November 23, 2020

Alex H. Krist, MD, MPH
Chairperson
U.S. Preventive Services Task Force
5600 Fishers Lane
Mail Stop 06E53A
Rockville, MD 20857

Dear Dr. Krist and esteemed members of the U.S. Preventive Services Task Force,

On behalf of our organization and millions of Americans at risk of, or diagnosed with, hereditary colorectal cancer please see the following comments regarding the Draft Recommendation Statement: Colorectal Cancer Screening.

These recommendations affect two crucial areas of health care in the U.S.:

1. The Task Force provides evidence-based guidelines on preventive services such as screenings, counseling services, and preventive medications with a focus on primary care clinicians.
2. The panel’s guidelines are cited in the Patient Protection and Affordable Care Act (ACA); thereby influencing access to care and insurance coverage of crucial preventive health services for a majority of Americans.

With the above in mind, we applaud the USPSTF for its recommendation to reduce the age of screening for those at average risk of colorectal cancer (CRC) to 45. This adjustment reflects current health trends and evidence that colorectal cancer diagnoses among people under age 50 is increasing.

**Patient Population Under Consideration**

The draft recommendation “applies to asymptomatic adults age 45 years and older who are at average risk of colorectal cancer (i.e., no prior diagnosis of colorectal cancer, adenomatous polyps, or inflammatory bowel disease or a family history of known genetic disorders that predispose them to a high lifetime risk of colorectal cancer [such as Lynch syndrome or familial adenomatous polyposis]).”

We agree with this recommendation and recognize that the epidemiology of CRC with regard to age at diagnosis is shifting, with individuals increasingly diagnosed before age 50 years. CRC screening leads to sizable reductions in the lifetime risk of developing and dying from colorectal cancer and increases life expectancy. All adults age 45 years and older are at risk for colorectal cancer and should be offered screening. However, direction is needed to stratify risk and inform the approach to screening for populations that may be at increased risk.
Assessment of Risk
While age is acknowledged as one of the most important risk factors for CRC, the recommendation also states that rates of colorectal cancer are higher in certain populations including, “Black adults and persons with a family history of colorectal cancer (even in the absence of any known inherited syndrome such as Lynch syndrome or familial adenomatous polyposis).” The Task Force expands on the information about screening for CRC in Black adults and concludes that “a separate, specific recommendation on colorectal cancer screening in Black adults” cannot be made at this time. Unfortunately, the Task Force fails to expand upon or clarify recommendations for other potentially high-risk populations.

Identification of High-Risk Population
Approximately one in 300 people are predisposed and thus at high-risk of colorectal and other cancers due to an inherited mutation in one of the five Lynch syndrome genes. In addition, there are other high-risk colorectal cancer genes including APC, BMPR1A, CHEK2, MUTYH, PTEN, SMAD4, STK11, TP53 and others. Importantly, although the population frequency of Lynch syndrome is estimated to be one in 300 (which is appreciably higher than the population frequency of pathogenic BRCA mutations, for which USPSTF specific guidance exists)—to date, the USPSTF has not developed guidelines to screen individuals for Lynch or other familial colorectal cancer syndromes.

Similar to other hereditary cancer syndromes, men and women who have inherited a pathogenic mutation that significantly increases their risk of colorectal cancer often develop cancer at younger ages than the average risk population. As shown in the table below, the average age at diagnosis for colorectal cancer for those at increased due to an inherited mutation in a Lynch syndrome gene is well below the average age at diagnosis for the general population, which is currently 68-72 years. Furthermore the average age at diagnosis for four of the five Lynch syndrome genes is under age 45, younger than the proposed updated range of 45-49 for those at average risk of CRC.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Average age at diagnosis</th>
<th>Cumulative lifetime risk for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPCAM</td>
<td>44</td>
<td>33%-52%</td>
</tr>
<tr>
<td>MLH1</td>
<td>44</td>
<td>46%-61%</td>
</tr>
<tr>
<td>MSH2</td>
<td>44</td>
<td>33%-52%</td>
</tr>
<tr>
<td>MSH6</td>
<td>42-69</td>
<td>10%-44%</td>
</tr>
<tr>
<td>PMS2</td>
<td>61-66</td>
<td>9%-20%</td>
</tr>
</tbody>
</table>

*Adapted from the NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal Version 1.2020
The USPSTF should address this difference in age at diagnosis for those at high-risk as it strives to achieve its mission “to improve the health of all Americans by making evidence-based recommendations about clinical preventive services.”

Many primary care providers are not familiar with the warning signs of hereditary colorectal cancer syndromes and may not ask the right questions to assess risk in their patients. Providers and their patients may not know that endometrial, ovarian, pancreatic, urothelial and gastric cancers are associated with Lynch and other CRC syndromes. As such, clinicians may not recognize patients at increased risk of hereditary CRC by overlooking a personal or family history of related cancers.

With guidance from the Task Force, primary care providers would be better equipped to identify asymptomatic patients with pertinent family history and refer them for genetic assessment or recommend a screening regimen appropriate for high-risk individuals. Given the absence of USPSTF recommendations to screen for Lynch syndrome, familial adenomatous polyposis or related colorectal cancer syndromes, we ask that the Task Force provide clear guidance on how to identify patients who may be affected by hereditary CRC—and the appropriate approach to screening these individuals.

**Research Needs and Gaps**
We support the USPSTF statements on the need for more research where evidence is lacking or inconclusive. In addition to the gaps outlined, we recommend additional research on hereditary cancer syndromes, including the risks attributed to specific mutations and ideal screening regimens based on those risks.

**Recommendations of Others**
As noted, a number of organizations have colorectal cancer screening guidelines for those considered to be at average risk of disease. The U.S. Multi-Society Task Force recommends beginning screening at age 45 years in Black adults and screening at age 40 years (or 10 years before the age at diagnosis of a family member, whichever is earlier) in persons with a family history for colorectal cancer. Missing from the list of recommendations are guidelines for those who may be affected by a hereditary colorectal cancer syndrome due to a family history of cancer such as endometrial or ovarian, but do not have a known family history of colorectal cancer.

To provide additional guidance on identifying individuals who are potentially at increased risk of colorectal cancer, we encourage the USPSTF to acknowledge the following recommendations:

- [NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Colorectal](https://www.nccn.org/professionals/physician_gls/pdf/genetic-familial_cancer.pdf)
- [European Society for Medical Oncology Clinical Practice Guidelines](https://www.esmo.org/guidelines) (endorsed by the American Society of Clinical Oncology),
Scope and Authority
We recognize that the scope of services considered by the USPSTF includes only primary or secondary prevention that can be used in or referred from the primary care setting. Identification of individuals who may be at increased risk of colorectal and other cancers unquestionably falls under this domain. As such, the Task Force would serve the needs of the broader population by providing guidance on hereditary cancer syndrome traits beyond “persons with a family history of colorectal cancer.” This limited description ignores evidence that other cancers—endometrial, ovarian, pancreatic, urothelial, gastric and others—are associated with a hereditary predisposition to colorectal cancer and should be considered when assessing risk.

In summary, the USPSTF guidelines play a critical role in guiding clinical decisions and access to care. The Task Force will better serve the public and its mission by expanding these recommendations to reflect current science related to hereditary colorectal cancer syndromes. Further information on risk-stratification will benefit providers and patients. We welcome the opportunity to discuss the concerns and suggestions outlined herein.

Sincerely,

Lisa Schlager
Vice President, Public Policy

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