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Screening for Colorectal Cancer in African Americans: Determinants and Rationale for an Earlier Age to Commence Screening

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Abstract

Colorectal cancer (CRC) screening is a highly cost-effective approach to reduce morbidity and mortality of patients, as well as reduce the prevalence of CRC in populations. Current recommendations for CRC screening for the asymptomatic general population begin at age 50 years, an age after which ~95% of cancers occur. Determinants that modify the timing and frequency for screening include a personal or family history of adenomatous polyps or CRC, the age of onset of these colonic lesions, and the presence or potential for a patient to harbor a higher-risk syndrome such as inflammatory bowel disease (IBD), familial adenomatous polyposis (FAP), or Lynch syndrome.. Although race, like family history, is a heritable factor, it has not engendered inclusion in the same broad systematic screening recommendations despite multiple studies demonstrating a disparity in the incidence and mortality from CRC, and the potential for targeted screening to reduce the disparity. In particular, African Americans, when compared to Caucasians, (a) have lower CRC screening utilization rates, (b) have an earlier presentation of CRC (0-8 years younger than Caucasians) and, more often have aggressive biological features more prone to metastasis, (c) have a higher CRC prevalence at all ages and a higher proportion of CRCs before 50 years of age (~11% vs 5% in Caucasians), (d) are less likely to know or transmit personal or family history of adenomas or CRC that might change their screening to an earlier age, (e) present with 7-15% excess right-sided CRCs that are not microsatellite unstable, (f) show higher frequencies of high-risk adenomas at every decile of age, and an excess of high-risk proximal adenomas that mirror the excess of proximal CRCs, (g) have cancers that demonstrate lower proportions of good prognostic biomarkers such as MSI and higher proportions of bad prognosticators such as EMAS, (h) may possess gut microbiota more conducive to initiating and/or propagating colonic neoplasia, and (i) may demonstrate worse outcomes with treatment for CRC. These epidemiological, biological, and genetic parameters put African Americans at higher risk from CRC irrespective of any socioeconomic issues, much like IBD, FAP, and Lynch syndrome patients. Including race as a factor to consider in national CRC screening guidelines, such as commencing screening at an earlier age than 50 years, seems rational based on the natural history and more aggressive behavior in this population.

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Introduction

Screening for colorectal cancer (CRC) is a cost-effective strategy to reduce the CRC prevalence in the general population [1,2]. Screening may find CRC precursors, such as adenomas, prior to malignant transformation, and locate colorectal cancers at an earlier stage compared to patients who have not undergone screening [3-6]. An abnormal finding at screening, such as the presence of occult blood or human hemoglobin, or visualizing a polyp or mass, should ultimately trigger a colonoscopic evaluation for polyp removal or biopsy of any found mass. Because colorectal carcinomas generally begin as adenoma precursors, removal of adenomas should reduce the overall incidence of colorectal cancer in the general population, and there is evidence that this is occurring [7,8]. Screening for colorectal cancer, which can consist of guaiac-based fecal occult blood testing, fecal immunochemical testing, fecal DNA tests, flexible sigmoidoscopy, CT colonography, barium enema, and/or colonoscopy, saves lives from colorectal cancer death, and the effect is durable in those who are screened [3,7,8]. No other human cancer put forth for a screening strategy has so many approaches to detect the cancer. The incidence (136,830 for 2014) and mortality (50,310 for 2014) of colorectal cancer in the U.S. population [5], along with its near equal lifetime risk between genders, make this cancer a prime target for screening strategies to reduce its incidence and mortality.

Epidemiological studies point to several factors that put a person at risk for colorectal cancer. Environmental factors are estimated to account for about 65% of the CRC risk with heritable factors contributing about 35% of the risk [9]. Environmental factors that contribute to the risk include those that indirectly or directly influence the colon epithelium, such as the effects of a high fat or red meat or high caloric diet, excess BMI, low fiber diet, the use of tobacco products, low serum selenium, low use or low serum levels of calcium or vitamin D, low use of fish oils [10-17], as well as the microbiome and its metabolites [15-17]. Environmental factors may have varying degrees of effect among populations, and are potentially modifiable (**Table 1**).

Heritable factors are largely related to a patient's family history of cancer, the age of onset of cancers in the family, and the race/ethnicity of the family. Patients with a strong family history are removed from the average screening pool and are placed in a more focused surveillance pool to assess potential adenomas and/or cancers at earlier and more frequent intervals [18]. Patients may be assessed for heritable cancer syndromes through genetic counseling and testing if appropriate.

Age itself is a powerful predictor of the development of adenomas and colorectal cancer, with 25% of the U.S. population possessing at least one, any-sized adenoma by age 50 [19], with a prevalence of ~5% for polyps >9mm [20], and the near exponential rise of subsequent colorectal cancer in the population around age 50, with ~94.5% of all colorectal cancers

occurring after this age [19]. Based largely on this age relationship for CRC, screening is recommended to commence by age 50 years in asymptomatic persons [18].

Race as a heritable factor has not been included in the screening recommendations in the same way as family history or age, despite multiple studies demonstrating a disparity in the incidence and mortality from colorectal cancer among African American patients in particular [5,21-28]. As shown in **Table 2**, African Americans demonstrate the highest male and female CRC incidence and mortality among all racial groups in the United States. When compared to Caucasians, African American colorectal cancer patients present with less localized and regional disease, but more distant metastasis [22,28]. African American colorectal cancer patients demonstrate lower survival at all stages of disease [22,28].

Despite overall trends over the past 2 decades showing a reduction in mortality from colorectal cancer for both African American males and females, the reduction has been more substantial among Caucasians, leaving a large disparity for colorectal cancer death [22,28,29]. There are a number of potential contributing factors that might generate this disparity for African Americans, including: (a) a lower socio-economic status, level of insurance coverage, and level of education, (b) less access to medical care, and in particular prevention approaches, (c) lower utilization of screening modalities for colorectal cancer, as well as less common use of an appropriate modality with evidence of more proximal polyps and cancers in African Americans, (d) a diet that may be more conducive to colorectal cancer development, (e) higher rates of obesity and reduced physical activity, (f) higher rates of tobacco use, (g) lower use of hormone replacement therapy and/or NSAIDs that are associated with reduced rates for colorectal cancer, (h) generational mistrust of the U.S. health system, and (i) differences in the biology of the cancer and/or metastasis [21,28-32]. Perhaps except for the issues of colonic site and biology which suggests genetics might be part of the racial disparity (and might be influenced or driven by environmental factors), most of the issues inferred to explain the higher mortality among African Americans are social, environmental, or behavior factors which in theory, are correctable. The racial disparity regarding colorectal cancer has been reported for decades [5,21-29], suggesting that either the relevant social, environmental and behavior factors are difficult to change (personally or societally) if they are the major cause of the disparity, and/or that other factors such as genetics might be playing a substantial role [33]. Additionally, other racial groups, such as Hispanics, have similar issues with social, environmental and behavior factors, yet their rates for colorectal cancer incidence and mortality are lower than non-Hispanic Caucasians and African Americans, meaning other issues must be at play for the observed disparities [5,29].

Screening Utilization Differences That May Contribute Towards the Disparity

Since there is evidence that screening for colorectal cancer can reduce morbidity and mortality and that the impact is durable, screening utilization is an important determinant of outcome in groups. Screening for colorectal cancer in African Americans lags behind Caucasians irrespective of whether endoscopy or fecal occult blood testing was the screening approach [28]. While overall screening rates have improved over the past 1-2

decades [4,23,28,29], a disparity for utilization still exists [21,22,28,34,35]. Furthermore, many of the screening tests used to detect colorectal cancer require a definitive colonoscopy for follow-up, biopsy, or removal of potential lesions [3,7]. Data from the PLCO Cancer Screening Trial indicates that African Americans were less likely to have follow-up colonoscopy within 1 year of an abnormal flexible sigmoidoscopy examination compared to Caucasians despite no detected difference in the prevalence of lesions of those screened, suggesting health care utilization could be a factor for disparity [36]. Interestingly, this disparity in follow-up is seen even in non-screening situations, such as in the evaluation of rectal bleeding [37].

A number of perceived and real barriers to utilization have been identified, ranging from fear of diagnosis and fatalism, scheduling issues, to the lack of provider recommendation for the screening test [21,29-32,38,39]. One successful approach to mitigate colonoscopy utilization disparity is to use professional or community-based peer navigators to help patients overcome barriers to completing a colonoscopy [39-43]. Navigator programs have substantially improved colonoscopy completion rates but it is too early to determine if this approach will change mortality rates. Colorectal cancer mortality did not differ between African Americans and Caucasians in an equal access military health system for those over the age of 50 years; however, in patients under age 50 years, African Americans still experienced a significant worse overall survival compared to Caucasians [44], suggesting that biological factors might be contributing. In one study, it was estimated that differences in screening accounted for 42% of the disparity in colorectal cancer incidence between African Americans and Caucasians, and 19% of the disparity in colorectal cancer death [45]. With utilization of screening colonoscopy, if an adequate initial examination shows no polyps, there is a small risk of finding an advanced polyp at 10 year surveillance, indicating that the first (and earliest) colonoscopic examination is pivotal for all patients [46]. A societal goal should be to have a high utilization of colorectal cancer screening across all groups to overcome this usage barrier, since there is evidence for it being cost effective, acceptable, possessing relatively high sensitivity and specificity, and reduces mortality [35,41].

Epidemiology of African American CRC Patients That May Contribute Towards the Disparity

Age

Multiple studies including SEER data point to an earlier age onset for colorectal cancer in African Americans [23,44,47-50], ranging from 0 to as much as 5-8 years younger than the mean age for Caucasians [21,34,48]. The younger age at presentation, coupled with the apparently more aggressive nature of African American colorectal cancers, has a number of implications. First, there is less time from age 50 years to the average age of colorectal cancer in this population, shortening the potential window period for screening and intervention. Second, younger age onset may have implications for other family members and their risk, and the approach to their screening. Third, younger colorectal cancer patients have a higher likelihood for possessing a genetic cancer syndrome [10,18,21,51,52], which would shift the patient from screening to intense surveillance. Fourth, since most colorectal

cancers begin as adenoma precursors, this would imply that adenomas may be initiated earlier than Caucasians, although the mechanism for earlier neoplastic initiation has not been defined.

Importantly, the proportion of cancers under the age of 50 years is a number to consider since such patients would present with colorectal cancer before typical screening is commenced. For Caucasians, ~5.5% of all colorectal cancers occur prior to the age of 50 years whereas for African Americans, ~10.6% of colorectal cancers occurring prior to this age [1,19]. If screening started at age 45 years for African Americans, then ~95% of colorectal cancers would occur after that screening age, mirroring that observed for Caucasians screened on or after age 50 years (**Table 3**) [1,53]. Furthermore, some of the increased younger prevalence in African Americans extends to under the age of 40 years in one population-based study, with later detection of these cancers compared to Caucasians for this age group [54].

Family History

At present, application of knowledge of patient family history for polyps and/or cancer is a key determinant in the screening guidelines for colorectal cancer. Screening is recommended to start at age 40 years or earlier of a patient with a significant family history in first- or second-degree relatives (10 years earlier than for those without a family history, or 10 years earlier than the youngest person with colorectal cancer in the family, whichever is earlier). Initiating screening at even earlier ages is recommended if the family history is striking or suspicious for a potential familial cancer syndrome [18].

About 1/3rd of all patients with colorectal cancer will have a family history for this cancer [3,5,51,52], which changes the approach towards their screening as it puts them at higher risk for developing colorectal cancer [18]. Family history is typically obtained from the patient, with the healthcare provider utilizing that information to inform the screening approach. In general, patients with a family history of CRC are more likely than those without to undergo CRC screening, but this varies by race. African Americans and Hispanics with a family history of CRC had the lowest likelihood of participation in screening [55]. To compound this issue, patients from African American backgrounds are less likely than Caucasians to know their paternal history of cancer [56], and family members screened are less likely to tell their relatives about a finding of colon polyps [57]. Thus, lack of information, or lack of knowledge and/or transmittal of information from the patient, may falsely put a patient in the sporadic colorectal cancer screening category, rather than the category of having a positive family history.

Anatomical Site of Colorectal Cancers Within the Colon

The intracolonic location of cancers has implications for the approach to screening in a population. Tests like fecal immunochemical tests or colonoscopy can identify potential cancers located anywhere in the colon, whereas imaging via flexible sigmoidoscopy is limited to the distal 60 cm of the colon [18]. Furthermore, proximal cancers may have a different genetic make-up (such as CpG island methylator phenotype (CIMP), microsatellite instability (MSI)) and possess different biological behavior (such as rapid growth, flat

superficial spreading morphology, serrated pattern, etc.), and grow to larger sizes without obstruction in the presence of liquid instead of solid stool; features that may delay detection and portend a poor prognosis [10,11,58,59]. The one exception is the presence of MSI, which predicts a more favorable outcome compared to patients whose tumors lack MSI [10,48,51,58,60]. It has been commented that the colon is “one lumen but two organs” due to right-left differences in embryonic origin, colon physiologic function, gene expression, morphology and genetics of polyps and cancer, and the approach to chemo- or radiation therapy [11].

African American patients with colorectal cancer have a 7-15% higher proximal distribution frequency than Caucasians in most studies (e.g. in one study, 62.5% vs. 52.9% were proximal, respectively) [4,14,23,24,48,60-63]. Even in population-based studies in which MSI cancers, which are predominantly right-sided, are removed from analysis, there remains ~10% increase for right-sided microsatellite stable (MSS) colorectal cancers in African American patients over Caucasians [48,62]. The right-sided predominant nature of cancers seem consistent in multiple studies and in the SEER data, as does the poor survival of African Americans who have a higher prevalence of these proximal cancers [4,14,23,24,48,61-63].

For African Americans, the increased prevalence of proximal cancers implies the need to perform colonoscopy rather than flexible sigmoidoscopy as the preferred endoscopic screening modality but colonoscopy is not equally effective in proximal and distal CRCs.. In the National Polyp Study, death from colorectal cancer in colonoscopic-screened individuals was estimated to be reduced by 53% overall [8]. However, there appears to be differences between the reduction in death from proximal cancers compared to distal cancers, with a 67-84% reduction in mortality for left-sided cancers, but only a 1-56% reduction in mortality for right sided cancers [64-66]. Thus, even with fully-utilized colonoscopic screening, there could be an excess of right-sided colorectal cancer deaths when compared to left-sided colorectal cancers, amplifying the magnitude of a disparity in groups with excess proximal cancers. Mortality reduction with colonoscopy is durable. In the long term follow-up (22 years) of the Nurses' Health Study and the Health Professionals Follow-up Study, patients who had had sigmoidoscopy or colonoscopy had a 41% or 68% reduction in CRC mortality, respectively [66]. Sigmoidoscopy offered no protection from mortality in the right colon, whereas patients post colonoscopy showed a 53% reduction in death from proximal cancers [66]. Despite the substantial right-left differences in mortality reduction with colonoscopy, it remains the best test to detect, visualize, and remove proximal pre-malignant lesions.

Frequency and Anatomical Site of Colorectal Adenomatous Polyps Within the Colon

Adenomatous polyps are the main precursors to colorectal cancer (Sessile Serrated Adenomas/Polyps will be discussed separately below). Thus, the pattern of adenomatous polyps in the colon, in particular those adenomas with advanced pathology (>9mm in diameter, or with villous histology or high grade dysplasia) should mirror the higher rates for cancer and the anatomical subsites for colorectal cancer observed in racial groups. Indeed, for most studies, this appears to be the case. Significant factors associated with

polyps >9mm among 141,413 patients who underwent colonoscopy in the Clinical Outcomes Research Initiative (CORI) data repository included increasing age, male gender, and African American race [6]. In a separate prospective study of CORI data for patients undergoing screening colonoscopy, African Americans demonstrated 7.7% polyps >9mm, while Caucasians showed 6.2% polyps >9mm [67]. Another study of 327,785 average-risk patients demonstrated that for men younger than 50 years of age, the presence of polyps >9mm were similar in African Americans and Caucasians, but differences became significant with age, with higher prevalence in African Americans age 50-54 years (7.1% vs 6.2%), age 55-59 years (8.5% vs. 7.4%), age 60-64 years (11.5% vs. 8.6%), and age 65-69 years (12.0% vs. 9.7%) [20]. Proximal polyps also appear to be more prevalent in African Americans than Caucasians, with an odds ratio of 1.15 (95%CI 1.03-1.29) using CORI data and 1.26 (95%CI 1.04-1.54) using Kaiser Permanente data [20,68] and differences are age dependent. The risk for proximal polyps are similar between races below age 60 years, but became significantly associated with African Americans older than 60 years of age [20,67,68]. While the aforementioned polyp studies used large datasets for analysis, three other small, single-site studies contrast those findings with no evidence for an association between any-sized polyp or polyps >9mm and African Americans, with one of the studies showing a higher correlation of frequency of advanced neoplasia in Caucasians over African Americans [63,69,70]. This last study did demonstrate a higher percentage of proximal advanced neoplasia in African Americans [63]. With acknowledgment of inadequate statistical power for subgroup analysis in these smaller studies [63], the published evidence suggests a higher frequency for polyps >9mm and a higher frequency of proximal polyps in African American than in Caucasian patients, correlating with the observations made for colorectal cancer.

Biological and Genetic Findings of African American CRC Patients that may contribute to the disparity

Polyp and cancer histopathogenetic characteristics

In addition to adenomas of advanced pathology, high risk polyps for cancer include sessile serrated adenomas (SSAs) [11,59]. SSAs may be the precursor to laterally-spreading or “flat” spreading neoplasms commonly found in the right colon. There are often flesh-colored, blending in with the normal colonic wall, making them very difficult to detect without enhanced endoscopic detection methods [11,59]. These lesions are much more likely to contain cancer than their polypoid counterparts [11,59], are proximally prevalent, and linked epigenetically to the CpG island methylator phenotype (CIMP) pathway and the hypermethylation of the DNA mismatch repair gene *hMLH1* which in turn results in microsatellite instability [11,59]. In addition, these tumors often lack *KRAS* mutations but contain *BRAF* mutations [11,59].

As described previously, there is evidence that the frequency of advanced polyps is elevated, and there are more proximal polyps in African Americans compared to Caucasians [6,20,67,68]. Given the proximal nature of SSAs and their more aggressive biology, it is tempting to link these lesions as a cause for colorectal cancer disparity for African Americans as they match some of the biological behavior observations for this group.

However, there is scarce data available to test this hypothesis. The notion of aggressive biological features such as high grade tumors have been associated with African American patients in prior studies [71]. Lifestyle factors such as aspirin use and folate supplementation reduce and increase, respectively, the risk for right-sided serrated polyps [72], and use of these compounds might influence their incidence. Among one of the few studies to address this issue reported the colonoscopic findings of 1172 Caucasians and 1681 African American patients, dysplastic serrated lesions were identified in 2 (0.2%) of Caucasians and 5 (0.3%) of African Americans ($P=0.71$) [63].

Examination of cancers for *KRAS* and *BRAF* mutations did not demonstrate a difference between African American and Caucasian patients in two studies [62,73], although one study indicated a higher proportion of *KRAS* mutations among microsatellite stable African American CRCs compared to Caucasian cancers (34% vs. 23%, $P=0.048$) [73].

Microsatellite Instability and right-sided cancers

Microsatellite instability (MSI) is a biological marker for defective DNA mismatch repair that has substantial biologic importance and is found in ~15% of sporadic colorectal cancers [10,58]. Its presence within the colorectal cancer depicts a more favorable outcome for patients, presumably due to an MSI-induced, neoantigen-driven attraction of intraepithelial CD8⁺ T lymphocytes. These immune cells infiltrate the cancer and surround it to form a “Crohn’s-like” lymphoid granuloma reaction which is thought to limit the tumor’s ability to spread, [10,52,58]. More than 70% of MSI cancers are located in the right colon, and the normal-adenoma-carcinoma sequence is greatly shortened in time compared to non-MSI tumors [10,52,58]. Additionally, patients with stage II/III MSI colorectal cancers have a muted response to 5-fluorouracil-based chemotherapy [74,75].

Evidence presented above indicates that African Americans have a higher prevalence of right-sided polyps and cancers, with more aggressive behavior and poor prognosis, two contradicting aspects associated with MSI tumors. Non-population based studies suggested no difference [73] to higher frequency of MSI among African American patients [76,77]. However, a population-based study with blinded analysis indicates that MSI is present in 14% of Caucasian tumors, and in only 7% of African American tumors [48], meaning that this good prognosticator is half as common in African Americans and may limit a benefit from improved survival in this population.

When MSI tumors, which are right-sided predominant, are taken out of the picture, a striking feature is that African American patients continue to show a higher rate of proximal microsatellite stable (MSS) CRCs, compared with Caucasians [48,62]. These MSS tumors may contribute to some of the excess death in African American patients compared to Caucasian patients [24].

Elevated Microsatellite Alterations at Selected Tetranucleotide Repeats

Elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) is another biomarker that appears to be driven by an acquired, somatic loss of function of the DNA mismatch repair protein *hMSH3* [49,78,79]. EMAST is more common than classic MSI,

observed in up to 60% of sporadic colon and 33% of sporadic rectal cancers [49,78,79]. Unlike MSI CRCs, which are associated with improved survival EMAST is associated with poor outcome and an increased rate of metastasis [49,80].

Among a population cohort of 147 patients with rectal cancers, overall 33% of cancers demonstrated EMAST; however, 49% of CRCs in African American showed EMAST compared to 26% of the CRCs in Caucasian ($P=0.014$) [49]. In this study, EMAST was also associated with advanced colorectal cancer stage and peri-tumor inflammation [49]. Thus, rectal cancers from African Americans demonstrated twice the rate of the poor prognosticator EMAST in one study, and half the rate of the good prognosticator MSI in another population-based study. These findings indicate biological factors may be important for outcome disparities in African Americans, and this information should influence the approach towards screening in this population.

Microbiome

There is growing evidence that the gut microbial community is influenced by the substrates available to it via ingestion, and in turn the microbiome can produce metabolites and other substances that modify individual cell and whole body metabolism [81]. Short chain fatty acids, for instance, are made by gut microbes and are necessary energy substrates to maintain healthy colonocytes [82]. Human-to-mouse microbiota transplant experiments show that obesity and kwashiorkor are transmittable through the microbiome [83,84], and it is well established that obesity is a risk factor for CRC [85]. Gut dysbiosis locally or broadly may also influence inflammatory pathways in the colon, which has secondary effects on DNA damage through reactive oxygen species generation and cytokine release. These, in turn, can lead to increased toll-like receptor signaling, as well as allowing increased oncogene expression and the silencing of tumor suppressor genes through methylation [86,87]. All of these effects favor proliferation and transformation of colonocyte stem cells into neoplastic lesions. Thus, there is substantial reason to examine differences in the colonic microbiota as a risk factor for CRC.

Exploration of the gut microbiome by race and colorectal cancer risk is scant. In one study comparing native Africans, African Americans, and Caucasians regarding dietary effects on the fecal microbiota, native Africans (who have a low risk for colorectal cancer and are on a staple diet of maize meal) produced more short chain fatty acids than both African Americans and Caucasians (who consume a Westernized diet high in animal protein and fat); Caucasians showed higher calcium and iron contents and African Americans showed higher zinc contents, but there was no difference in nitrogen content among the three groups [17]. Another study of native Africans compared to African Americans additionally showed that the microbiota from African Americans possessed genes encoding secondary bile acid production, with higher fecal concentrations of secondary bile acids that might be more carcinogenic [15,88]. These dietary and microbiota metabolite differences might contribute to changes in colonocyte proliferation [88] but much more research needs to be done in this arena before we will know if they are truly related to CRC risk, much less whether they account for any of the racial disparities in CRC risks and outcomes.

Adjuvant Treatment

Treatment responses vary by race. Patients who are treated for stage II/III colorectal cancer beyond surgery with adjuvant chemotherapy do not have a uniformly high success rate in lengthening survival [51]. For instance, African Americans did not show the same benefit in 5-year survival with adjuvant chemotherapy for stage III colorectal cancer as Caucasians [89,90]. African Americans have poorer recurrence-free survival rates but similar recurrence-free intervals reflecting that the survival difference is unlikely related to the actual effect of the treatment [89,90]. Other studies suggest that if everything was equal between races – equal proportions of patients from each race who undergo surgery, receiving chemotherapy, receiving radiation therapy, as well as enrollment in treatment studies – that there would be no difference in overall survival between African Americans and Caucasians [91,92]. It is not clear if overcoming socioeconomic issues and providing equal access can fully override observed biological factors that might make a colorectal cancer behave more aggressively in a population and equalize the likelihood to respond to and improve survival with standard approaches to treatment.

Is there a Rationale for a change in screening recommendations for African Americans?

In addition to socioeconomic determinants, the above evidence and discussion suggests that there are epidemiological, biological, and possibly genetic factors that contribute to the disparity in colorectal cancer between African Americans and Caucasians (**Table 4**). Disparities in screening utilization still exists, and perhaps increased utilization among all racial groups can close the disparity and reduce the prevalence of colorectal cancer. However, this sole approach without a change in age to commence screening still leaves a relatively high proportion of African Americans developing cancers under the age of 50 years before screening would start [1], and shortens the time for screening to actual cancer since African Americans develop colorectal cancer at earlier ages. The knowledge and transmittal of family history for colorectal polyps and cancer, a key determinant for changing the approach and age for screening, is also much less likely among African Americans [52,55]. Race is a heritable factor that cannot be modified, and like age and family history, which are currently included in screening guidelines has a substantial impact on CRC risk.

Screening approaches generally reflect the the biology and natural history that places groups of patients or individuals at high risk. As above, younger age of onset and/or family history in first and second degree relatives change the timing for screening [18]. Specific high risk conditions are addressed in the guidelines due to the biology of those conditions. For instance, those with increased numbers of adenomas or those who have had colorectal cancer are advised to have more frequent intervals for screening [18]. Individual patients with inflammatory bowel disease are screened for colorectal cancer based on the length of time of colitis, and are screened at frequent intervals [18]. Patients and family members with diagnosis or are at risk for familial adenomatous polyposis or Lynch syndrome are advised to start screening earlier and at more frequent intervals due to the biology of these conditions [18,93]. If a condition suggested: (a) an early age of onset, (b) higher morbidity and

mortality at that younger age, (c) higher prevalence of proximal polyps that is mirrored by a higher prevalence of proximal cancers, leading to higher mortality, and in addition, (d) having potential evidence that biology, such as lower rates of MSI and higher rates of EMMAP contributing to higher mortality, then most reasonable practitioners would seriously consider screening such a group more aggressively. Indeed, the biology and epidemiology of that reported to date for African Americans suggest that their polyps and cancers develop earlier and/or at a more rapid pace than Caucasians. This provides the rationale to consider a change in the current screening guidelines, which do not currently address this higher risk group [18]. Stratification by age and family history is incorporated in colorectal cancer screening guidelines [18] and the evidence warrants inclusion of stratification by race as well.

Screening approaches should address an at-risk group, be sensitive, specific, reduce mortality, and be cost-effective. Screening for colorectal cancer is the most cost-effective for African Americans compared to any other racial group due to the earlier age for presentation, regardless of whether screening was through a combined sigmoidoscopy and fecal occult blood test approach, or a colonoscopic approach [1,53].

This author believes that there is plenty of rationale presented in this article to recommend starting screening of African Americans for CRC earlier than age 50. This recommendation is based on the belief that targeting this population, with the evidence as presented, would lower the mortality and find lesions at an earlier stage of development much like targeted screening among IBD, FAP, and Lynch syndrome patients. Concurrent with this recommendation is overall increased utilization of screening for this population, and all patients at average risk. Much like IBD, FAP, and Lynch syndrome, recognition of the African American population for targeted earlier screening would have the secondary benefit of calling this group to attention among providers and patients, and likely raise overall screening rates. Even without several points of data presented here, several national organizations have published recommendations to screen African Americans at an earlier age. The American College of Gastroenterology (ACG) recommends screening African Americans beginning at age 45 years via colonoscopy [34,94]. This recommendation would equate the proportion of colorectal cancers under age 45 years in African Americans with the proportion of colorectal cancers under age 50 years for Caucasians. In addition, the ACG recommends developing educational programs for gastroenterologists and endoscopists for awareness of the different cancer behavior in African Americans, and to include culturally-sensitive health education programs for minority groups [34,94]. The American College of Physicians (ACP) recommends that clinicians perform individualized risk assessment for colorectal cancer in all adults, and places African Americans in a high risk pool for which screening begins at age 40 years, or 10 years younger than the youngest affected relative [95]. This recommendation is similar to the current guidelines for patients with a family history of either colorectal cancer or adenoma in a first-degree relative or in two second-degree relatives [18]. The Institute for Clinical Systems Improvement (ICSI), much like the ACG, recommends colorectal cancer screening to commence at age 45 years in African Americans, [95]. Groups that have not recommended a change for African Americans, to date, include the U.S. Multisociety Task Force on Colorectal Cancer (whose recommended guidelines are generally followed by gastroenterologists), the American Cancer Society, and

the United States Preventive Services Task Force (**Table 5**) [18,28,96]. With realization that African Americans possess epidemiological and biological factors that places them above average risk for colorectal cancer, these other groups in addition to the three that have changed guidelines may recommend a change in their national guidelines.

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Abbreviations

PLCO	Prostate, Lung, Colorectal and Ovarian cancer screening trial
CRC	colorectal cancer
SEER	Surveillance, Epidemiology and End Results program
MSI	microsatellite instability
MSS	microsatellite stable
CORI	Clinical Outcomes Research Initiative
ACG	American College of Gastroenterology
ACP	American College of Physicians
ICSI	Institute for Clinical Systems Improvement
USPSTF	United States Preventive Services Task Force
ACS	American Cancer Society
EMAST	elevated microsatellite alterations at selected tetranucleotide repeats
SSA	sessile serrated adenoma
CI	confidence interval
NSAID	non-steroidal anti-inflammatory drug
CT	computed tomography
HRT	hormone replacement therapy

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Table 1

Modifiable and non-modifiable patient risk factors associated with the development of colorectal cancer.
NSAID, non-steroidal anti-inflammatory drug; HRT, hormone replacement therapy

Non-modifiable patient risk factors	Potentially modifiable patient risk factors
Age	Diet, diet supplements, nutrition, microbiome
Family history	Socioeconomic factors, insurance, safety-nets
Race	Screening utilization rates
	Health care access
	Education level
	Physical activity
	Tobacco usage
	NSAID and HRT usage

Table 2

Incidence and death rates for colon and rectal cancers (combined) by race and ethnicity, 2006 to 2010. Rates are per 100,000 and age-adjusted to the 2000 U.S. standard population. Adapted from references [5,22].

	All	Caucasian	African American	Asian/ PI	American Indian	Hispanic/Latino
Incidence						
Male	51.7	50.9	62.5	40.8	51.7	47.3
Female	39.1	38.6	46.7	31.0	42.7	32.6
Deaths						
Male	19.6	19.2	28.7	13.1	18.7	16.1
Female	13.9	13.6	19.0	9.7	15.4	10.2

Table 3

Proportions of colorectal cancer in populations based on age cutoffs. Adapted from references [1,53].

	Proportion of Cancers under target age for group	Proportion of Cancers over target age for group
Caucasians (age 50 years)	5.5%	94.5%
African Americans (age 50 years)	10.6%	89.4%
African Americans (age 45 years)	5%	95%

Table 4

Relative differences in epidemiology, biology, and outcome for colorectal cancer between African Americans and Caucasians. MSI, microsatellite instability; EMAST, elevated microsatellite alterations at selected tetranucleotide repeats

Distinguishing Characteristics of Colorectal Cancer in African Americans
Higher morbidity
Higher mortality
Younger age of onset
Higher proportion of cancer under age 50 years
Less knowledge of Family History
Increased right-sided location of cancers (non-MSI)
Increased right-sided location of polyps
Reduced MSI in colon cancers
Elevated EMAST in rectal cancers
Poorer response to standard treatment for stage III cancer

Table 5

Professional groups and their recommendations for age of commencement for colorectal cancer screening among African Americans. ACG, American college of Gastroenterology; ACP, American College of Physicians; ICSI, Institute for Clinical Systems Improvement; ACS, American Cancer Society; USPSTF, United States Preventative Services Task Force

Society	Age for Screening	Reference
ACG	45 years	34
ACP	40 years	95
ICSI	45 years	95
U.S. Multisociety Task Force	50 years (standard)	18
ACS	50 years (standard)	28
USPSTF	50 years (standard)	96