Colorectal Cancer Screening: mainstay of prevention

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ABSTRACT

Screening for colorectal cancer clearly reduces colorectal cancer mortality. Effective, safe, and relatively inexpensive methods for screening for the disease have been available for decades. Screening is recommended by a number of professional organizations, including the Multidisciplinary Expert Panel, the US Preventive Services Task Force and the American Cancer Society. However, no consensus has been reached on which screening modality to use. This article aims to critically assess the evidence for use of available colorectal cancer screening tests, including fecal occult blood tests, sigmoidoscopy, colonoscopy, double-contrast barium enema, and newer tests such as virtual colonoscopy and stool-based molecular screening.

INTRODUCTION

Epidemiology

Colorectal cancer (CRC) is the third most common cancer in both men and women and the second most frequent cause of death from cancer worldwide.[1] CRC is more common in developed countries with a lifetime incidence of 5%. 90% of cases occur after the age of 50.[1] Over the last 20 years, the mortality from colorectal cancer has been steadily decreasing (Figure 1). In Ireland, approximately 1488 men (15.3% of total cancer incidence in males) and 1232 women (12.8% of total cancer incidence in women) are diagnosed with CRC annually. The average mortality rate in Ireland from CRC is 840 deaths in men (14.4% of cancer deaths in males) and 716 deaths in females (13.7% of cancer deaths in females).[2]

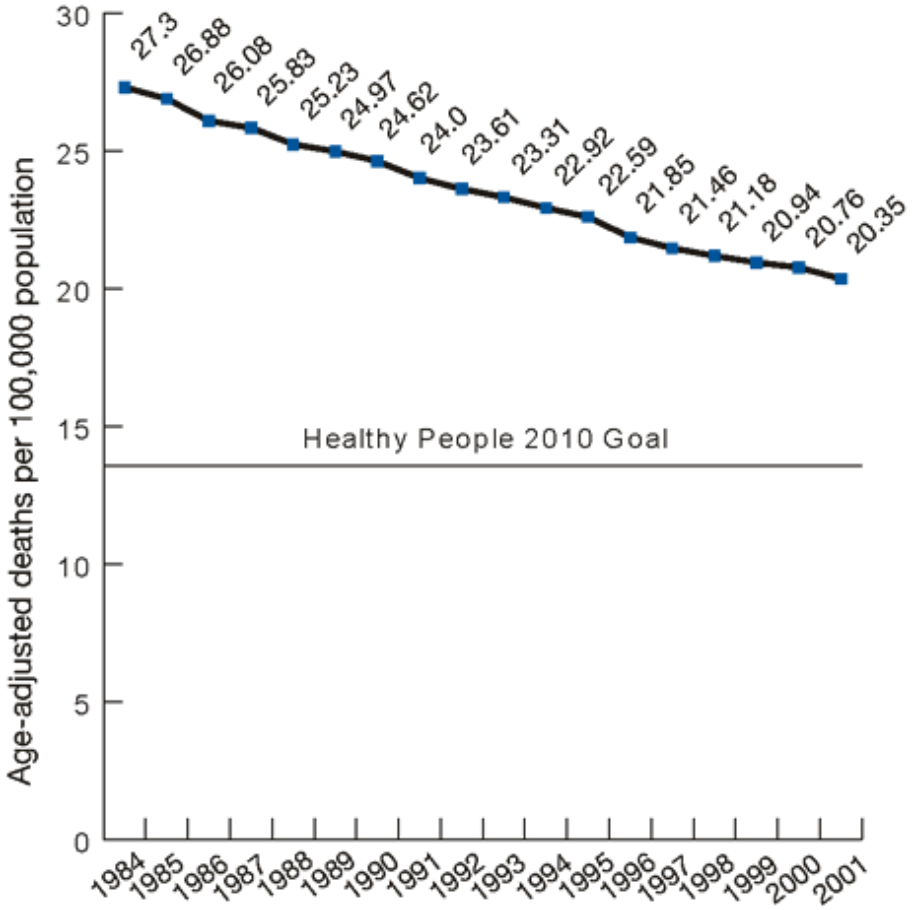

Figure 1: Mortality from colorectal cancer (Centers for Disease Control and Prevention National Center for Health Statistics data National Vital Statistics System-Mortality, analyzed by National Cancer Institute)

Pathology of colorectal cancer

Most CRCs result from malignant changes in polyps (adenomas) which develop in the lining of the bowel 10-15 years earlier.[3] A schematic of the morphologic and molecular changes in the adenoma-carcinoma sequence is shown in Figure 2. Individuals may be born with one mutant allele of the tumour suppressor gene *APC* or one normal copy is lost early in the sequence. This is the "first hit" according to Knudson's hypothesis. The loss of the remaining normal copy of *APC* follows ("second hit"). Mutations of the oncogene *k-ras* occur next and additional mutations inactivate the tumour suppressor genes *DCC* and *p53*, leading to the emergence of carcinoma. Although there seems to be a temporal sequence of changes as shown, the accumulation of mutations, rather than their occurrence in a specific order, is more important. A second pathway is characterised by genetic defects in DNA mismatch repair genes: *MSH2, MSH6, MLH1, PMS1* and *PMS2* giving rise to Hereditary Non Polyposis Colorectal Cancer (HNPCC). There is

accumulation of mutations but unlike the adenoma-carcinoma sequence, there are no clearly identifiable morphologic correlations.[4]

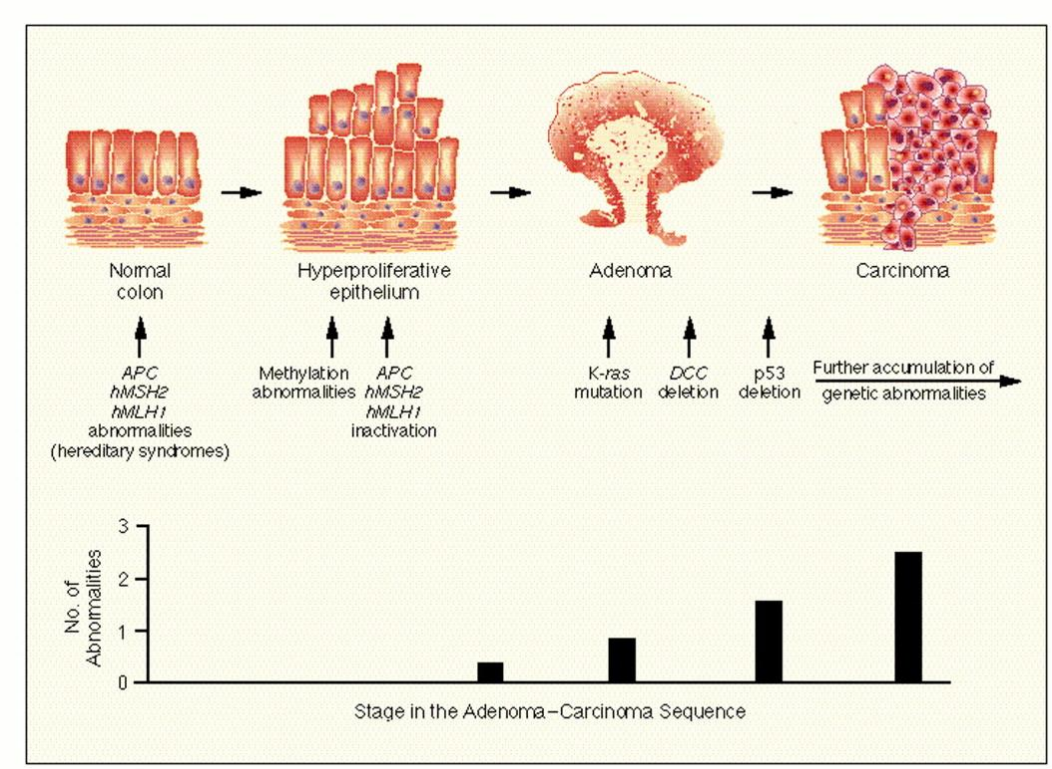

Figure 2. Adenoma-Carcinoma Sequence: molecular and morphological changes. [5]

Screening Rationale

Evidence suggests that only 10% of 1cm adenomas become malignant after 10 years.[6] The incidence of adenomatous polyps in the colon increases with age and although adenomatous polyps can be identified in 20% of the population, most of these are small and unlikely to undergo malignant change. As it takes a relatively long time for malignant transformation from adenoma to carcinoma to occur and outcomes are markedly improved by early detection of adenomas and early cancers, the potential exists to reduce disease mortality through screening asymptomatic individuals.[6]

There is a consensus that people who have no additional risk factor other than their age (i.e. of average risk) should begin regular screening at age 50 [7,8,9]. Between the ages of 40 and 49, there is a low yield for screening colonoscopy[10] and there is no evidence for capping the upper age limit of screening.[8]

SCREENING TESTS

Faecal occult blood test (FOBT)

Blood vessels at the surface of colorectal polyps, adenomas or carcinomas are often fragile and easily damaged by the passage of faeces. The damaged vessels usually release a small amount of blood in the faeces. FOBT is the only non invasive screening test for CRC with proven effectiveness, reducing both incidence and mortality when used systematically. In a randomised control trial evaluating the effectiveness of FOBT in reducing death rate from CRC, the use of annual FOBT was found to significantly reduce the incidence of CRC. A positive FOBT was followed by sigmoidoscopy and double contrast barium enema (DCBE) or by colonoscopy. The ratios of the cumulative incidence rates in the screening groups to that in the control were 0.80 (95% CI: 0.70 to 0.90; $p< 0.001$) for the annual screening group and 0.83 (95% CI: 0.73 to 0.94; $p= 0.002$) in the biennial screening group. The significant reduction in the incidence of CRC was due to the identification and removal of precursor lesions for CRC. It was argued that the high colonoscopy rate could account for the reduction in incidence rather than the effectiveness of FOBT since the former would enable detection of non bleeding lesions which FOBT would miss.[11]

FOBT on its own has a sensitivity of 23.9% as found in a study by Liebermann and colleagues with a positive predictive value (PPV) of 39.7% and negative predictive value (NPV) of 87.8%. When followed by sigmoidoscopy, the sensitivity of combined testing improves to 75.8% compared to sigmoidoscopy alone (70.3%). These statistics refer to detection of advanced neoplasia when a positive FOBT is followed by sigmoidoscopy alone compared to follow up by colonoscopy. It was also found that this combination of FOBT followed by sigmoidoscopy failed to detect a quarter of all distal advanced neoplasia and half of all advanced proximal neoplasia.[12]

The Minnesota Colon Cancer Study found that annual FOBT followed by colonoscopy and DCBE results in reduced mortality from CRC by 33% (Rate ratio=0.67; 95% CI: 0.50-0.87). Of note the incidence of Dukes D (distant metastases) CRC in the control group (no screening) was twice as many as that in the screening group. The study also recorded a greater incidence of Dukes A (confined to the bowel wall) CRCs most likely due to increased detection by screening. Survival was better in the annually screened group compared to control group. The 13 year cumulative mortality per 1000 from CRCs was 5.88 for the annual FOBT group (95% CI: 4.61-7.15): 8.33 for the biennial screening group (95% CI: 6.82-9.84) and 8.83 for the control group (95% CI: 7.26-10.40).[13] As the biennial group showed a cumulative CRC mortality rate greater than control group, it was decided to extend the follow up to 18 years. A 21% reduction (rate ratio=0.79; 95% CI: 0.62-0.97) in mortality was then found compared to 6% for the 13-year follow-up. There were 32% fewer Dukes D CRCs in the biennially screened group. Little screening was offered between years 13 and 18.[14]

In the Nottingham Study, patients selected from general practices were randomly assigned to biennial screening or to no screening. This study showed a 15% reduction (OR=0.85; 95%CI: 0.74-0.98) in CRC mortality in the biennial screened group. 4.3% more CRCs were detected in the screened group and the proportion of Dukes A tumours was significantly higher in the screening group than in the control (20 vs 11%; $p<0.001$). Incidence of Dukes C (involvement of regional nodes) and D stage CRC was lower in the screening group than in controls (ratio= 0.91; 95% CI: 0.80-1.04). Overall CRC incidence was higher in the screening group than in the control group (1.49 vs 1.44 per 1000 person years). There was a significant survival advantage for individuals in the screening group over those in the control group ($p<0.0001$). All cause mortality was similar in the screening and control groups. Sensitivity was calculated as 53.6%. Follow up was for an average of 7.8 years.[15]

Faecal DNA testing

A new non-invasive test, the faecal DNA test detects *k-ras*, *APC* and *p53* mutations; *MSI* marker *BAT-26* and a marker of long DNA thought to reflect disordered apoptosis of cancer cells sloughed in the colonic lumen. This was compared to FOBT for CRC screening in an average risk population. Faecal DNA detected 18.2% of samples with advanced neoplasia whereas Haemoccult II FOBT detected 10.8%. The sensitivity of the DNA panel for advanced adenomas was lower than previously reported, although CI overlapped. A decrease in exfoliation of cells owing to smaller adenoma size could be responsible. Specificity of Haemoccult II FOBT was 95.2% whereas that of faecal DNA was 94.4%.[16] Faecal DNA testing is not part of any published screening guidelines.

Sigmoidoscopy

Sigmoidoscopy has been acknowledged as an effective screening tool in CRC, however, data from randomized control trials are lacking. In a case-control study to determine whether sigmoidoscopy is associated with a reduction in CRC mortality, a single examination with sigmoidoscopy was found to lower the mortality rate by 80%. Individuals were found to be at lower risk compared to those who had not had any screening (OR =0.21, 95% CI: 0.08-0.52).[17]

In a population-based case-control study to evaluate the effectiveness of sigmoidoscopy in relation to screening interval, sigmoidoscopy was associated with a statistically significant and sustained reduction in the incidence of distal CRC. Compared with individuals who never had a screening sigmoidoscopy and those who had, the OR for distal CRC was 0.24 (95% CI: 0.17-0.33). The OR was similar to the OR for distal CRC among those who had a single screening sigmoidoscopy (OR: 0.30; 95% CI: 0.20-0.43). This association between screening sigmoidoscopy (whether single or multiple) and reduced incidence of distal CRC was observed for individuals who reported having

a screening sigmoidoscopy during the past 16 years relative to diagnosis or interview. Results from studies showed that optimal screening interval for sigmoidoscopy was longer than the 5-year interval recommended by the American Cancer Society.[18]

Sensitivity for the detection of potential lesions using sigmoidoscopy can be limited by a number of factors including poor bowel preparation and length of the endoscope. Prospective studies reveal that poor preparation precludes adequate rectosigmoid evaluation in 20% of examinations. Confinement of the scope to the rectum and sigmoid colon in 75-80% of attempts only leads to identification of 30-40% of lesions with a risk of perforation of 1 in 10,000. A 60cm sigmoidoscope is available, but even when passed to the splenic flexure, this can reach only 40-50% of neoplasms.[18]

Double-contrast barium enema (DCBE)

The strongest support for DCBE is based on the observation that treatment of early cancer in asymptomatic individuals lowers disease specific mortality and removal of adenomatous polyps reduces cancer incidence. Expense of DCBE is slightly higher than that of sigmoidoscopy. However DCBE is safer. No studies use DCBE as primary procedure and other studies have weak statistical power.[19] There is also considerable inter-observer error for the diagnosis of neoplasia on DCBE.[20]

In one study, 190 patients who underwent DCBE were randomly selected for colonoscopy. The sensitivity was 81% and specificity 96% for adenomas larger than 1cm.[21] In another study in which colonoscopy and DCBE were used for surveillance in patients with previous adenomas, the sensitivity for lesions larger than 7mm was 71% and the specificity was 98%. Most overlooked lesions measured between 7 and 10 mm.[22]

Therefore DCBE can probably detect at least three quarters of adenomas larger than 1cm, and possibly an even higher percentage of patients with such lesions. The cumulative benefits of periodic screening and the influence of the long natural history should also be considered.[19]
For polyps larger than 1cm sensitivity of DCBE and colonoscopy are highly comparable. For polyps smaller than 1cm colonoscopy has better test performance than DCBE, but the clinical significance of small polyps remains controversial.[23]

Colonoscopy

Colonoscopy is considered the ‘gold standard’ for CRC screening. A negative finding on colonoscopy can preclude the need for further screening for at least a further 5 years. The sensitivity of colonoscopy is influenced by the operator’s experience. In most published articles, a

highly experienced endoscopist performs the colonoscopy but in many centres, availability of such expertise may be a limiting factor to successful screening.

There is dispute that colonoscopy can avert CRC and deaths; it can find most polyps and nearly all large polyps and cancers. It also has the further advantage that lesions can be removed simultaneously. Furthermore, colonoscopy finds a significant amount of proximal lesions that would otherwise be missed by performing sigmoidscopy [24, 25, 26]

To date there are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from CRC in people at average risk by means of a randomised control trial.[8] The National Cancer Institute is currently sponsoring a pilot study of colonoscopy screening but the results from a large randomised control trial, if undertaken, will not be available for many years.

Colonoscopy has been shown to reduce the incidence of CRC in two cohort studies of individuals who had adenomatous polyps removed at colonoscopy: the US National Polyp Study and the Italian Multicentre Study. The US National Polyp Study estimated that 76 percent to 90 percent of CRC could be prevented by regular colonoscopy screening, based on comparison with historic controls.[27] However, these results should be interpreted with some caution. The comparison groups were not from the same underlying population, which could introduce bias. All participants in the study had polyps detected and removed, thereby limiting the applicability of the results to the average screening population. The Italian Multicentre Study Group found that intervention in the adenoma-carcinoma sequence through conventional colonoscopic screening and polypectomy has the potential to reduce the incidence of CRC. During a mean follow up of 10.5 years, 6 CRCs were ascertained while the expected number was 17.7 (Expected number was calculated from the reference general population). Also a significant reduction OR of 0.34 (95% CI: 0.23-0.63 $p<0.01$) in the incidence of CRC was observed in the cohort with respect to the general population.[28]

It is difficult to calculate the sensitivity of colonoscopy as a screening tool, as it is commonly used as the ‘gold standard’ examination. In a study that assessed the sensitivity of colonoscopy for detection of polyps by performing colonoscopy twice in one day by different but experienced endoscopists in 183 patients, the initial procedure missed 27 percent of adenomas <5 mm in size, 13 percent of adenomas 6 to 9 mm in size, but only 6 percent of adenomas >10 mm in size.[29]

The specificity for colonoscopy with biopsy is generally reported to be 99% to 100%. However, this assumes all detected adenomas represent true-positive results and develop into cancer. If detection of an adenoma that will not become cancer is considered a false-positive result that subjects a patient to risk without benefit, then the actual specificity of colonoscopy would be much lower.[8]

The caecum is reached in 85-95% of attempts, depending on the experience of the operator. Suboptimal preparation, incomplete examination and faster rate of progression to carcinoma compared to the usual estimates have implications for the 10-year interval recommended between screenings. The superiority of colonoscopy is demonstrated by its ability to detect right sided neoplasms. If screening colonoscopy is performed only in patients with distal polyps detected by sigmoidoscopy, about half the cases of advanced proximal neoplasms will not be detected. The data in this study suggest that a substantial proportion of advanced proximal neoplasms are not associated with any distal sentinel lesion thus limiting screening with flexible sigmoidoscopy.[24]

The Veterans Affairs Cooperative Study Group found that the majority of advanced lesions occurred in the colon distal to the splenic flexure (7.3% of study population compared to 4.1%in the proximal colon). This shows that sigmoidoscopy would pick up almost half of total colon lesions. But since 48.4% of proximal neoplasia is associated with distal colon lesion, examination of the distal colon to the splenic flexure followed by colonoscopy would identify 79.9% of patients with advanced neoplasia. Of note, prevalence of advanced proximal neoplasia in patients with no polyps of any kind in the rectum and sigmoid or descending colon was 2.7% of study population compared to 3.7% when distal colon was defined as the sigmoid colon and rectum. Patients with large adenomas (≥10mm) or small adenomas (<10mm) in the distal colon were more likely to have advanced proximal neoplasia than were patients with no distal adenomas (OR= 3.4, 95% CI= 1.8-6.5, OR=2.6 95% CI= 1.7-4.1). So an adenoma increases the risk of advanced proximal lesion, regardless of its size. Patients with distal hyperplastic polyps had a risk of advanced proximal neoplasia that was similar to patients without any polyps. Of note, the prevalence of advanced proximal lesion increases with age.[25]

Colonoscopy, which uses sedation and requires skilled support personnel, is more expensive and has a higher risk for procedural complications than other screening tests, particularly when polypectomy is performed. Two recent studies examined the incidence of complications from colonoscopy performed in screening populations. The Veterans Affairs Cooperative Study Group found that 10 out of 3121 patients (0.3%) had major complications during or immediately after the procedures. Of these 10 patients, 6 had bleeding that required hospitalisation and the others had a stroke, myocardial infarction, Fournier gangrene and thrombophlebitis respectively. Three other patients died within 1 month, probably of causes unrelated to the procedure.[25] In a study of employees of a large corporation, Imperiale and colleagues found that among 1994 persons 50 years of age and older who underwent colonoscopy, 1 (0.05%) had a perforation that did not require surgery and 3 (0.15%) had bleeding that required A&E visits but not admission or surgery.[24]

Virtual colonoscopy (VC)

This is a new method of imaging the colon in which thin section, helical computed tomography is used to generate high resolution, two-dimensional axial images. Three-dimensional images of the colon simulating those obtained with conventional colonoscopy are then reconstructed offline. Virtual colonoscopy (VC) is relatively safe, minimally invasive and does not require intravenous sedation but still requires the normal bowel preparation but no intravenous sedative is needed. In a study by Fenlon and colleages,[30] 82 of the 115 polyps (71%) in a high risk population seen on conventional colonoscopy were correctly identified on the basis of location and size. The sensitivity of VC was related to the size of the polyp. Only 29 of the 53 polyps between 1 and 5mm in diameter (55%) were correctly identified on virtual colonoscopy. The sensitivity for detection of polyps that were 6 to 9mm and those 10mm or larger was significantly higher (82 and 91% respectively, p= 0.001). The performance of VC was also related to histologic type: detection of hyperplastic polyps 1-5mm in diameter was significantly lower than detection of adenomatous polyps of the same size (48 against 67%, p=0.003). The sensitivity of VC was 71% for hyperplastic polyps 6 to 9mm in diameter and 90% for adenomatous polyps. Including polyps of all sizes, per patient sensitivity of VC was 82% and specificity was 84%. False positive findings were due to inadequate bowel preparation, poor distention and diverticular disease (other bowel pathologies). However, caution must be taken when reporting false positives, although colonoscopy is used as the ‘gold standard’, between 10-20% of colonic polyps and up to 5% of CRC may be missed on colonoscopy. Hence it is possible that the true specificity and PPV of VC are higher than reported in that study.

Adequate expertise in VC interpretation is important in evaluating the competence of this test. With CT colonography, scanning can be performed at peripheral sites and interpretation done at

central sites by experienced radiologists with electronically sent data, implying expertise in interpreting need not be a limiting factor if CT colonography were to be used for screening.

One of the limitations of this study is that the performance of VC in high risk patients may be overestimated and that VC might not do as well in average risk patients. Hence the validity of this technique for screening is not established.[30]

CONCLUSION

Guidelines for CRC screening in an average risk population are available from several professional organisations including the US Preventative Services Task Force, Multidisciplinary Expert Panel and the American Cancer Society (Table 1). All organisations recommend commencing screening a population of average risk at 50 years.

Screening tool	**US Preventative Services Task Force[8]**	**Multidisciplinary Expert Panel[9]**	**American Cancer Society[7]**
FOBT	Annually	Annually	Annually
Sigmoidoscopy	Recommeded, "periodicity unspecified"	Every 5 years	Every 5 years
FOBT + sigmoidoscopy	Recommended as an option	Annual FOBT with sigmoidoscopy every 5 years	Recommended over FOBT alone
Double-contrast barium enema	"Insufficient evidence to recommend either for or against"	An option every 5-10 years	Every 5 years
Colonoscopy	"Insufficient evidence to recommend either for or against"	Every 10 years	Recommended as an option every 10 years

Table 1: Current Colorectal Cancer Screening Guidelines

The mortality from CRC can be reduced by the detection of asymptomatic early-stage disease. Secondary prevention can be achieved by detection and removal of colorectal adenomas, from which more than 95 percent of CRC arise.

Several factors must be accounted for when recommending screening for CRC. These include the effectiveness, sensitivity, false-positive rate, safety and convenience of the test, on top of the cost and cost-effectiveness of the programme. Consideration must also be given to what is best for the individual patient, in addition to clinical policy in general.

Faecal DNA testing and virtual colonoscopy are in their infancy as screening tools. In the future our growing understanding of the pathogenesis of CRC will hopefully lead to more sensitive and specific methods of screening.

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