

Consensus Conference: Colorectal Cancer Screening and Surveillance in Inflammatory Bowel Disease

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Abstract: The idiopathic inflammatory bowel diseases, ulcerative colitis and Crohn's colitis, are associated with an increased risk for developing colorectal cancer. To reduce colorectal cancer mortality in inflammatory bowel disease, most patients and their physicians choose to follow a program of surveillance colonoscopy in an attempt to detect early neoplastic lesions at a curable stage. Colectomy is typically reserved for patients whose biopsy findings are indicative of heightened cancer risk based on interpretation by pathologists. Despite the absence of prospective controlled clinical trials to formally evaluate the benefits, risks, and costs of this approach, enough circumstantial evidence has accrued to warrant its widespread adoption in practice. Nevertheless, no standardized guidelines have yet been set forth to guide the gastroenterologist in performing surveillance. A panel of international experts was assembled to develop consensus recommendations for the performance of surveillance. The findings are presented herein.

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The idiopathic inflammatory bowel diseases (IBDs), ulcerative colitis (UC) and Crohn's colitis, are associated with an increased risk for developing colorectal cancer (CRC).¹ In the past, some experts recommended prophylactic colectomy for patients with extensive longstanding UC in an effort to reduce CRC mortality. With the availability of colonoscopy and the discovery that dysplastic changes in colitic mucosa are correlated with CRC risk in UC patients,

efforts to limit CRC mortality while avoiding total proctocolectomy were developed. This has resulted in the practice of surveillance colonoscopy, whereby serial colonoscopic examinations are performed, during which biopsies are taken from suspicious lesions as well as multiple regions of flat mucosa. Colectomy is typically reserved for patients whose biopsy findings are indicative of heightened cancer risk based on interpretation by pathologists. Despite the absence of prospective controlled clinical trials to formally evaluate the benefits, risks, and costs of this approach, enough circumstantial evidence has accrued^{2,3} to warrant its widespread adoption in practice and its inclusion in published practice guidelines.⁴⁻⁶ Nevertheless, no standardized guidelines have yet been set forth to guide the gastroenterologist in performing surveillance.

In March 2000, the Crohn's and Colitis Foundation of America convened a workshop "Colon Cancer in IBD: Science and Surveillance" in Palm Harbor, Florida (see Appendix). A group of international experts in relevant scientific disciplines began the process of coming to a consensus on guidelines for screening and surveillance colonoscopy in patients with IBD. The group reconvened (with some additional members) in October 2004 in New York City to complete the guidelines.

This consensus statement contains these guidelines, which are based on the best available evidence and the opinion of international experts. Specifically, they address (1) the identification of IBD patients who might benefit from colonoscopic surveillance and (2) the appropriate practices of surveillance colonoscopy. Patients with Crohn's colitis, like those with UC, are at increased risk of developing CRC compared with the general population.^{7,8} This document first addresses surveillance guidelines for UC patients, for which more is known, followed by surveillance guidelines for patients with Crohn's colitis. The entities of collagenous colitis and lymphocytic colitis (collectively considered microscopic colitis) are not included in this statement because an increased risk of CRC has not been documented in these conditions. It should be emphasized at the outset that surveillance for CRC in IBD entails more than performing serial colonoscopic examinations. Regular evaluation of patients' symptoms, medication use, and updated personal and family medical history are critical components of the cancer prevention strategy.³

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This manuscript is dedicated to the memory of Dr. Rodger C. Haggitt.

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DEFINITIONS

In this statement, the term *dysplasia* is defined histologically as an unequivocal neoplastic change of the intestinal mucosa in the setting of IBD. A *screening examination* is defined as the first colonoscopic examination in a patient with UC or Crohn's colitis performed for the purpose of detecting dysplasia or CRC. *Surveillance examinations* are subsequent endoscopic examinations performed periodically for the same purpose.

CRC SCREENING AND SURVEILLANCE RECOMMENDATIONS FOR PATIENTS WITH UC

Risk Factors for CRC

Based on previously published practice-based and population-based studies, the duration of UC and the anatomic extent of disease have been shown to be independent risk factors for the development of CRC in UC. As such, special attention to these 2 variables is crucial in the practice of surveillance. Additional risk factors are indicated below, along with comments as to their implications for the practice of surveillance.

Duration of Disease

There is no uniform definition for the duration of UC. Although some studies define duration based on the date of radiologic, endoscopic, or histologic diagnosis, a preferred approach is to define it based on the onset of UC-like symptoms. Because the risk of CRC becomes greater than that of the general population after 8 to 10 years from the onset of disease,⁹ the Committee recommends that a *screening* colonoscopy be performed 8 to 10 years after the onset of symptoms attributable to UC. The purpose of this examination is to reestablish disease extent and also look for evidence of dysplasia. Regular surveillance colonoscopy should be initiated after a screening examination.

Anatomic Extent

Different criteria also exist regarding classification of the extent of colitis. Most early reports of surveillance programs used barium enema results at diagnosis as the standard for defining disease extent; however, endoscopic and histologic evidence of inflammation are valid alternative criteria. Unfortunately, these different criteria do not correspond with each other in all cases, and moreover, their respective implications for CRC risk are uncertain. The classification of disease extent may be further confounded by the phenomena of disease extension or partial healing over time. Thus, it is not known how the risk of CRC among patients whose disease has anatomically extended over time compares with that of patients with limited disease or those with extensive disease from the outset. Cancer and dysplasia can arise in areas of the colon that show histologic evidence of disease even without endoscopic

abnormalities.¹⁰ In view of these uncertainties, for the purposes of classifying patients as high risk (i.e., likely to derive benefit from a surveillance regimen), extent should be defined by both endoscopic and histologic evaluation, whichever reveals more extensive involvement. The extent of involvement should be defined either at diagnosis or screening, whichever reveals more extensive involvement. Colonoscopy is preferred to flexible sigmoidoscopy for this purpose.

Patients with UC should be classified by extent into 1 of 3 categories:

- Extensive: if there is evidence of UC proximal to the splenic flexure,
- Left-sided: if UC is present in the descending colon up to, but not proximal to, the splenic flexure,
- Proctosigmoiditis: if disease is limited to the rectum with or without sigmoid colon involvement

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) can affect individuals with both UC and Crohn's disease. In light of clinical studies implicating PSC as a risk factor for CRC,¹¹ all patients with PSC not previously known to have IBD should undergo a colonoscopy to determine their status. This procedure should include biopsies from normal-appearing mucosa, because microscopic evidence of colitis may not be visually apparent. For those patients shown as having IBD, screening and subsequent surveillance should begin at the time of PSC onset.

Age of Onset

Although there is some evidence to support a higher relative risk for CRC among UC patients diagnosed at a young age,^{9,12,13} there is insufficient evidence to support starting screening and surveillance before 8 years of disease in these patients. Thus, screening and surveillance should be pursued based on other risk factors, regardless of age of colitis onset.

Positive Family History of CRC

The findings from several studies suggest that a positive family history of CRC is a risk factor for CRC in UC patients.^{3,14,15} At this time, however, there is insufficient evidence to warrant altering either the initiation of surveillance or the interval between examinations based on this information. Nonetheless, it is sound clinical practice to obtain a detailed family history for intestinal and extraintestinal neoplasia and to incorporate any evidence of heightened risk into the clinical decision making.

Degree of Endoscopic and Histologic Activity

A recent study has shown that increased severity of inflammation, both endoscopically and histologically, correlates with increased frequency of dysplasia.¹⁶ As we await

confirmation of these findings, it is important also to realize that patients with longstanding quiescent colitis remain at risk for developing CRC.

Factors that May Modify Risk

Aminosalicylate use and possibly folic acid intake have been suggested to be cancer chemopreventive agents in patients with UC.¹ Ursodeoxycholic acid has been shown to be chemopreventive in the subset of colitis patients with PSC.^{17,18} Although these agents may prove to be beneficial to patients at risk for CRC, there is insufficient evidence to modify screening and surveillance in UC patients who use these medications, and use of these medications should certainly not replace surveillance colonoscopies.

Timing of Screening and Surveillance Exams

All recommendations concerning timing and performance of screening and surveillance colonoscopy assume that appropriate surveillance techniques are followed.

Screening

A screening colonoscopy should be performed in UC patients to rule out colonic neoplasia (dysplasia or cancer) 8 to 10 years after the onset of UC symptoms. At the time of this examination, extent of disease should also be evaluated, with possible reclassification of extent if there is significant change.

Surveillance

Patients with *extensive colitis* or *left-sided colitis* who have a negative screening colonoscopy should begin surveillance within 1 to 2 years. This interval is based on studies reporting that interval cancers can develop within 2 years after a surveillance examination.^{19,20} With a negative surveillance colonoscopy, subsequent surveillance examinations should be performed every 1 to 2 years. With 2 negative examinations, the next surveillance examination may be performed in 1 to 3 years until UC has been present for 20 years. At that time, consideration should be given to performing surveillance every 1 to 2 years, based on the concept that CRC risk increases with longer duration of colitis.²¹

Patients with PSC should undergo surveillance yearly. Patients with other risk factors, such as positive family history of CRC, may require shorter surveillance intervals.

Patients with *proctosigmoiditis*, who have little or no increased risk of CRC compared with the population at large,¹² should be managed according to standard CRC prevention measures as defined in consensus Gastrointestinal Consortium recommendations and guidelines.⁶ Despite a lack of data, the presence of a so-called "cecal patch" of erythema with microscopic inflammation in patients with proctosigmoiditis should not alter this recommendation. However, if biopsies are positive for colitis proximal to 35 cm, even though macroscopic disease is limited to the distal sigmoid and rectum, it is suggested that the patient follow a UC-type surveillance approach.

Management of Abnormal Findings

Any examination in which a single biopsy reveals mucosal changes interpreted as "indefinite for dysplasia," "low-grade dysplasia" (LGD), "high-grade dysplasia" (HGD), or "adenocarcinoma" is considered an abnormal finding. The number of biopsies taken at colonoscopy can affect whether a sampling error is present, and thus, if high-grade dysplasia and/or cancer has been missed.²² Patients who have <33 biopsies performed at each colonoscopy are more likely to have a missed diagnosis of neoplasia. The decision for recommending colectomy should be considered in light of the quality of colonoscopic surveillance that was performed, namely the quality of the preparation, whether sufficient biopsies were taken to have confidence in the final diagnosis, and the presence of active inflammation that can occasionally make interpretation of the biopsies difficult.

In recent years, it has become clear that the management of polypoid (raised) dysplasia differs from that of flat dysplasia. It is also becoming apparent that, although so-called "flat" dysplasia in IBD has been considered invisible to the naked eye, dysplastic areas can often be slightly raised or elevated.²³ For the purposes of this statement, the term flat mucosa implies tissue that is not believed to be raised.

Recommended management strategies for abnormal findings are as follows.

Indefinite for Dysplasia in Flat Mucosa

One or more biopsies reported "indefinite for dysplasia" should be reviewed by an experienced gastrointestinal pathologist. If the diagnosis is confirmed, a follow-up surveillance examination should be performed within 3 to 6 months.

LGD in Flat Mucosa

Any biopsies reported "positive for LGD" should be confirmed by an experienced gastrointestinal pathologist. Controversy exists about the management of LGD because the natural history is unknown at this time. For patients complying with a strict surveillance program, finding flat LGD during surveillance may not carry the same high risk of progression to HGD or cancer as finding flat LGD on initial screening examination.^{24,25} Several studies have suggested an ~50% to 55% 5-year rate of progression from LGD to HGD or CRC,^{19,26,27} whereas others show a much lower rate.^{20,28} There is evidence that with LGD as the worst histologic diagnosis at colonoscopy, an unrecognized synchronous CRC may already be present in up to 20% of individuals who undergo surgery shortly thereafter.^{24,27} Therefore, competing options should be discussed with each patient. A prophylactic colectomy should be offered given the possibility of a synchronous adenocarcinoma, particularly if the number of colonoscopic biopsies is insufficient. A discussion with a colorectal surgeon of the possible complications of restorative proctocolectomy should

be included when counseling the patient about options. Possible complications include an increased risk for infertility in women, as well as the standard complications of stricture, incontinence, adhesions, cuffitis, and pouchitis.

A patient confirmed to have *multifocal* flat LGD (2 or more biopsies with LGD from a single screening or surveillance examination) or *repetitive* flat LGD (2 or more examinations with at least a single focus of LGD), should be strongly encouraged to undergo prophylactic total proctocolectomy. Recent evidence indicates that the 5-year rate of progression to HGD or CRC for patients with confirmed unifocal LGD (only 1 biopsy positive for LGD in a screening or surveillance examination) seems to be similar to that of multifocal LGD.²⁷ Therefore, such a patient should also be offered the option of undergoing prophylactic proctocolectomy.

Regardless of the focality of flat LGD, if an operative strategy is deferred and the patient elects to continue with surveillance, a repeat examination should be performed within 3 months and no later than 6 months from the discovery of LGD. Repeat exams should include sufficient sampling so that there is no error in the histologic diagnosis.

It must be stressed that for patients who elect to pursue a nonoperative strategy for LGD, a subsequent negative examination (i.e., no dysplasia) is not sufficiently reassuring to return to routine surveillance.^{25,27} Therefore, continued, more frequent exams (≤ 6 mo) should be pursued. Again, an extensive biopsy protocol is recommended to ensure that the diagnosis is correct.

HGD in Flat Mucosa

As with LGD, a finding of HGD should be confirmed by a pathologist from an expert center. If confirmed, total proctocolectomy should be performed, given the high rate of synchronous and metachronous adenocarcinoma.^{19,24}

Raised Lesions (Polyps) with Dysplasia

Raised lesions encountered within areas of colitis may include 1 or more polyps that visually resemble sporadic adenomas and may be amenable to complete polypectomy.²⁹⁻³¹ If polypectomy is complete and biopsies of surrounding mucosa (4 biopsies taken immediately adjacent to the raised lesion and submitted separately) are negative for dysplasia, and in addition, there is no dysplasia elsewhere in the colon, a follow-up examination should be performed within 6 months, with regular surveillance resumed if no dysplasia is found. However, if dysplasia is present in the surrounding mucosa, or if the dysplastic polypoid lesion is nonresectable or does not resemble a typical adenoma (referred to in the literature as dysplasia-associated lesion or mass), a high risk of associated synchronous CRC would justify recommending a complete proctocolectomy. The alternative option of segmental colectomy has not been evaluated in the literature and should be restricted to carefully selected patients with serious mitigating circum-

stances. In cases of uncertainty regarding technique or management, referral to a tertiary center is appropriate. Marking a raised lesion with India ink at the time of colonoscopy before referral to an expert center should also be considered.

Adenoma-like polyps encountered in areas of the colon that are endoscopically and microscopically free of disease involvement may be managed according to standard recommendations for postpolypectomy follow-up of sporadic adenomas.⁶

CRC SCREENING AND SURVEILLANCE RECOMMENDATIONS FOR PATIENTS WITH CROHN'S COLITIS

Patients who have only had small intestinal Crohn's disease without colonic involvement are not considered to be at high risk for CRC but should be managed according to general population CRC screening guidelines.⁶ For patients with Crohn's colitis, the Committee endorses the notion that the risk of CRC is similar to that of UC if there is comparable surface area involvement and disease duration. Screening and surveillance recommendations for Crohn's colitis are thus similar to those for UC. It should be noted that knowledge about CRC risk in Crohn's colitis is based on more limited data than in UC, with most observations derived from retrospective studies,⁸ population-based studies,⁷ and 1 recent prospective study.³² Very little is known about chemoprevention in patients with Crohn's colitis.

Risk Factors for CRC

Duration of Disease

As with UC, duration of disease in Crohn's colitis is defined from the onset of symptoms of colitis, not from the date of diagnosis. Although data are limited, it is believed that, as with UC, increased CRC risk in Crohn's colitis occurs after 8 to 10 years of disease, and screening should start at this time.

Extent of Disease

Inclusion in a screening and surveillance program is recommended for Crohn's colitis patients who have major involvement of the colon. This has been defined somewhat arbitrarily as more than one-third of the colon involved with disease as determined endoscopically (not on biopsy material).³²

PSC

PSC can affect individuals with both UC and Crohn's disease. In light of clinical studies implicating PSC as a risk factor for CRC,¹¹ all patients with PSC not previously known to have IBD should undergo a colonoscopy to determine their status. This procedure should include biopsies from normal-appearing mucosa, because microscopic evidence of colitis may not be visually apparent. For those patients shown as having IBD, screening and subsequent surveillance should begin at the time of PSC onset.

Family History of CRC, Early Age at Onset, and Degree of Endoscopic and Histologic Activity

There is insufficient evidence to support altering the schedule of screening and surveillance for these variables.

Screening and Surveillance

Patients with major colonic involvement (at least one-third of the colon involved) who have harbored disease for 8 to 10 years from onset of symptoms should undergo a screening colonoscopy.³² If no dysplasia or cancer is found, a surveillance examination protocol should be started within 2 years.

After a negative surveillance colonoscopy, subsequent surveillance should be performed every 1 to 2 years. With 2 negative examinations, the next surveillance examination may be performed in 1 to 3 years until Crohn's colitis has been present for 20 years. At that time, surveillance should be performed every 1 to 2 years.

Management of Abnormal Findings

The recommendations for management after an abnormal finding in Crohn's colitis are identical to those for UC. For patients with segmental Crohn's colitis, if a dysplastic or cancerous lesion is detected and surgery is planned, it is not known whether a segmental resection alone is sufficient or whether a UC-based approach of total proctocolectomy should be considered.

COMPLIANCE AND CONSENT

It should be emphasized and conveyed to patients that, although a program of surveillance colonoscopies is the best approach currently available, it has its limitations. Thus, even with the most compliant patient and in the hands of a highly skilled endoscopist, surveillance cannot guarantee against the development of CRC. It is suggested that, before initiating a program of screening and surveillance, perhaps a general form be signed by both the patient and physician outlining the surveillance program. This document should state potential risks and benefits of a surveillance program and the need for both patient and physician compliance in adhering to a schedule of exams. The importance of patient compliance and consent in undertaking a program of screening and surveillance cannot be overemphasized. There should be regular call back for all participating patients so that no patients are lost to follow-up. Patient noncompliance should trigger a series of letters including a comment about the potential risk for developing CRC in the absence of follow-up.

MECHANICS OF SCREENING AND SURVEILLANCE EXAMS

Patient selection, colonoscopic practice, tissue handling, and histologic interpretation all impact the effectiveness of a surveillance examination. Clinicians and pathologists should strive toward performing screening and surveillance exami-

nations with greater uniformity, and it is essential that the clinician and pathologist directly communicate with each other, particularly regarding an abnormal histologic finding. As with all diagnostic and therapeutic colonoscopies, screening and surveillance examinations should be performed in a well-prepared colon using standard preparation techniques. The following criteria for an effective surveillance examination should be used by clinicians performing surveillance.

Patient Selection

In an effort to minimize unreliable histologic interpretation of dysplasia, efforts should be made to minimize disease activity in all UC and Crohn's colitis patients before a screening or surveillance examination.

Colonoscopic Practice

For patients with extensive disease, a minimum of 33 biopsies should be performed. This involves taking 4-quadrant biopsies every 10 cm throughout the colon. In patients with less extensive microscopic disease found at screening, 4-quadrant biopsies should be taken from the proximal extent of disease and every 10 cm distally. Particularly in UC, consideration should be given to taking 4-quadrant biopsies every 5 cm in the lower sigmoid and rectum, because the frequency of CRC is higher in this region.²⁵

Tissue Handling

Ideally, the colonoscopist and his/her assistants should place all biopsies from a given segment in a separate specimen jar. If feasible, biopsies should be "unrolled" from their ball-like shape after removal from biopsy forceps to facilitate histologic interpretation. Use of jumbo biopsy forceps should be considered to minimize sampling errors. There is often a limit to the number of biopsies that can be physically embedded in 1 tissue block; it is suggested that no more than 4 biopsies should be placed in any 1 jar. Specimens from raised or suspicious lesions should be placed in separate, appropriately labeled jars.

Histologic Interpretation

All pathologists rendering a histologic interpretation of surveillance biopsies should be familiar with and adhere to the recommendations of the "IBD Dysplasia Morphology Working Group" findings published in 1983.³³ These definitions remain the standard by which surveillance specimens are interpreted. The only exception is that the proposed formal subclassification of "indefinite for dysplasia" into "probably positive," "probably negative," and "unknown" is optional. Nonetheless, pathologists are encouraged to elaborate on any uncertainties and the degree of concern with which they are viewed.

It should be noted that disease activity per se does not preclude accurate pathologic interpretation of biopsies in general, although it may introduce uncertainties in some cases. Accordingly, endoscopic examinations in patients with active

disease should not be deferred for great lengths of time merely for the purpose of increasing diagnostic accuracy. Nonetheless, any intervention that reduces inflammation is acceptable if it leads to a minor postponement.

Special Clinical Situations

Pseudopolyps

In the event of multiple or massed pseudopolyps, several options exist, none of which is adequately supported in the medical literature. These options include referral to an endoscopist with expertise in IBD, colectomy or segmental resection, complete polypectomy of all lesions if feasible, or routine surveillance of flat mucosa areas and removal of all *suspicious* polypoid lesions. When in doubt, referral to an expert center is recommended.

Stricture in UC

A stricture in UC is a strong indication for colectomy because of the high rate of underlying carcinoma.^{34,35} If the stricture proves to be negotiable using a standard pediatric (11 mm) colonoscope, multiple biopsies and even brushings for cytology should be taken from the stricture site. Even if these biopsies and brushings prove to be negative for CRC or dysplasia, the patient may be at very high risk for a malignancy; repeat colonoscopy should be performed within 3 to 4 months, and consideration should be given to performing a computed tomography scan. Additionally, a diagnosis of Crohn's and not UC should be considered.

Stricture in Crohn's Colitis

If the endoscopist is able to traverse a stricture in Crohn's colitis, repeat endoscopic evaluation within 1 year is appropriate. If the endoscopist is unable to pass the stricture and perform surveillance with a standard pediatric (11 mm) endoscope, a barium enema or computerized tomographic colonography should be considered to evaluate the proximal colon, with possible referral to an expert center. If there is >20 years of disease, the ~12% rate of concomitant CRC warrants consideration of surgery (total colectomy or segmental resection) if the endoscopist is unable to evaluate the colon proximal to the stricture.³² Endoscopic balloon dilation works best for de novo and anastomotic Crohn's strictures that are relatively short (<6 cm).³⁶ Dilation of long narrow strictures runs the risk of perforation.

Anal Stricture

In the event of an anal stricture, an examination under anesthesia should be performed to rule out malignant disease in this area, given the increased risk of cancer in this situation.³⁷ Because there are no data to result in specific interval recommendations, an annual examination under anesthesia should be considered in patients with an anal stricture.

New Endoscopic Techniques

Recent studies indicate that chromoendoscopy can greatly enhance the endoscopic detection of dysplastic lesions in colitic colons.^{38,39} The Committee endorses the incorporation of chromoendoscopy into surveillance colonoscopy for appropriately trained endoscopists. We hope that the development of newer techniques will further refine our current surveillance recommendations and our understanding of the natural history of dysplasia.

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APPENDIX

Participants of the First Workshop

COLON CANCER IN IBD: Science and Surveillance

Palm Harbor, Fla.

March 10–12, 2000

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Robert E. Petras, MD	Cleveland Clinic Foundation, Cleveland, Ohio
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Peter H. Rubin, MD	Mount Sinai School of Medicine, New York, NY
David B. Sachar, MD	Mount Sinai School of Medicine, New York, NY
Charles A. Sninsky, MD	Vanderbilt University, Nashville, Tenn.
Thomas A. Ullman, MD	Mount Sinai School of Medicine, New York, NY
Jerome D. Waye, MD	Mount Sinai School of Medicine, New York, NY

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Participants of the Second Workshop

COLON CANCER IN IBD: Science and Surveillance

New York, NY

October 14, 2004

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Steven Itzkowitz, MD	Mount Sinai School of Medicine, New York, NY

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