what is the harm of requiring a risk assessment tool prior to testing for Lynch syndrome, particularly if that risk assessment tool will miss a significant number of positive cases? In other words, does the risk assessment tool have a significant "false negative" rate and this can only be determined if the study also includes genetic testing when there is not a prior enrichment for cases more likely to carry pathogenic variants. See also comments on key question 2.
- 3b. False positive rates of the genetic assay are minimal. Penetrance is variable and based on the gene and its variants. This should also be balanced with risk of the intervention (compliance to colonoscopy screening recommendations) vs the risk of late detection (colonoscopy screening compliance at an all-time low).



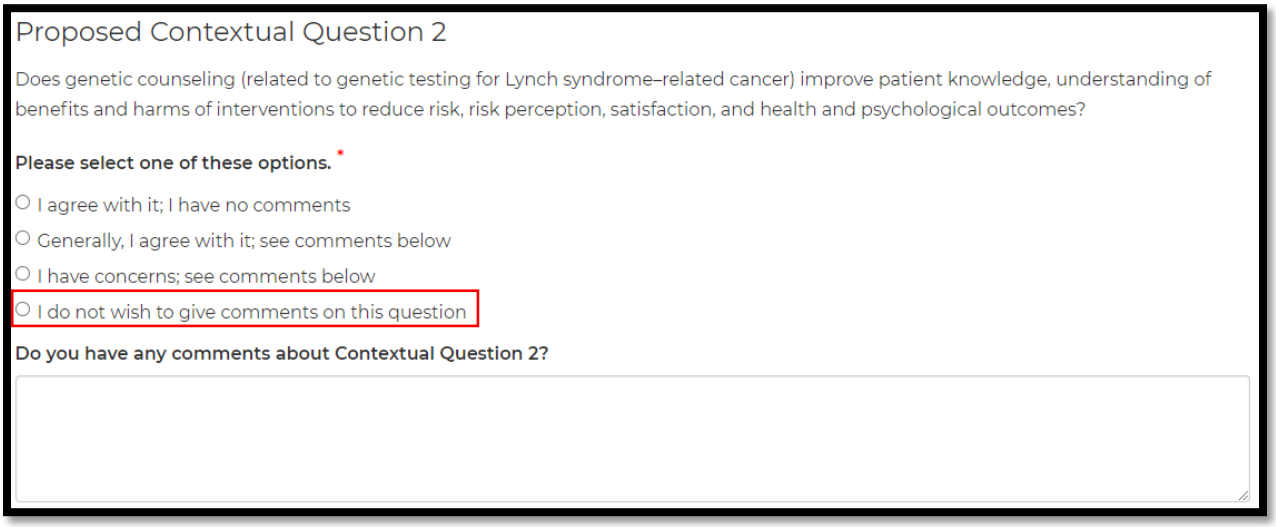
- This is fraught with confounders – depends on the quality of care, of the veracity of screening (which we know underperforms for reasons of compliance, insurance, lost-to-follow-up, other) and other variables unrelated to the underlying value of the approach, if well executed.
- Will this approach consider other benefits such as the cost of early detection and treatment vs later stage detection and treatment?



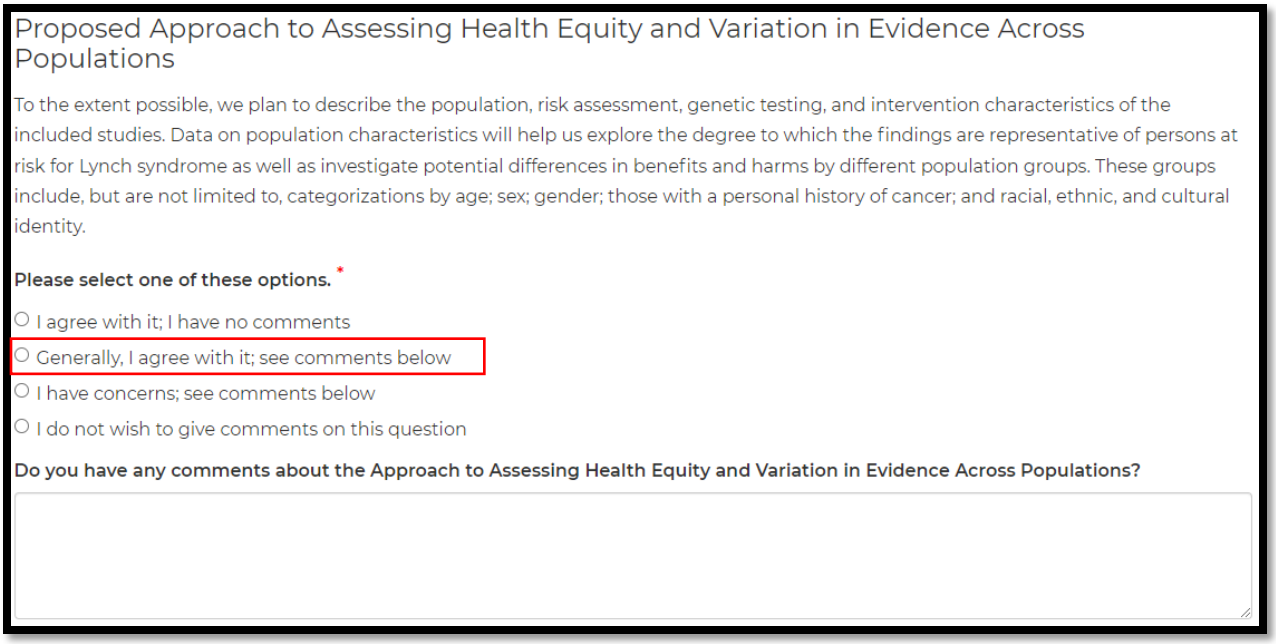
- It is unclear what domains of harm are sought here. E.g., Was it financially harmful? Lose part of one's colon due to resecting an early-stage tumor (not excluded see Interventions in table)? Are those considered harms?



- This could be a two-part question. If the analysis allows for the question of whether or not risk assessment is necessary prior to genetic testing, and it is determined that it is not necessary, then the question of when to do risk assessment is less pertinent. The study could also evaluate that if a risk assessment is done, not for exclusion but rather for further enrichment, then what factors make than risk assessment most valuable (likely related to the size of family, age of family members, and/or knowledge of family health history could impact quality of risk assessment).



- [no comments]



Proposed Approach to Assessing Health Equity and Variation in Evidence Across Populations

To the extent possible, we plan to describe the population, risk assessment, genetic testing, and intervention characteristics of the included studies. Data on population characteristics will help us explore the degree to which the findings are representative of persons at risk for Lynch syndrome as well as investigate potential differences in benefits and harms by different population groups. These groups include, but are not limited to, categorizations by age; sex; gender; those with a personal history of cancer; and racial, ethnic, and cultural identity.

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Do you have any comments about the Approach to Assessing Health Equity and Variation in Evidence Across Populations?

- We agree with the effort to identify limitations to the data and identifying areas for which additional data is needed or may be helpful. See examples of previous efforts related to breast cancer – "It is important to proactively reach those populations that are underusers of cancer screening and ensure that barriers that stop people from accessing cancer screening are explored and adequately addressed." (https://doi.org/10.3389/fpubh.2021.699108)

Proposed Research Approach

The Proposed Research Approach identifies the study characteristics and criteria that the Evidence-based Practice Center will use to search for publications and to determine whether identified studies should be included or excluded from the Evidence Review. Crite overarching as well as specific to each of the key questions.

Category	Include	Exclude
Populations	**KQs 1–3:** Asymptomatic adults (older than age 18 years); persons with or without a personal or family history of cancer **KQs 4, 5:** Adults with Lynch syndrome **All KQs:** Specific populations of interest include those defined by sex, gender, race, or ethnicity	**KQs 1–3:** Children, persons with symptoms; persons with a very recent diagnosis of colorectal cancer undergoing tumor testing (e.g., for microsatellite instability that, if abnormal, would lead to genetic testing for Lynch syndrome) **KQs 4, 5:** Children
Interventions	**KQ 1:** Risk assessment initiated by a primary care clinician, pretest genetic counseling, genetic testing, and posttest counseling **KQs 2a, 3a:** Risk assessment tools that are applicable to primary care, such as the PREMM5 (and previous iterations of PREMM) or other brief cancer risk assessment tools **KQs 2b, 3b:** Germline genetic testing with targeted next-generation sequencing of DNA isolated from blood, saliva, or buccal swab to identify variants in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* genes associated with Lynch syndrome **KQs 4, 5:** Earlier and more frequent cancer screening (e.g., colonoscopy), use of risk-reducing medications (e.g., aspirin), or prophylactic surgery	**All KQs:** No assessment; other assessment and testing modalities; and testing of tumors **KQs 4, 5:** Chemotherapy, radiation therapy, and natural therapies

Comparisons	**KQ 1:** No screening or usual care **KQs 2a, 3a:** Targeted next-generation sequencing or Sanger sequencing **KQs 2b, 3b:** Sanger sequencing **KQs 4, 5:** No intervention or usual care	Studies without a comparison group; comparative effectiveness studies (head-to-head studies comparing interventions)
Outcomes	**KQ 1:** All-cause mortality, cancer-specific mortality and morbidity, and quality of life **KQ 2:** Sensitivity and specificity **KQ 3:** False-positive results, anxiety, psychosocial harms (including any caused by the detection of variants of uncertain significance), irritation, pain, bleeding, overdiagnosis, and additional tests and subsequent harms **KQ 4:** All-cause mortality, cancer-specific mortality and morbidity, and quality of life **KQ 5:** Irritation, pain, bleeding, infection, altered bowel functioning, altered urinary functioning, altered sexual functioning, bowel perforation, and surgical morbidity or mortality	Cost
Study designs	Controlled trials are eligible for all KQs **KQ 2:** Studies evaluating accuracy are also eligible **KQs 3, 5 (harms):** Prospective cohort studies and case-control studies are also eligible	All other designs
Study duration	Any length	

Settings	Primary care settings or settings referable from primary care	Other settings
Countries	Studies conducted in countries categorized as "Very High" on the Human Development Index (as defined by the United Nations Development Program)	Studies conducted in countries that are not categorized as "Very High" on the Human Development Index
Language	English	Non-English
Study quality	Good or fair	Poor (according to design-specific USPSTF criteria)

Abbreviations: KQ=key question; USPSTF=U.S. Preventives Services Task Force.

Please select one of these options. *

- ○ I agree with it; I have no comments
- ○ Generally, I agree with it; see comments below
- ○ I have concerns; see comments below
- ○ I do not wish to give comments on this question

Do you have any comments about the Research Approach?

- Populations: Would be helpful to include adults *without* LS in KQs 4,5 as comparison group.
- Interventions:
  - KQ1 should include studies of general interventions not specifically focused on LS, such as screening for family history of early or clustered GI or female organ cancers.
  - KQs 2a, 3a – What about non-tool assessments that are commonly used by PCPs? Primary tools are continually changing.
  - Restricted to physical methods such as colonoscopy or could cell-free DNA methods be included?
  - Unclear why chemotherapy, radiation therapy, and natural therapies are excluded from evaluation, which presumably leaves surgery only.
- Comparisons:
  - Comparison to Sanger sequencing is obsolete. Equivalency or superiority of NGS has been well established. Asking to compare to an obsolete, relatively cost-ineffective approach is wasteful.
  - No intervention would seem to be an odd group to compare if cancer is presumably detected (KQs 4,5). I suppose the harms of no-intervention could be the study design.
  - Excluding comparative effectiveness studies could exclude studies that (ethically) screen for progressive cancer without surgical/Rx intervention compared to surgery. That seems odd if accepting no intervention as a comparator.
- Outcomes:
  - See earlier comments.
- Study designs:

    - Controlled trials and prospective studies are much more challenging to do in rare disorders – have to be multi-site. Will this exclude studies that include other disorders screened for as well, or does one have to just screen for LS and nothing else?
    - Literature review and resulting recommendations need to consider that care will not be able to be provided solely by primary care. Flexibility in screening settings is recommended.
- Study durations: OK
- Countries: This could introduce a bias in the results that would impact its applicability to the growing diversity present in our country. Studies should be evaluated on their scientific merit and applicability to the study.

General comments – See reference: Genetic testing for inherited colorectal cancer and polyposis, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG) https://doi.org/10.1038/s41436-021-01207-9

For topics related to heritable conditions, the Task Force should consider inclusion of a certified genetics healthcare professional experienced with the disease in question as a consult when developing research plans and when evaluating public comments.