**AGA White Paper: Roadmap for the Future of Colorectal Cancer Screening in the United States**

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***Abbreviations used in this paper:*** ADR, adenoma detection rate; AN, advanced neoplasia; BMI, body mass index; CCE, colon capsule endoscopy; CTC, computed tomography colonography; CRC, colorectal cancer; EHR, electronic health record; FIT, fecal immunochemical test; MT-sDNA, multi-target stool DNA; NHIS, National Health Information Survey; PLCO, Prostate Lung Colorectal and Ovarian screening trial.

The American Gastroenterological Association's (AGA) Center for GI Innovation and Technology (CGIT) convened a consensus conference in December 2018, entitled, "Colorectal Cancer Screening and Surveillance: Role of Emerging Technology and Innovation to Improve Outcomes."[1] The goal of the conference, which attracted more than 60 experts in screening and related disciplines, including the authors of this paper, was to envision a future in which colorectal cancer (CRC) screening and surveillance are optimized, and to identify barriers to achieving that future. This white paper originates from that meeting and delineates priorities and steps needed to improve CRC outcomes, with the goal of minimizing CRC morbidity and mortality.

The CGIT invited a diverse pool of prominent North American clinical and basic gastrointestinal researchers to attend the two-day consensus conference. A recently published meeting summary[1] detailed the organizational structure and targeted goals of the conference, from which this document emerges. The overarching objectives of the conference were to: (1) identify barriers to screening uptake, (2) assess the efficacy of available screening diagnostic methods, and (3) consider the potential integration of novel diagnostic approaches into screening and surveillance paradigms. These objectives were determined from responses to a pre-conference survey, which asked respondents to identify the current main limitations to screening, and to specify what kind of clinical research output they would most value. The most commonly mentioned limitation to screening was compliance with screening across the eligible population, and the most frequently mentioned desired output was development of an affordable, highly accurate, noninvasive test.

Each of the authors of this white paper participated in the consensus conference and was chosen to develop this document based on their specific expertise in the above areas. Although the

conference featured a discussion of emerging endoscopic technologies, this topic will be featured in a follow-up document. This paper pertains specifically to North American practice, in which opportunistic colonoscopy is currently the dominant screening methodology.

**Summary Statement**: A "one-size-fits-all" approach to CRC screening has not and is unlikely to result in increased screening uptake or desired outcomes due to barriers stemming from behavioral, cultural, and socioeconomic causes, especially when combined with inefficiencies in deployment of screening technologies. Overcoming these barriers will require (1) efficient utilization of multiple screening modalities to achieve increased uptake; (2) continued development of noninvasive screening tests, with iterative reassessments of how best to integrate new technologies; and (3) improved personal risk assessment to better risk-stratify patients for appropriate screening testing paradigms. Development of structured organized screening programs, rather than solely opportunistic screening driven by provider recommendation, will ultimately be needed to achieve target screening rates and reductions in CRC morbidity and mortality. Table 1 delineates key position statements and strategies for achieving those goals.

**Section 1. Strategic modifications to CRC screening can improve uptake and outcomes.**

**Position statement 1.** A paradigm that addresses present barriers, incorporates shared decision-making, and makes multiple modalities available will lead to improved screening uptake and the key desired outcomes of reduced incidence and mortality. Including personalized risk as part of shared decision-making may improve uptake of screening and choice of test: colonoscopy for those at high risk, or initial noninvasive testing for those at lower risk.

### 1.1.1. Current efforts to improve screening uptake have had modest but suboptimal success.

In 2014 the National Colorectal Cancer Roundtable announced its "80% by 2018" program goal of achieving 80% screening uptake for adults aged 50 and older by 2018.[2] The ambitious initiative set a high bar and achieved mixed results. "80% by 2018" showed that organizations could align over a common effort to improve screening uptake. Over 1,700 organizations across 50 states signed onto the initiative.[3] Coordinated efforts modestly improved screening of all eligible Americans from 66.2% in 2014 to 67.3% in 2016.[4,5] However, while some states approach rates close to 80%, most have fallen short. At least one-quarter of eligible Americans have not undergone any CRC screening and rates vary widely between states.[6,7]

Opportunistic colonoscopy is the most prevalent strategy in the U.S. It is questionable if 80% uptake is achievable in a primarily opportunistic screening environment. Organized screening offers an opportunity for systematic improvements via several key elements: (1) defined target populations; (2) organized invitations to screen; (3) timely access and follow-up; (4) quality assurances; (5) tracking of outcomes, including complications; (6) greater protection against harms from over-screening[8]; (7) improved detection of advanced neoplasia (AN) when available tests (e.g., fecal immunochemical testing [FIT]) are used in a programmatic sequential process rather

than as a one-time test[9,10]; and (8) systematic opportunities for shared decision- making. In a shared decision-making process, which accounts for individual patients' needs and preferences[11], patients are active partners, and clinicians offer acceptable medical options as well as the risk-benefit profile for each option.

An organized screening program could improve efficiency by incorporating noninvasive testing. A 2018 Kaiser Permanente study reported that implementation of organized screening with both annual mailed FIT and colonoscopy alternatives led to attainment of ≥80% screening and decreased incidence of both early and advanced-stage CRC.[12] Another study estimated that achieving ≥80% uptake by colonoscopy alone would require 16 million colonoscopies in the first year and 12 to 13 million each year afterward; in contrast, a program offering both colonoscopy and FIT would require 13 million colonoscopies in the first year and 5 million per year thereafter.[13]

### 1.1.2. Racial, socioeconomic, and geographic healthcare disparities limit screening efficacy.

Access to screening is a major problem that disproportionately burdens African-American and Hispanic-American communities[14-18], as well as individuals in rural areas.[19-21] African-Americans experience higher rates of CRC than any other ethnic group in the U.S.[22] Differences in screening accounted for 42% of the disparity in CRC incidence between blacks and whites and 19% of the disparity in CRC mortality.[7,23] National Health Information Survey (NHIS) data from 2000 through 2015 demonstrate that recent CRC screening was least likely to be reported by individuals with annual income <139% of the federal poverty level and those with less than a high school education, as well as subsets of some minorities.[24] Berkowitz and

colleagues used county-level U.S. data to demonstrate substantial interstate and intra-state variation in CRC screening utilization, with pronounced differences in various racial cohorts.[7]

**1.1.3. Screening efficacy varies at multiple levels of service: patient, provider, and health care system.** (See Supplemental material online at www.cghjournal.org)

**1.1.4. Integration of a stool testing option can increase participation rates in comparison to colonoscopy alone.**

In meta-analyses, the pooled sensitivity of programmatic FIT testing for CRC was 79% (95% confidence interval [CI], 69% to 86%) with a specificity of 94% (95% CI, 92% to 95%) and a mortality benefit of 20%-30%.[25] FIT had been shown in diverse environments to outperform colonoscopy in terms of uptake. In a Spanish controlled trial of over 55,000 patients randomized to either FIT or colonoscopy, the participation rate in the first cycle was greater for FIT than for colonoscopy (34.2% vs. 24.6%).[26] Though there was limited uptake in this study, it illustrates that participation for FIT is higher than upfront colonoscopy in the first round, partially offsetting its lower single-application sensitivity for CRC. FIT is far simpler to administer than colonoscopy, which requires dietary manipulation, bowel preparation, and entails time off from work as well as the need for a chaperone and/or driver.

In a cluster randomized design study, completion of screening in those offered fecal occult blood testing (FOBT) or colonoscopy (69%) was superior to those who were only recommended colonoscopy (38%). Nonwhite participants were more adherent to stool testing. This study shows that offering upfront stool testing as an option in addition to colonoscopy increases screening uptake.[27] A challenge for health care systems that offer noninvasive testing is the need to follow-up

on positive results with referral for diagnostic colonoscopy and on negative results with repeat testing at the appropriate interval.

A multi-target stool DNA test (MT-sDNA) has emerged as an alternative to FIT and has unique benefits and limitations in relation to FIT. MT-sDNA combines an immunoassay for hemoglobin with molecular assays for hypermethylated CpG islands (NDRG4 and BMP3) and mutant KRAS. In the pivotal trial comparing MT-sDNA to FIT, CRC detection was 92% in the MT-sDNA arm and 74% in the FIT arm. Both stool tests detected a minority of AN, which was defined as cancer or advanced adenomas with any of the following characteristics: size ≥10 mm, high-grade dysplasia, or villous histology. MT-sDNA demonstrated a detection rate of 42%, compared to 24% for FIT. MT-sDNA outperformed FIT for detecting sessile serrated lesions (42% with MT-sDNA vs. 5% with FIT). The improved sensitivity of MT-sDNA over FIT comes at the price of reduced specificity (87% vs. 95%) for those without AN.[28]

Other limitations of MT-sDNA include higher cost ($595, compared to approximately $25 for FIT testing)[29] and lack of data on long-term outcomes of patients with negative and positive MT-sDNA. Consequently, the optimal between-test interval is not yet defined. There remains uncertainty in interpreting a positive MT-sDNA followed by negative colonoscopy for risk of an alternate aerodigestive cancer; although initial studies suggest no significantly increased risk of CRC in this scenario, further work is needed.[30,31]

### 1.2.1. Strategy 1: Incorporate adjunct noninvasive testing to improve screening rates.

In a Kaiser Permanente study, integration of an organized FIT program within an existing

organized colonoscopy program increased participation from 39% to 83%. The increase correlated with 25.5% and 52.4% reductions in CRC incidence and mortality, respectively.[12] In comparison to MT-sDNA, FIT has a markedly reduced cost and a lower rate of false positives; in contrast, MT-sDNA has higher sensitivity.[28] In a Markov model that assumed equal participation rates, FIT and colonoscopy were more effective and less costly than MT-sDNA.[32] However, participation rate (i.e., uptake) is a critical variable that can determine a test's effectiveness[33]; thus, individual preferences should be considered. Figure 1 depicts a shared decision-making model for screening test selection.

### 1.2.2. Strategy 2: Minimize inappropriate colonoscopy usage.

The common practice of performing re-screening and surveillance colonoscopy sooner than recommended by guidelines is ineffective, inefficient, and depletes limited resources that could have been allocated otherwise to address gaps in screening/surveillance (e.g., previously unscreened individuals facing barriers to colonoscopy).[34] In the Study of Colonoscopy Utilization within the Prostate Lung Colorectal and Ovarian (PLCO) screening trial (N=3,876), up to a quarter of those without adenoma had undergone repeat colonoscopy by five years from their initial colonoscopy; by Year 7, 10.4% had undergone multiple colonoscopies.[35] Colonoscopy was underused in those with high-risk adenoma, which is the group at highest risk for subsequent CRC[36], presumably those most likely to benefit from colonoscopy surveillance. Colonoscopy is inefficient when performed at earlier intervals in patients without adenoma, as the yield of finding AN is low.[37,38] Following completion of a high-quality colonoscopy examination in which no colonic neoplasia is found, there is no need for further screening tests for a 10-year interval.[39] We should actively foster a culture that minimizes inappropriate overuse of colonoscopy for screening and surveillance.

### 1.2.3. Strategy 3: Reconsider surveillance strategies for individuals with history of adenomatous polyps.

Adenoma detection rates (ADRs), which are inversely correlated with post-colonoscopy CRC rates[40,41], have increased over time[42], though individual colonoscopists may find this metric challenging to increase.[43-45] Increased ADRs result in expansion of the population placed into colonoscopy-based surveillance programs.[42] In a setting where opportunistic screening predominates, the extent to which the burden of surveillance colonoscopy for polyps limits the ability to bring new patients to screening is undefined but may constrain colonoscopy resources.[46,47] In addition, intensification of surveillance may not be necessary for everyone.

Data suggest that history of small adenoma alone may not be a strong predictor of metachronous AN, and the benefit of surveillance colonoscopy at intervals less than 10 years is not entirely clear.[48,49] Further, higher ADRs and consequently increased surveillance theoretically carry corresponding harms of additional procedures, including associated complications and cost[50] — although a microsimulation model-based study contended otherwise. Meester and colleagues estimated that the lifetime risk for CRC was 12.5 per 1,000 patients for high adenoma detectors and 26.6 per 1,000 patients for low detectors. Although the estimated number of colonoscopies per 1,000 patients was greater in the "high adenoma detector group" by an average of 4.6%, there were fewer cancers and lower overall cancer-care costs, which offset the increased costs for screening.[51]

One possible solution to the ever-increasing demand for surveillance colonoscopy is to prolong the surveillance interval for non-advanced adenomas. The recently updated U.S. Multi-Society Task Force (USMTF) on Colorectal Cancer surveillance guidelines have extended the interval between

colonoscopies for low-risk adenomas.[52] Another approach is to consider noninvasive testing for the large subgroup of patients with low-risk adenomas as an alternative to surveillance colonoscopy. Interval FIT analyses can be used to detect missed or rapidly developing lesions in surveillance programs.[53] In an English study, replacing three yearly colonoscopy surveillance procedures in intermediate-risk patients with annual FIT had the potential to reduce colonoscopies by 71% and significantly cut costs, but could miss 30%-40% of CRCs and 40%-70% of advanced adenomas.[54] The optimal way to integrate noninvasive stool tests for cohorts with adenoma surveillance is not well defined and deserves further study.

### 1.2.4. Strategy 4: Develop targeted methods to motivate and guide individuals undergoing first-time screening. (See Supplemental material online)

## Section 2. There is a need for continued development of noninvasive and minimally invasive tests for screening.

**Position Statement 2.** The ideal noninvasive or minimally invasive screening test would be widely adopted and identify those at risk for CRC with high accuracy.

### 2.1.1. The ideal noninvasive or minimally invasive screening test has yet to be developed.

An ideal test would identify lesions with high short-term potential to progress to CRC and should do so with high sensitivity and specificity in a convenient, low-risk, low-cost, and operator-independent manner. Such a test should be easy to complete and achieve high uptake in the

screening-eligible population. Presumably, a blood test would be the most effective vehicle, because of a markedly reduced barrier to compliance.

CT colonography (CTC) and colon capsule endoscopy (CCE) are comparable to optical colonoscopy in their ability to detect lesions 10 mm or larger.[55] However, these approaches have yet to achieve widespread adoption and are unlikely to do so.[56] Limitations of these methodologies include the need for bowel preparation, and in the case of CCE, a prep currently more burdensome than colonoscopy, with a high proportion of screen failures.[57] CTC and CCE show suboptimal detection of serrated lesions, which are flat and minimally vascular.[58]

Efforts to develop and evaluate CRC screening markers need to address the following questions: (1) How can we optimally combine different types of markers to achieve high detection rates? (2) What is the desired combination of sensitivity and specificity? (3) Is AN the most appropriate target lesion metric, or is it preferable to have a marker that is also inclusive of advanced sessile serrated lesions? (4) How should we determine screening frequencies and intervals for tests using noninvasive biomarkers? (5) Will these biomarkers be generalizable to different molecular sub-types of advanced lesions and CRCs?

Noninvasive testing results should be reproducible, have low coefficient of variation at specified cut-offs, and be easy to sample in clinically realistic volumes. Their assessment via automated, high-throughput technology would facilitate quality control.

**2.1.2 The process by which novel diagnostics for CRC screening are developed should have a defined pathway with key milestones leading to eventual clinical use.**

Comparing new CRC screening tests using CRC mortality as the endpoint will not be feasible given sample size requirements, time, and cost. Thus, simpler studies with surrogate endpoints (e.g., detection of AN) are needed. The comparator is a test with known abilities to improve CRC outcomes, such as FIT.

A general pathway for cancer screening test development starts with a discovery phase to identify promising markers, followed by a validation phase to evaluate the performance of one or more markers in the intended clinical setting. This is followed by a clinical impact phase to assess whether use of the biomarker actually improves patient outcomes.[59] Once an accuracy threshold is established, subsequent testing would entail randomization on an intention-to-screen basis.[13] A 2016 World Endoscopy Organization working group proposed a study design pathway for eventual integration of CRC-specific diagnostic tests into screening programs. Phase 1 would compare test accuracy in a retrospective cohort in CRC cases and controls. Phase 2 would entail a prospective evaluation of performance across the continuum of neoplastic lesions (advanced adenoma, CRC). Phase 3 would be an actual programmatic outcomes assessment, ideally with randomization versus an alternative screening modality (such as FIT); this phase would address patient uptake and participation; outcomes at one screening round would be addressed on an intention-to-screen basis. Phase 4, the final phase for consideration, would consist of a more comprehensive evaluation, including multiple rounds of screening, with additional assessments of safety and cost-effectiveness.[60]

There are several genomic, proteomic, biochemical, epigenomic, and microbiome markers that might be integrated into screening tests, provided they address accuracy, ease of use, noni nvasiveness, and cost-effectiveness. Biomarkers can be categorized into studies that consider

CRC detection alone and those that combine CRC detection with prevention (i.e., via detection of precancerous lesions). For those that seek a preventive effect, detection of advanced adenoma (lesion ≥10mm in size or of any size with advanced features) is an important endpoint. The rationale for considering advanced adenoma comes from studies in which the cumulative CRC incidence by initial adenoma status is significantly higher in those with an advanced adenoma, but not in those with any non-advanced adenoma.[36]

The most appropriate target lesion for noninvasive screening is currently not entirely defined. The USMTF describes AN as inclusive of CRC and adenomas with high-grade dysplasia or with ≥25% villous histologic features or measuring ≥1 cm, but their definition of AN does not include sessile serrated lesions even of advanced size.[52] In some instances, such as in the pivotal trial for MT-sDNA, investigators assessed an endpoint that is also inclusive of advanced sessile serrated lesions.[28] Further work will need to link the added benefit and cost of these differing screening target endpoints to endpoints pertaining to cost, cancer incidence, and mortality.

### 2.2.1. Strategy 5: Set an aspirational target for developing a minimally invasive, easy-to-use test that will detect advanced adenomas and advanced serrated lesions with a one-time sensitivity and specificity of no less than 90%.

At present, new diagnostic tests need to be evaluated against a comparator. It is reasonable to compare new biomarkers to FIT with respect to sensitivity, specificity, and mortality, as well as to accuracy, uptake, and ease of use. We propose an aspirational goal of developing a non-invasive test capable of detecting advanced adenomas and advanced serrated lesions, as described in the USMTF guidelines[52], at a rate comparable to colonoscopy (≥90%) with a sensitivity of 90%. Such a marker would, in terms of detection capabilities, challenge the current rationale for

upfront colonoscopy, as it would have comparable sensitivity with colonoscopy along with high specificity for identifying individuals with important target lesions. When considering aspirational rates of specificity for AN for noninvasive markers, it is worth noting that no neoplasia is found in a high percentage of average-risk patients undergoing screening colonoscopy. In this sense, no direct therapeutic benefit of colonoscopy for cancer prevention in those cases is derived.[61] When considering the rates of colonoscopy for screening for advanced precancerous lesions the rate of "negative colonoscopy findings" is even higher.

Future integration of CTC and CCE uptake into screening will require improvements from existing technology, including (1) development of methodologies to eliminate or reduce bowel preparation; (2) identification of methodologies to improve imaging of suboptimally detected lesions such as sessile serrated polyps and certain segments of the colorectum; (3) integration of imaging technologies with artificial intelligence to detect and differentiate lesions and reduce provider reading times; (4) enhanced accuracy; and (5) development of methodologies with improved ease of use, potentially allowing for home use.

**Section 3. Improved personal risk assessment is critical to optimized programmatic screening.**

**Position statement 3.** There is a need for improved assessment of individual risk to enhance the process of risk stratification for risk-based screening and surveillance.

### 3.1.1. Current approaches to risk stratification frequently utilize inaccurate and incomplete information, limiting appropriate decision-making for screening and surveillance.

Current guidelines for risk assessment utilize familial and personal colorectal neoplasia risk.

However, there are numerous additional factors (e.g., sex, race, smoking, body mass index [BMI]) associated with CRC risk that could potentially be used to tailor screening.[62] Risk stratification requires reliable information of the considered risk factors. Family history and prior adenomatous polyp burden are frequently challenging to obtain reliably and often not well recorded. Less than 40% of individuals with a family history of CRC have discussed this information with their health care provider.[63] Family history is often not obtained due to a lack of patient awareness and the provider's limited ability to derive and record the information.[63-65]

Currently the burden of ensuring accuracy of family history is typically placed on providers at the time of clinical visits. One disadvantage of this model is that family histories may remain static following initial documentation, even if the patient subsequently learns of new, pertinent family history. The increasing use of patient portals presents an opportunity to both involve patients in their own care as well as to keep family histories updated and/or accurate. Evaluation of this model for patient data entry outside of clinical visits deserves further study.

### 3.1.2. Strategy 6: Enable electronic health record (EHR) integration to permit providers working in different settings to accurately estimate a mutual patient's risk based on all pertinent data.

Currently, barriers exist to interrogating a patient's EHR outside of the patient's health system in order to reliably obtain the requisite personal or familial history for risk stratification. (See Supplemental material online)

### 3.2.1. There are multiple significant challenges to incorporating new approaches to risk assessment in CRC screening and surveillance.

Risk assessment tools have typically utilized different endpoints. "CRC risk" can either be

considered as a future/lifetime risk for CRC or as the current or present risk for CRC or AN. The National Cancer Institute's Risk Assessment Tool for Colorectal Cancer has been prospectively validated for the outcome of AN at colonoscopy.[66,67] Other models have been used for estimating long-term or lifetime risk for CRC.[68,69]

Incorporating risk assessment tools into clinical practice will be challenging. Systems would integrate with EHRs, identifying factors already available in the EHR and querying the user for information not present in the EHR, with the end result of producing risk estimation with or without linkage to a preferred screening strategy. Models require testing and validation in the target population, along with determining whether and by how much they improve CRC screening uptake, adherence, satisfaction, and efficiency. It will be important to ensure that overall participation rates are not affected adversely due to the complexity and additional administrative burden from using risk stratification.

### 3.2.2. Risk assessment tools must better define individual risk to stratify patients for appropriate CRC screening test selection.

Individuals with a higher likelihood of advanced adenoma or CRC would be directed to colonoscopy, currently the most sensitive test with the ability to remove advanced adenoma and some early-stage CRCs. Lower-risk individuals would be directed to less-invasive approaches that offer a reduced side effect profile but may have higher uptake. Numerous predictive models have been developed to predict CRC risk and guide screening decision-making.[70-72] In a predictive model using age, sex, waist circumference, cigarette smoking, and family history of CRC, AN detection was 10 times higher in the high-risk group than in the very low-risk group.[72] In a comparison of 17 previously published risk models, Peng and colleagues found

only a modest ability to predict the presence of AN; the authors recommended that subsequent models consider integrating genomic features, with the goal of increasing discriminatory power.[73]

### 3.2.3. Strategy 7: Integrate CRC risk assessment approaches incorporating lifestyle/anthropometric, environmental, and polygenic risk factors. (See Supplemental materials online)

### 3.2.4. There is a need for improved assessment of individual risk to improve risk stratification for re-screening and surveillance.

Much less work has been done in the area of risk stratification for re-screening and general surveillance as compared with primary screening. Currently, re-screening tests other than colonoscopy are infrequently offered to a patient with a previous negative colonoscopy. A microsimulation analysis by Knudsen and colleagues found that in persons with a negative screening colonoscopy, re-screening using any of the other recommended strategies provided the same subsequent benefit in terms of life-years saved and with fewer complications and lower costs than colonoscopy every 10 years.[74] Optimal predictive models to risk-stratify the patient after colonoscopy will need to incorporate findings of that colonoscopy (i.e., presence and extent of neoplasia) with other associated predictors for CRC to guide future clinical decision-making.

Some associated risk factors for metachronous AN, including age, sex, and location in the proximal colon, are currently not used in determining the surveillance interval.[75] Not considering these and possibly other factors may explain the relatively poor discriminatory power for estimating risk for AN and the low yield of surveillance colonoscopy, especially for persons with non-advanced neoplasia. In a pooled analysis of data from 9,167 adults aged 22-80 with previously

resected colorectal adenomas, risk factors such as older age, number and size of adenomas, and villous histology – each of which guides delineation of surveillance intervals – all separately increased the risk of future metachronous AN by ORs of no more than 1.7.[76] Several studies have examined risk for AN on the second surveillance colonoscopy based on the previous two colonoscopies.[77-80] We envision a future in which guided risk assessment accounts for the patient's past colonoscopy historical profile. Electronic health record (EHR) capture of data needs to be more accurate and reliable to ensure accurate population-based data in relation to CRC screening. Interfacing between EHRs across institutions is a further challenge.[81,82] As health care systems and EHRs continue to evolve, subsequent studies will be able to link baseline findings, phenotypic features, and surveillance colonoscopy to hard clinical endpoints of CRC incidence and mortality.

### 3.3.1. The consequences of expanding screening recommendations to an earlier age have yet to be defined.

While the overall incidence of CRC has declined over the last two decades in the U.S., it has risen in those under the age of 50.[83] The proportion of CRC in adults under 50 has doubled since 1990.[84] The increase in the incidence of CRC in the 40-49-year-old group, which amounts to a roughly 1.3% annual risk increase since the mid-1990s[84], has heightened interest in initiating screening earlier (age 45). Such an approach would prevent CRC in an estimated three per 1,000 persons screened, or an estimated 66,000 cancers in 22 million eligible persons aged 45-49.[85] Potentially, knowledge of such benefits might motivate more people aged 50-54 to get screened, possibly enabling identification of earlier-stage cancers, though there are no clear data supporting this concept. Moreover, there are multiple challenges to initiating screening at age 45.[86] One potential consideration is that if patients are screened by colonoscopy, they would most likely undergo more colonoscopies over their lifetimes than if screening begins at age 50 or later.

In areas of high colonoscopy demand, it is unclear how the need to screen younger patients would be balanced against limited endoscopic capacity, as initiating screening at age 45 would add 21 million people to the current pool of 94 million eligible persons – an increase of 22%. Moreover, a cost-effectiveness analysis showed that greater benefit, at lower cost, could be achieved by increasing screening participation rates for currently unscreened older and higher- risk persons than by screening lower-risk, younger patients.[85] Steering younger individuals toward low-cost screening approaches such as stool-based tests may therefore avoid a large increase in resource utilization.[86]

### 3.3.2. Strategy 8: Support research to better characterize the benefits and risks of initiating CRC screening at a younger age.

Studies should focus on the cost-effectiveness of screening younger patients, the performance characteristics of screening tests in specific cohorts of younger people, and how factors such as BMI, lifestyle, and family history impact risk in younger patients. There is also a need for studies to address adherence to different screening test methods by younger patients, as well as their likelihood of screening participation and compliance with recommended surveillance intervals. The increasing incidence of CRC in people under 50 years of age may be secondary to changes in dietary patterns, activity levels, the gut microbiome, or other factors. The impact of these factors on the risk of colorectal cancer could be measured with novel assays that assess the colon mucosa for field cancerization or pro-tumorigenic early changes in cancer development.[87,88]

## Conclusions

In the opportunistic screening environment in the U.S., where colonoscopy is the most prevalent method, CRC screening has not reached aspirational goals in terms of uptake, reduction in CRC incidence, and disease burden. Ultimately, the development of organized screening programs that can identify and navigate the unscreened to screening should be considered. Efforts to significantly decrease CRC incidence rates and disease-related outcomes will require greater integration of additional alternative testing modalities to colonoscopy to increase uptake. Stool testing by FIT is currently the most readily available alternative, though novel molecular biomarkers hold promise for making screening more accurate and efficient.

The desired future of CRC screening is one in which screening is readily available to at-risk individuals, with no significant disparities in access to screening. Such a future will also feature noninvasive testing methods that are highly accurate, easy to use, and facilitate referrals to colonoscopy only for those patients most likely to benefit.

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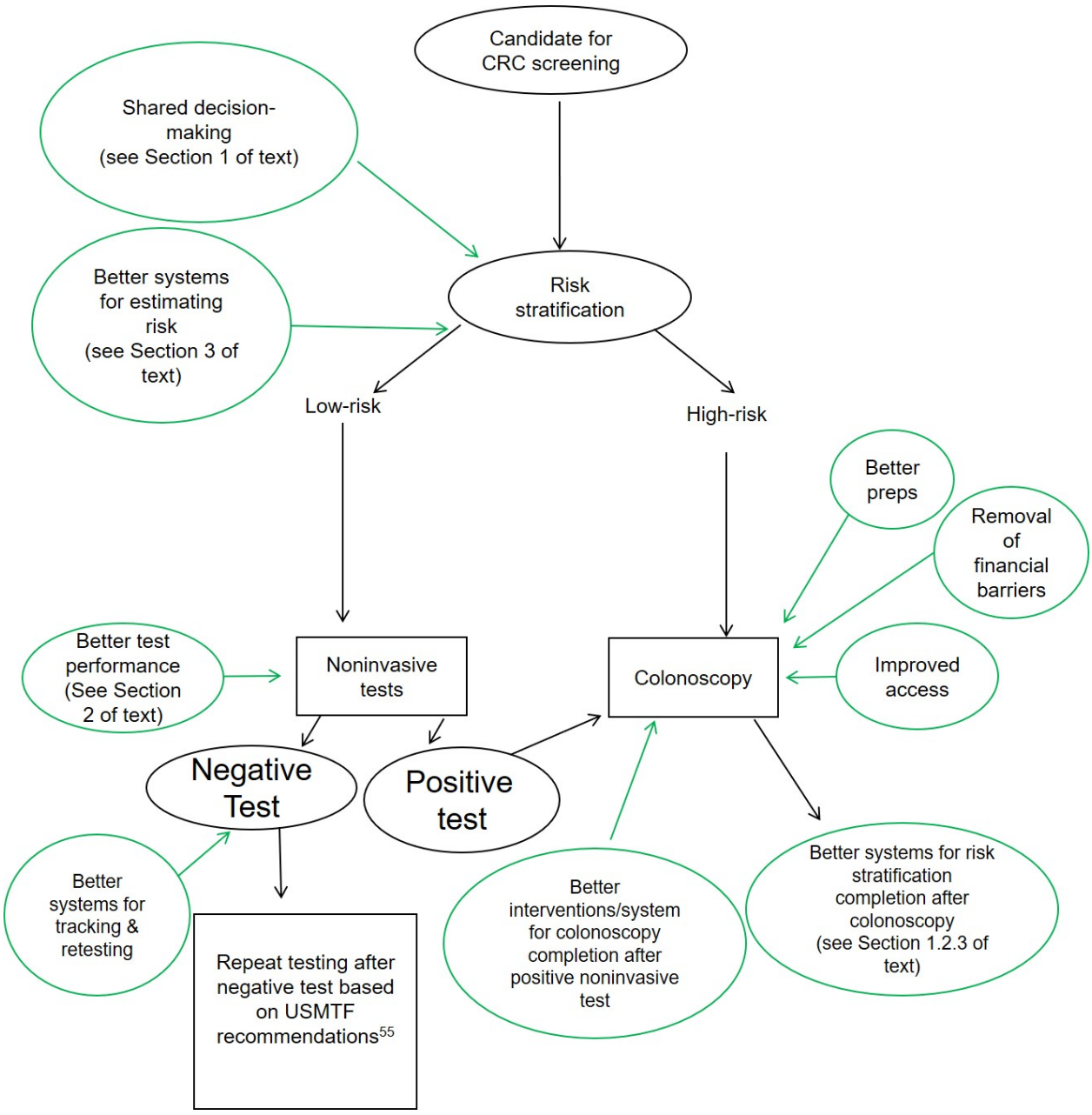
**Table 1: Barriers and Strategies for Improving Colorectal Cancer Screening in the United States**

| **Position Statement 1.** A paradigm that acknowledges present barriers, incorporates shared decision-making, and makes multiple modalities available will lead to improved screening uptake and outcomes. | **Position Statement 2.** The ideal non-invasive or minimally invasive screening test would be widely adopted and identify those at risk for CRC with high accuracy. | **Position Statement 3.** There is a need for improved assessment of individual risk to better stratify patients for appropriate screening and surveillance. |
|---|---|---|
| **Barriers** | **Barriers** | **Barriers** |
| 1.1.1. Suboptimal screening uptake | 2.1.1. Lack of an ideal non-invasive or minimally invasive screening test | 3.1.1. Inaccurate and incomplete information to inform risk stratification |
| 1.1.2. Racial, socioeconomic, and geographic healthcare disparities | | 3.2.1. Challenges to incorporating new approaches to risk assessment in CRC screening and surveillance |
| 1.1.3. Varying screening efficacy varies at multiple levels of service | 2.1.2. Lack of a defined pathway and key milestones for developing novel diagnostics for CRC screening | 3.2.2. Suboptimal definition of individual risk in risk assessment tools |
| 1.1.4. Challenges to integration of a stool testing option | | 3.2.3. Need for improved assessment of individual risk to better stratify patients for appropriate re-screening and surveillance |
| | | 3.3.1. Undefined consequences of expanding screening recommendations to an earlier age |
| **Strategies** | **Strategies** | **Strategies** |
| 1. Incorporate adjunct non-invasive testing to improve screening rates. | 5. Set an aspirational target for developing a minimally invasive, easy-to use test that will detect advanced adenomas and advanced serrated lesions with a one-time sensitivity and specificity of no less than 90%. | 6. Enable EMR integration to permit providers working in different settings to accurately estimate a mutual patient's risk based on all pertinent data. |
| 2. Minimize inappropriate colonoscopy usage. | | 7. Integrate CRC risk assessment approaches incorporating lifestyle/anthropometric, environmental, and polygenic risk factors. |
| 3. Reconsider surveillance strategies for some individuals with low risk | | 8. Support research to better characterize the benefits and risks of |

| | | |
|---|---|---|
| adenomatous polyps as candidates for surveillance by noninvasive methods. | | initiating CRC screening at a younger age. |
| 4. Develop targeted methods to motivate and guide individuals undergoing first-time screening. | | |

**Figure 1**. **Risk Assessment Model with Shared Decision-Making l for CRC Screening.** Colonoscopy is recommended for high-risk patients, such as individuals with a family history of colorectal cancer (CRC) in a first-degree relative. Better risk assessment tools are needed to risk-stratify patients' risk of CRC and guide the initial screening test of choice. Shared decision-making is incorporated into risk assessment. Noninvasive testing is prioritized for those patients with lower risk profiles; colonoscopy is prioritized for those at higher risk for CRC. When noninvasive tests (i.e., stool tests) are negative, risk stratification of patients can guide establishment of the post-test interval for re-screening. The interval may be delayed for lower-risk patients with negative stool test results. Those with no neoplasia or only non-advanced neoplasia at colonoscopy may be considered for future noninvasive testing. Tools for re-stratification post-colonoscopy should incorporate procedural findings to define either future surveillance intervals for colonoscopy or suitability for alternative noninvasive testing.


Candidate for CRC screening
Shared decision-making (see Section 1 of text)
Better systems for estimating risk (see Section 3 of text)
Risk stratification
Low-risk
High-risk
Better preps
Removal of financial barriers
Better test performance (See Section 2 of text)
Noninvasive tests
Colonoscopy
Improved access
Negative Test
Positive test
Better systems for tracking & retesting
Repeat testing after negative test based on USMTF recommendations[55]
Better interventions/system for colonoscopy completion after positive noninvasive test
Better systems for risk stratification completion after colonoscopy (see Section 1.2.3 of text)

**AGA CGIT CRC Screening White Paper**
**Supplemental Material**

### 1.1.3 Screening efficacy varies at multiple levels of service: patient, provider, and health system-wide.

More than 20 million eligible U.S. adults have not participated in CRC screening. Failure to complete screening can stem from socioeconomic barriers, including challenges entering the health care system (e.g., lack of insurance coverage); inability to access a location that provides screening in a reasonable time frame; inability to find a trusted provider to guide the patient through the screening process[1,2]; and inability to take time off from work for colonoscopy and/or find transportation for the procedure. Other barriers include personal objections related to hygiene risk, fear of testing procedures, and embarrassment.[3-5]

Primary care physicians (PCPs) can serve as important advocates for CRC screening. A systematic review showed that PCP recommendations improved screening rates for both colonoscopy and stool-based testing.[6,7] However, unconscious biases can limit this effect: racial disparities in physician recommendations lead to disparities in screening.[8] A program that provides oversight of screening access and completion in the U.S. may improve future screening uptake and the ability to scale screening efforts beyond individual private health systems.

### 1.2.4 Strategy 4: Develop targeted methods to motivate and guide individuals undergoing first-time screening.

Motivation by peers, community leaders, and celebrities can potentially influence patient behavior. Currently, it is unclear how to select individuals who may benefit most from navigator- based, provider-based, or digital navigation methods. Several studies have successfully implemented patient navigation programs to improve CRC screening compliance.[9-14] Additionally, the American Cancer Society has developed materials to facilitate shared decision–making for CRC screening.[15] However, there are few high-quality randomized studies that apply a rigorous comparative assessment of different methods to improve screening outcomes.[16] Although digital tools are appealing, an estimated 19% of Americans – including 34% of those with less than a high school degree – do not own a smartphone.[17,18] Thus, digital approaches alone are unlikely to reach a significant group of those eligible for CRC screening, and may miss those with greatest need for testing.

Navigation efforts targeting patients who would otherwise undergo screening anyway is a poor use of resources. A key targeted population for interventions should be those who fail to complete prior screening efforts. When less-invasive methods such as fecal immunochemical testing (FIT), multi-target stool DNA (MT-sDNA), colon capsule endoscopy (CCE), and computed tomographic colonography (CTC) are positive, follow-through to colonoscopy completion is the rate-limiting step for enhancing screening effectiveness. In a review of electronic medical records (EMRs) of 1,267 low socio-economic status patients aged 50-64 years with positive FIT results, 42% failed to undergo follow-up colonoscopy within one year.[19] In a Kaiser Permanente study of patients with a positive FIT, if colonoscopy was delayed >6 months, there was a higher risk of any CRC and advanced-stage disease.[20]

### 3.1.2 Strategy 6: Enable EMR integration to permit providers working in different settings to accurately estimate a mutual patient's risk based on all pertinent data.

We envision a future where the EMR is integrated across health systems and information needed for risk assessment is readily available. Development of a systemic methodology to verify a patient's individual and familial neoplasia burden will not only enable monitoring of compliance with guideline-recommended screening intervals; it will also allow for high-quality assessment of additional predictive variables in risk prognostication. This will need to be done without violating patient privacy.

### 3.2.3 Strategy 7: Integrate CRC risk assessment approaches incorporating lifestyle/anthropometric, environmental, and polygenic risk factors.

The modest ability of current models to predict risk of advanced neoplasia (AN) underscores the need for alternative approaches. In one colonoscopy cohort study a greater than 30-pack-year history of smoking yielded an odds ratio (OR) of 3.39 (95% CI, 2.47-4.66) for the presence of advanced adenoma; this was significantly greater than the OR for having a first-degree relative with CRC: 1.37 (95% CI, 0.94-2.00).[21] Multiple anthropometric measures have been associated with CRC risk including BMI and hip-to-waist ratio.[21,22]

Jeon and colleagues created a potential prototype of a model that incorporates genetic and environmental factors. The combined genetic risk score (based on 63 CRC-associated single-nucleotide polymorphisms [SNPs]) and environmental risk score (based on 19 lifestyle and environmental factors) had an area under the receiver operating characteristic (ROC) curve value

for estimating CRC risk of 0.63 (95% CI, 0.62–0.64) for men and 0.62 (95% CI, 0.61-0.63) for women. The study shows polygenic risk score in combination with environmental risk factors and family history offer promise for improved risk stratification. Similar approaches incorporating algorithmic risk assessment should be actively investigated.

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