
Incidental Findings in CT Colonography: Literature Review and Survey of Current Research Practice

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Just over ten years ago, the first human trials of virtual colonoscopy, or computed tomography (CT) colonography, were performed.¹ CT colonography (CTC), as it is now called, is a low radiation dose CT examination of the abdomen and pelvis following bowel purgation cleansing and insufflation (inflation) of the colon and rectum. High spatial resolution CT datasets of the abdomen and pelvis are obtained while the patient is lying in the prone and supine positions, with the entire procedure lasting about ten minutes. The resulting images are interactively reviewed on a dedicated computer workstation using 2D multiplanar images and 3D endoluminal displays of the colon. Over the past decade, rapid technological advancements in image acquisition, 3D display techniques, colonic insufflation, and stool tagging (i.e., labeling of stool with ingested radio-opaque contrast) have occurred, which have greatly improved the ability of CT colonography to detect colorectal polyps and cancer.

Probably due to physician-researchers conducting early CT colonography research, the importance of incidental findings (IFs) discovered during CT colonography was quickly recognized. Several early studies suggested that the incidence of extracolonic findings that require further medical investigation or medical/operative treatment was 10-11 percent and surpassed the incidence of large colorectal polyps in asymptomatic research subjects undergoing CT colonography.²

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Moreover, while the benefits of identifying extracolonic findings were potentially life-saving in a small percentage of patients (0.5-1.3 percent),³ such benefit came with a cost and potential morbidity.⁴ From an individual patient's perspective, the medical work-up that follows the detection of a significant extracolonic incidental research finding can be dramatic, often necessitating further imaging, or less likely, invasive or surgical techniques. While imaging studies can frequently be performed to quickly arrive at a definitive diagnosis, the medical work-up can be protracted and require long-term imaging surveillance. The work-up may also result in morbidity if invasive procedures are employed.

seen by these researchers as an unavoidable responsibility. This scenario may be different from that in other research fields in which the researcher may not be trained to provide clinically relevant interpretations and so may not readily accept responsibility for recognizing and interpreting IFs. The NHGRI-sponsored consensus project on managing IFs in human research has determined that researchers have a moral obligation to research subjects to inform them of the possibility of discovering an IF, explain the potential risks and benefits of the discovery of IFs, recognize and evaluate IFs for potential medical significance, and develop standardized methods for detecting and communicating IFs.⁶

In general, slightly more than half of research subjects in screening or asymptomatic populations had any type of extracolonic finding (median, 52 percent; weighted mean, 53 percent of research subjects). In contrast, when research subjects were comprised of symptomatic patient populations or patients with known colorectal disease, this frequency was higher (and could even be the large majority of subjects; median, 69 percent; weighted mean, 59 percent of research subjects).

A consensus project led by the University of Minnesota's Consortium on Law and Values in Health, Environment & the Life Sciences supported by a grant from the National Human Genome Research Institute (NHGRI) has recently addressed the management of IFs in human subjects research. An incidental finding has been defined by the project as "a finding concerning an individual research participant that has potential clinical significance and is discovered in the course of conducting research but is beyond the aims of the study."⁵ Incidental findings in CT colonography are largely extracolonic findings, in addition to non-neoplastic colonic disease. Colonography research is continuing with aims to reduce or eliminate radiation dose (i.e., using CT and magnetic resonance [MR], respectively) and to eliminate bowel purgation cleansing (one of the largest barriers to public acceptance and compliance with colorectal cancer screening tests).

CT colonography research offers a model for managing IFs in human subject translational research in academic medical centers and, in particular, departments of radiology. Like many imaging and translational researchers, CTC researchers are usually clinicians engaged in research who interpret images in their medical practice routinely. Recognition and interpretation of extracolonic findings have consequently been

In this study, we sought to review IFs in CTC research to determine how they have been handled over the past decade by CT colonography researchers. The purpose of this study is to describe the frequency, categorization, and spectrum of IFs in CTC research; to survey current CT colonography researchers to determine how IFs in research studies are handled; and to summarize emerging consensus regarding the detection and handling of IFs in CTC.

Methods

To investigate this question, we employed both a search of the medical literature and a survey of experts in the field.

Literature Review

To ascertain the spectrum and incidence of IFs in CT colonography research, we surveyed the medical literature using the PubMed service of the National Library of Medicine from 1996 to present for all relevant articles. Specifically, we focused on CT colonography studies examining extracolonic findings that met the following criteria: (1) studies of more than 100 consecutive research subjects who were recruited prospectively; (2) studies with a clearly defined research subject population (e.g., screening, surveillance or symptomatic patients, or patients referred to endos-

copy); and (3) studies with methods or results sections including a definition of “significant” or “medically important” extracolonic findings or that divided extracolonic findings into severity categories. From these studies we extracted the sample size; research subject population characteristics; definitions and categorization of extracolonic findings; frequency of IFs in the entire sample; the percentage of research subjects who had any IF; the percentage of subjects who had “significant” or “medically important” extracolonic findings; the percentage of subjects who underwent

serve as a useful indicator of the frequency of IFs in CTC research.

Survey of CT Colonography Research Programs

In addition to trying to ascertain the frequency of IFs in CTC research, we distributed a questionnaire to presenters at the plenary sessions of the 5th Annual Virtual Colonoscopy Symposium (October 2004) (an annual, multidisciplinary international gathering of physicians and imaging scientists investigating CT colonography to reduce colorectal cancer mortality), in

order to determine how IFs in CTC research are handled by colonography research programs. This questionnaire asked principal investigators or their study coordinators the following: what information is discussed with human subjects, prior to their CT colonography research exam, relating to extracolonic findings (e.g., the potential for extracolonic findings, whether extracolonic findings will be communicated to the research subjects, and the potential for cost associated with the medical work-up of an IF); how medically significant extracolonic findings are conveyed to the subject or their physician; how and when the search for IFs is performed; and how such information is summarized or presented to research subjects in the consent process.

Results

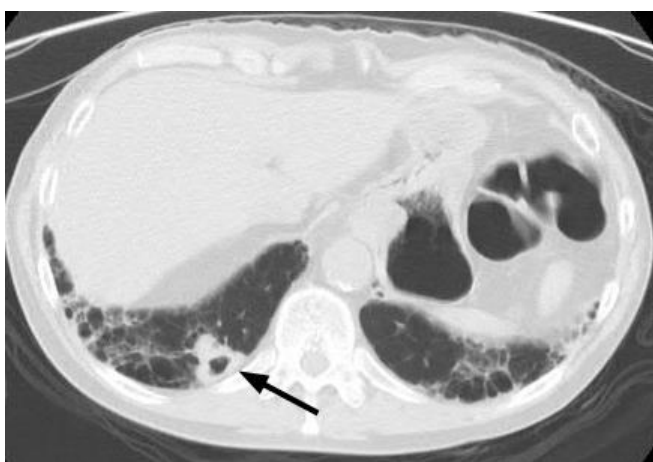
Literature Review

Our research review identified 9 studies that described extracolonic findings in CT colonography in more

than 100 consecutive research subjects, used a well-defined subject population, and included a categorization of gravity for the extracolonic findings (Table 1). Most studies defined significant extracolonic findings as imaging findings requiring further investigation, having an impact on the medical treatment the subject was receiving (based on the correlation of the findings with the subject’s symptoms or history), or requiring image-guided or operative treatment.

In general, slightly more than half of research subjects in screening or asymptomatic populations had any type of extracolonic finding (median, 52 percent; weighted mean, 53 percent of research subjects).⁷ In contrast, when research subjects were comprised of symptomatic patient populations or patients with

Figure 1



69-year-old male ex-smoker with a history of pulmonary fibrosis underwent CT colonography for research purposes. The transverse image of the lower chest shows a large pulmonary nodule with cavitation (arrow). The biopsy demonstrated multifocal squamous cell carcinoma. The subject was not a candidate for any curative therapy, and he died within six months, succumbing to different pulmonary complications. In this instance, the discovery of a significant incidental finding resulted in lead time bias, and no change in mortality.

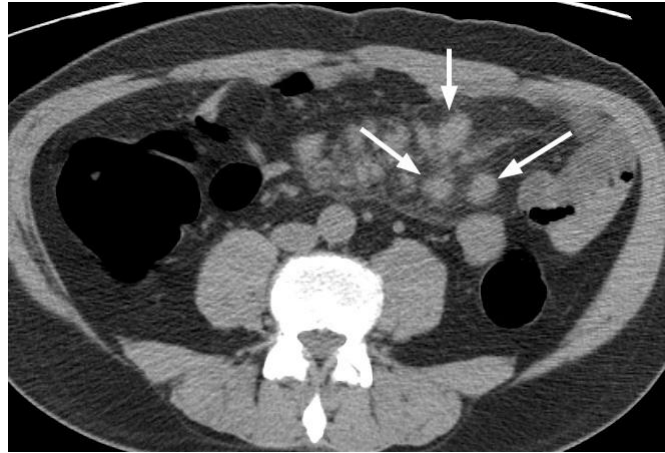
follow-up visits, further investigation, or surgery as a result of extracolonic findings; and the estimated added cost per subject incurred as a result of the work-up of IFs. We realize that not all extracolonic findings are truly “incidental” because some studies aim to collect data on extracolonic findings (e.g., the National CT Colonography Study has a sub-aim to examine the frequency of extracolonic findings in CT colonography exams). However, in the great majority of CTC studies, extracolonic findings are indeed beyond the aims of the study and are IFs. We felt that the spectrum of subject populations in our literature analysis reflected the spectrum of populations studied in CT colonography research as a whole, and the frequency of extra-colonic findings in our sample would thereby

known colorectal disease, this frequency was higher (and could even be the large majority of subjects; median, 69 percent; weighted mean, 59 percent of research subjects).⁸ Across all studies, research subjects often had more than one IF. However, the frequency of extracolonic findings of potential medical significance was significantly less. Across CT colonography studies examining asymptomatic research subjects, the proportion of research subjects having a significant extracolonic finding that necessitated further investigation or medical/surgical treatment was eight percent weighted average (median nine percent; range 5-11 percent), with the largest study of over 1200 patients having five percent of subjects with such findings.⁹ In studies examining symptomatic subjects, 16 percent (weighted average) of research subjects (median 17 percent; range 8-25 percent)¹⁰ had a significant extracolonic findings that necessitated further investigation or medical/surgical treatment. The number of subjects who underwent any subsequent type of medical or surgical intervention was highly variable, ranging from 1.3-2.3 percent in asymptomatic subject groups¹¹ to 6-19 percent in symptomatic subject groups.¹² The mean for both groups was 7.8 percent (SD 6.3 percent). Very few subjects in the asymptomatic population underwent surgery as result of identification of IFs (<2.3 percent).¹³ This percentage was higher (up to 15 percent) in the symptomatic population.¹⁴

While the mean cost for the work-up of IFs appears minimal on a per-subject basis (approximately \$25-\$34, based on Medicare reimbursement rates), these estimates do not include the therapeutic cost of treating the discovered abnormality (e.g., nephrectomy for renal cell carcinoma). Moreover, the financial burden incurred from the work-up and treatment of extracolonic findings can be significant for any individual. For example, one prominent radiologist underwent a CT colonography exam that resulted in negative colonic findings, but identified multiple indeterminate extracolonic findings. He then underwent multiple investigations to elucidate the nature of these indeterminate imaging findings, including two invasive procedures (a thoracoscopy and a liver biopsy). None of these addi-

tional tests or procedures resulted in the identification of a serious or acute disease, but his health care costs exceeded \$50,000 and included in-hospital recovery time.¹⁵

Figure 2



50-year-old asymptomatic male with no comorbidities underwent CT colonography for research purposes. The transverse image of the abdomen shows incidentally noted mesenteric adenopathy (arrows pointing to enlarged lymph nodes). The colon itself was negative for any precancerous lesions. A CT-guided biopsy demonstrated follicular B-cell lymphoma. The subject was treated with chemotherapy and responded with complete remission. He continues to be completely free of disease after seven years.

The medical importance of even extracolonic findings categorized as “significant” — that is, those for which most physicians would agree that further investigation or medical/surgical intervention is needed — can be highly variable. Some findings reported as highly significant will eventually prove medically insignificant after further work-up is performed. Some of the most common significant IFs, such as renal cell carcinomas or large abdominal aortic aneurysms, are easily treatable with clear benefit to the subject. However, the impact of discovering an advanced cancer (to which the subject will eventually succumb) is less clear, e.g., a patient with an advanced lung cancer that is detected at a late stage (Figure 1). In this instance, research CTC exams result in lead time bias (i.e., the screening test detects a disease before it is symptomatic, but this earlier identification and treatment of the disease does not result in change in outcome or time of death).

CT colonography research exams can detect some early cancers that can be treated at curable stages (Figure 2). A recent meta-analysis examined the identification of early cancers (i.e., surgically resectable

cancers without nodal or distant metastases) across published colonography studies, and found that such cancers were identified in 0.9 percent of research subjects (or 0.6 percent, when excluding elderly and frail patients who likely could not undergo curative surgery because of comorbid conditions),¹⁶ and noted that this frequency is similar to the 0.7 percent estimated frequency of limited (i.e., non-metastatic) colon cancers detected by colonoscopy in asymptomatic adults.¹⁷

Figure 3



57-year-old asymptomatic female with no comorbidities underwent CT colonography for research purposes. The transverse image of the abdomen shows 4 cm cystic adnexal structure in the pelvis. The colon itself was negative for any precancerous lesions. Following the identification of this significant incidental finding, a transvaginal ultrasound was performed, which showed septations suspicious for a malignant, cystic ovarian neoplasm. She underwent a bilateral salpingo-oophorectomy without complication, with histopathology demonstrating a benign ovarian serous cystadenoma.

The study of 1253 asymptomatic subjects we included in our review discovered eight cases of unsuspected extracolonic malignancy (one case per 200; 0.6 percent).¹⁸ Similarly, Thomas Gluecker et al. reported uncovering at least seven unsuspected neoplasms in a healthy screening population of 681 subjects (one percent).¹⁹ Amy Hara et al. reported discovering two renal cell carcinomas that necessitated curative surgery in a smaller screening sample (264 patients).²⁰

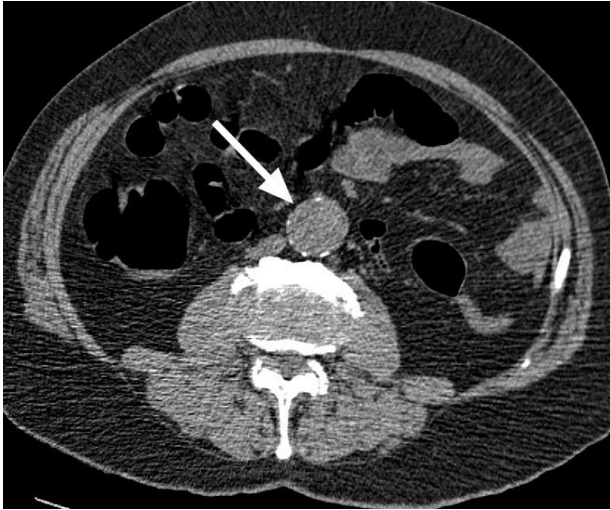
While research CTC may discover extracolonic malignancies at an early (treatable) stage, the CT colonography imaging technique does not permit detection and characterization of all intra-abdominal pathologies. This is because research CTC exams generally employ a low radiation dose without intravenous contrast, while clinical abdominal CT exams generally

use a standard radiation dose and intravenous contrast. Hara et al.²¹ reported that 12.5 percent (3/24) of subjects undergoing research CTC had extracolonic findings that were radiographically occult (i.e., not detectable) on their low-dose, non-contrast research CTC exam, but which were subsequently seen on normal-dose, contrast-enhanced CT done within one year. Changes in acquisition techniques therefore directly affect the number and type of significant IFs referred for further evaluation. Adrian Spreng et al. examined symptomatic subjects referred for colonoscopy using normal radiation doses and intravenous contrast in some CTC exams.²² He found that with these changes in acquisition technique and in his subject population, the proportion of subjects with IFs was very large (75 percent) and that nearly one-fifth of subjects underwent treatment for an extracolonic finding.²³ Consequently, research subjects need to be informed of the potential for significant extracolonic findings according to the type of exam they are undergoing, and should be cautioned that imaging of the abdomen and pelvis may not reveal all abnormalities.

While the clinical import of many significant extracolonic findings is understood (e.g., abdominal aortic aneurysms or lymphomas), there are many findings such as lung nodules, ovarian masses, and low-attenuation masses in solid organs that are indeterminate in nature, thus requiring further imaging or surveillance (Figures 3 and 4).²⁴ In addition, most grading schemes for the severity of extracolonic findings include a “medium” significance category in which the import of an IF depends upon the clinical symptomatology (e.g., gallstones, kidney stones, hiatal hernia of the stomach, and diverticulosis of the colon). Extracolonic findings in the musculoskeletal system are rare and usually clinically insignificant, except for the rare spondylolysis or unsuspected osseous metastases.²⁵ The frequency of IFs in CT colonography research is similar to the frequency in other studies using unenhanced CT of the abdomen and pelvis.²⁶

Radiologists have developed a formal classification system for extracolonic findings in patients undergoing CT colonography for their own health care (i.e.,

Figure 4



73-year-old asymptomatic male with no comorbidities underwent CT colonography for research purposes. The transverse image of the abdomen shows incidentally found 3.3 cm aortic aneurysm. The primary physician was communicated, and the patient was advised to seek annual ultrasound surveillance of the aortic aneurysm.

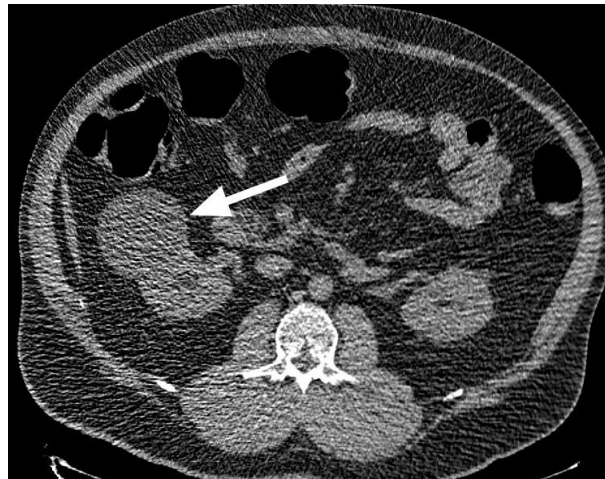
not research subjects).²⁷ The Virtual Colonoscopy Working Group proposed a reporting system (C-RADS) with five categories named E0 through E4 in increasing order of clinical importance. The E0 category includes exams in which evaluation of extracolonic abnormalities is severely limited by imaging artifacts. E1 denotes normal extracolonic structures or normal anatomic variants, and E2 encompasses findings that do not merit further work-up or management (Figure 5). Examples of E2 include simple liver or renal cysts, vertebral hemangiomas, and asymptomatic cholelithiasis. While E0, E1, and E2 correspond to imaging findings of low medical significance, E3 is used for findings of indeterminate significance such as a complex renal cyst. Findings of indeterminate significance are findings, which are probably (but not definitively) benign, and for which further work-up or treatment might occur at the discretion of the patient and her physician.

All potentially important findings are classified in the E4 category, including solid renal masses, lymphadenopathy, aortic aneurysms, and non-uniformly calcified pulmonary nodules greater than or equal to 1 cm.

The effects of C-RADS categorization were recently reported by two practices, one reporting that the incidence of E4 lesions was 2.2 percent,²⁸ and the other reporting a significant difference in the frequency of E4 lesions between screening and non-screening populations (with the former having more).²⁹

We also reviewed the literature on whether potentially significant extracolonic findings are communicated to subjects or their primary care physicians. Perry Pickhardt et al. did not relay IFs directly to subjects, but communicated such findings to their primary care physicians.³⁰ Judy Yee et al. also notified the primary care physician by telephonic communication, but no official report was generated.³¹ Similarly, Hara et al. communicated by sending letters notifying the primary care physician when a highly important lesion was found and wrote a formal CT report.³²

Figure 5



57-year-old asymptomatic male underwent CT colonography for research purposes. The transverse image of the abdomen shows a 6.5 cm simple renal cyst that was categorized as an insignificant finding. No follow-up was recommended.

While it may appear unusual that CTC researchers have reported contacting subjects' physicians rather than subjects themselves, a report by Giovanni Casola and colleagues presented at the Fourth International

Table 1

Incidental Extracolonic Findings in CT Colonography Research

AUTHOR	RESEARCH SUBJECT POPULATION	SAMPLE SIZE	RISK FOR COLON CA	CATEGORIZATION OF INCIDENTAL FINDING SEVERITY	DEFINITION OF SIGNIFICANT IFs
Pickhardt et al. (2003)	Screening	1253	Asymptomatic (Normal or Increased Risk)	High, Moderate, and Low Potential	Require Surgical or Medical Treatment or Further Investigation
Gluecker et al. (2003)	Screening	681	Asymptomatic (Increased Risk)	High, Moderate, and Low Potential	Require Surgical or Medical Treatment or Further Investigation
Yee et al. (2005)	Screening	500	Asymptomatic (Normal or Increased Risk)	Important vs. Unimportant	Findings that Necessitated Further Investigation
Chin et al. (2005)	Screening	432	Asymptomatic (Average Risk)	Clinically Relevant or Irrelevant	NA
Hara et al. (2000)	Screening/ Surveillance	264	Asymptomatic (High Risk)	High, Moderate, and Low Potential	Require Surgical or Medical Treatment or Further Investigation
Edwards et al. (2001)	Diagnostic	100	Symptomatic or High Risk	Significant/Insignificant	Require Further Investigation
Khan et al. (2007)	Diagnostic	225	Symptomatic or High Risk	2 Groups	Further Action Taken (Investigation/Hospital Visit/Treatment)
Spreng et al. (2005)	Referred to Evaluate Symptoms by Colonoscopy	102	Symptomatic or High Risk	2 Groups	Finding That Will Either Lead to Further Work-Up or Have an Impact on Therapy
Hellstorm et al. (2004)	Referred to Evaluate Symptoms by Colonoscopy	111	Known or Suspected Colorectal Disease	Major, Moderate, and Minor	Finding That Has a Definite or Potential Major Clinical Importance

Table 1 Continued on Next Page

Symposium on Virtual Colonoscopy exposed the potential for subjects to ignore or delay the work-up of significant IFs if primary care physicians are not contacted.³³ Casola et al. reviewed clinical radiology reports from a group of 1200 self-referred patients who paid out-of-pocket expenses for a screening body CT at a whole-body screening center. These patients had CT reports mailed to them. Casola et al. counted reports that identified “indeterminate or suspicious findings for malignancy” or findings “highly suggestive of malignancy or life-threatening condition” and

contacted these patients five years later.³⁴ Nearly one-third of patients were unaware of their worrisome CT findings from five years before, suggesting that many of these patients never pursued medical consultation or follow-up of worrisome findings. Considering the potentially life-threatening consequence of at least some of these findings, it appears that leaving the evaluation of these lesions to the discretion of the subject (who may be unaware of their gravity or speed with which the finding should be pursued) is problematic.

Table 1

Incidental Extracolonic Findings in CT Colonography Research (Continued)

SUBJECTS WITH IFs (%)	MEAN IFs/PATIENT (TOTAL IFs/# OF PATIENTS)	SUBJECTS WITH HIGHLY IMPORTANT IFs (%)	SUBJECTS WITH ANY FURTHER TREATMENT BASED ON AN IF	SURGICAL INTERVENTION BASED ON AN IF	MEAN COST PER SUBJECT ACROSS THE STUDY
NA	NA	56 (5%)	NA	2 (0.2%)	NA
469/681 (69%)	1.8 (858/469)	71 (10%)	9/681 (1.3%)	7/681 (1%)	\$34
315/500 (63%)	1.9 (596/315)	45 (9%)	13/500* (2.6%)	5 (1%)	\$28
118/432 (27%)	1.2 (146/118)	32 (7%)	NA	NA	\$24
109/264 (41%)	1.4 (151/109)	30 (11%)	20/264* (8%)	6 (2.3%)	\$28
15/100 (15%)	1.1 (16/15)	8 (8%)	6/100* (6%)	2 (2%)	NA
116/221 (52%)	1.8 (211/116)	24 (11%)	NA	12 (5.3%)	\$153
91/102 (89%) 75% IV 25% No IV	3.3 (303/91)	26 (25%)	19/102 (19%)	15 (15%)	NA
94/111 (85%)	2.5 (232/94)	26 (23%)	14/111 (13%)	NA	NA

* Includes both subjects who underwent treatment as well as those who underwent subsequent imaging follow-up.

Survey of CT Colonography Research Programs

To study how CTC research programs have handled IFs, we surveyed by e-mail the CTC researchers presenting during the plenary session of the 5th Annual Virtual Colonoscopy Symposium (October 2004, n=25). Speakers at the plenary sessions of this conference generally represented academic medical centers with large, active research programs in colonography. Ten principle investigators (7 U.S.; 3 European) or their study coordinators (n=2; both U.S.) responded to the survey. All research programs (12/12; 100 percent) reported having a radiologist examine every CT

dataset for potentially significant extracolonic findings, 92 percent (11/12) on the same day that the CT research exam is performed. A slight majority (7/12; 58 percent) reported all extracolonic findings, whereas 42 percent (5/12) reported only potentially significant extracolonic findings. The mechanism of conveying extracolonic findings varied widely, and a slight majority (7/12; 58 percent) reported using two or more methods to relate potentially significant extracolonic findings to research subjects and/or their physicians. Eighty-three percent (10/12) of researchers generated a clinical report to detail extracolonic findings, with

slightly less (8/12; 67 percent) contacting the subject's physician directly (by letter 3/12, 25 percent; or phone/fax 5/12, 42 percent). Forty-two percent (5/12) of researchers contacted the subject directly. Thirty-three percent (4/12) of studies generated only a clinical report.

In contrast to what the patient was told verbally during the consent process, only 42 percent (5/12) of researchers reported that their written consent form told subjects if and when extracolonic findings would be reviewed, and only 17 percent (2/12) of consent forms told subjects how potentially significant extracolonic findings would be reported to them.

All but one institution (11/12; 92 percent) discussed the potential for discovering incidental (extracolonic) findings of medical significance verbally during the informed consent process. Seventy-five percent (9/12) of researchers discussed the potential for needing extra medical tests to address IFs discovered, while a similar number discussed the non-specificity of image findings at CT colonography (explaining that further testing or imaging could be necessary). In contrast to what the patient was told verbally during the consent process, only 42 percent (5/12) of researchers reported that their written consent form told subjects if and when extracolonic findings would be reviewed, and only 17 percent (2/12) of consent forms told subjects how potentially significant extracolonic findings would be reported to them. Only one of the researchers surveyed reported that studying extracolonic findings was a primary aim of his research colonography studies.

Discussion

Extracolonic findings occur frequently in CT colonography research. Slightly more than half of asymptomatic screening patients have any extracolonic finding, and the majority of patients with symptoms or known colorectal disease possess extracolonic findings (Table 1). Significant extracolonic findings requiring further investigation or medical or surgical intervention occur in about 5-8 percent of research subjects in an asymptomatic screening population and in about 16 percent in symptomatic populations. The number of research subjects undergoing subsequent medical or surgical intervention was 1.3-2.3 percent in asymp-

tomatic populations and 6-19 percent in symptomatic populations. Since 4-6 percent of asymptomatic subjects have adenomatous polyps of 10 mm or more, the target polyp size for most CT colonography research studies,³⁵ the percentage of asymptomatic subjects with a large polyp parallels the percentage of subjects with an incidental finding of potential medical significance.

In the context of incidental findings encountered during CT colonography research, significant extracolonic findings encompass nearly all incidental findings of potential medical significance, the sole exceptions being the discovery of benign colonic diseases such as diverticulitis or colitis. All colonography research programs queried report significant IFs to subjects and/or their physicians (usually on the day of the CT research exam). Many

programs generate a clinical report for each research exam, detailing these findings. Such practices have arisen independently in different laboratories, probably because CTC research has been conducted by academic physician radiologists, who are familiar with the clinical follow-up and consequences of IFs. Examining CT research scans for IFs and reporting them represents a non-trivial investment in time, study design, and resources by CTC research teams. However, CTC researchers seem to feel an obligation to do this. The moral and legal underpinnings for this obligation are outlined fully in the consensus document described earlier, printed at the beginning of this symposium,³⁶ and include respect for persons and the researcher's duty to warn of foreseeable harm. Another basis for this obligation is the reality of subjects' expectations. Judy Illes et al. have also shown that subjects overestimate the potential benefit that research exams may provide.³⁷ They demonstrated that even when subjects are informed that research imaging studies will not be systematically reviewed by imaging clinicians, the majority of subjects still expect research scans to detect pathology, if present,³⁸ and that more than 90 percent of subjects wanted IFs communicated to them.³⁹

While all CT colonography researchers surveyed reported review of research CT studies for potentially significant extracolonic findings, a range of methods is used to contact subjects or their physicians about such findings. Although most researchers discuss with the subject the potential for extracolonic findings of medical significance and the potential for further work-up

based on their research exam verbally as part of the informed consent process, the methods used for conveying significant IFs, and their potential benefits and burdens, are not routinely stated in consent forms. CTC consent forms have generally detailed the risks associated with the CTC procedure itself; thus, inclusion of IF language would bring written documents into harmony with the widespread recognition of the importance of IFs in CTC research and the spirit of federal regulations that require the consent form to explain all risks that the subject may face due to participation in research.⁴⁰

Development of a well-established and clearly articulated mechanism to notify subjects and their physicians of potentially important IFs is necessary for research subjects to realize any potential benefit from IFs. The whole-body CT screening experience reported by Casola suggests that patients and subjects

able to ask subjects at the time of consent who their primary physician is, and if they would object to IFs being reported to this individual.

CTC research will continue to face the IFs problem unavoidably. A recent study conducted by Ari I. Jonisch et al. investigated whether high-attenuation renal cysts could be differentiated from renal cell carcinoma with unenhanced CT,⁴³ the technique which is employed in most CTC studies. The prevailing dogma was that only renal masses of low x-ray density could be considered to be benign. However, Jonisch et al. found that a homogenous renal mass, which had a very high x-ray density (measuring greater than 70 HU) had a greater than 99.9 percent chance of representing a benign hemorrhagic renal cyst rather than a renal carcinoma. Similarly, pulmonary nodules are one of the most common IFs at CTC, but the Fleischner Society of Thoracic Radiology recently recommended

When research images are acquired that are anatomically and clinically meaningful and IFs are anticipated, researchers should develop a plan for detecting and communicating IFs to research subjects and their physicians.

Further, the benefits and burdens of IFs should be discussed with subjects during the informed consent process, with the mechanism for contacting them about IFs of potential medical significance clearly communicated to subjects in both discussions and written consent documents.

may ignore or delay the work-up of significant IFs if only patients are contacted.⁴¹ Most CTC research programs in our survey contacted the subject's primary care physician directly or via an official medical report in the medical record, so that a physician with a therapeutic relationship with the subject could explain the urgency and importance of the findings, review potential alternatives for surveillance or therapy, and integrate recommendations for surveillance or treatment into the patient's overall health care. Surprisingly, only 42 percent (5/12) of research programs contacted research subjects directly to relate incidental findings. More researchers may wish to notify subjects directly of IFs out of reciprocity, respect for the fact that IFs may reveal private health information, and the desire to maximize potential research benefit to subjects as the issue of IFs in human subjects research gains attention.⁴² Because the informed consent process is the natural setting in which to explain how subjects will be notified in case an incidental finding of potential medical significance is detected, it may be reason-

that indeterminate pulmonary nodules less than 4 mm (in the absence of known neoplastic disease or associated high-risk factors) need not be followed by surveillance imaging, as such nodules have a 99 percent chance of being benign.⁴⁴ Studies like these can help guide the radiologist evaluating an IF, in understanding the necessity for further imaging or surveillance given non-specific extracolonic findings, or in recommending the next appropriate imaging study.

Researchers designing CTC studies will also continue to face IF issues in determining the technique and acquisition parameters to be used for acquiring CTC images, as those study attributes directly affect the frequency and type of IFs discovered in CTC research.⁴⁵ Using intravenous contrast will increase the visual conspicuity of more intra-abdominal findings and convey greater information and specificity than non-contrast exams. On the other hand, ultra low-dose CT techniques can severely limit meaningful visualization of solid organs, reducing the expected frequency of IFs. In other types of imaging research,

changing the field of view or using a limited number of pulse sequences or contrast agents could potentially be used by researchers as a means of reducing research-related IFs, if such changes do not affect the ability to successfully carry out the primary aims of the study.

The approach to IFs in CTC research offers a useful paradigm for handling IFs in imaging research more generally. When research images are acquired that are anatomically and clinically meaningful and IFs are anticipated, researchers should develop a plan for detecting and communicating IFs to research subjects and their physicians. Further, the benefits and burdens of IFs should be discussed with subjects during the informed consent process, with the mechanism for contacting them about IFs of potential medical signif-

primary care physician. While a majority of researchers surveyed discuss the benefits and burdens of IFs with subjects verbally during the informed consent process, the written consent forms usually did not address IFs and how they would be communicated back to the research subject.

We expect the medical significance of many IFs will change, given evolving research and increased experience with indeterminate findings on unenhanced, low-dose CT in asymptomatic screening populations. We anticipate that subjects participating in many other types of imaging research studies expect and would benefit from systematic review of anatomically meaningful research images, but the frequency of IFs across imaging research studies is unknown and requires

Because the informed consent process is the natural setting in which to explain how subjects will be notified in case an incidental finding of potential medical significance is detected, it may be reasonable to ask subjects at the time of consent who their primary physician is, and if they would object to IFs being reported to this individual.

icance clearly communicated to subjects in both discussions and written consent documents. Many types of imaging research studies may not generate anatomically or clinically meaningful images, in which case IFs would be expected to be rare.

Conclusions

Extracolonic IFs are frequently encountered in CTC research, far surpassing colonic findings in frequency. While the majority of research participants have an IF, only about 5-8 percent of subjects in an asymptomatic screening population have an extracolonic finding of potential medical significance and 1.3-2.3 percent of such subjects eventually receive some kind of medical or surgical intervention. In symptomatic populations, about 16 percent of subjects have an incidental finding of potential medical significance, with 6-19 percent receiving such an intervention. The frequency of IFs in CT colonography depends both on research subject factors (e.g., asymptomatic vs. high-risk populations) and CT acquisition methods (radiation dose and intravenous contrast usage). While the effect of discovering IFs can be life-saving, IFs can also cause research subject anxiety, morbidity, and significant cost.

All CT colonography research programs surveyed anticipate and actively look for IFs. Most communicate IFs by generating a report or by contacting the

further investigation. Moreover, the relative medical benefit vs. burden of disclosing such potentially important IFs is difficult to determine. Despite these ambiguities, CTC research practice clearly shows that early treatable cancers are detected and that subjects can benefit from detection and disclosure of IFs in a timely fashion.⁴⁶ Imaging researchers should consider the potential frequency of IFs arising from their study design, in addition to considering how IFs will be detected, evaluated, and conveyed to research subjects. When IFs of potential medical significance are anticipated, research subjects should be informed of the potential for discovering such findings, their benefit and burden, and how any important findings will be relayed to them.

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