Colorectal Cancer Screening

Quality and Benchmarks

Aasma Shaukat
John I. Allen
Editors

Springer

Colorectal Cancer Screening

Aasma Shaukat • John I. Allen
Editors

Colorectal Cancer Screening

Quality and Benchmarks

Springer

Editors
Aasma Shaukat
Department of Gastroenterology
Minneapolis VA Medical Center
Minneapolis
Minnesota
USA

John I. Allen
Section of Digestive Disease
Department of Medicine
Yale University School of Medicine
New Haven
Connecticut
USA

ISBN 978-1-4939-2332-8 ISBN 978-1-4939-2333-5 (eBook)
DOI 10.1007/978-1-4939-2333-5

Library of Congress Control Number: 2014956665

Springer New York Heidelberg Dordrecht London

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Dr. Shaukat: I would like to thank my husband Dan for his love and endless support, and my children Myra and Rayaan for their patience
Dr. Allen: I would like to thank my wife Carolyn, and my children Jennifer and Joshua

Foreword

Colorectal cancer (CRC) screening originated from the work of Dukes at St. Marks Hospital in London in the 1930s who developed a staging system for CRC and observed that survival correlated with early stage diagnosis and treatment. He and Lockhart-Mummery, unbeknownst to them at the time, also provided the basis for today's CRC screening goals of detecting both curable CRC and preexisting adenomas by demonstrating the link between the two. These concepts were challenged for decades until FOBT randomized trials showed that CRC screening reduced CRC mortality, the colonoscope was introduced into clinical practice, colonoscopic polypectomy was shown to be feasible, and CRC incidence was observed to be reduced by colonoscopic polypectomy.

This amazing series of developments, beginning in the 1970s, culminated in 2012 with the report of a reduced CRC mortality following colonoscopic polypectomy, which proved the concept of the polyp-cancer sequence and the effectiveness of screening for both CRC and adenomas. This resulted in the explosion of CRC screening worldwide which we are seeing today. In the USA, CRC screening is now being performed by about two thirds of the at-risk men and women, according to a recent CDC report. Most (90%) of those screened in the USA have been with colonoscopy, while the majority of those screened elsewhere have been primarily with FIT, and to a much lesser extent with flexible sigmoidoscopy. All roads lead to colonoscopy, whether as a screening test or for diagnosis in those with a positive first step screening test.

If screening is to be successful, it needs to be part of a multistep "package," which includes screening, timely diagnosis (pathology of polyps, cancer), timely treatment (cancer surgery, polypectomy) and follow-up surveillance. If one step in the process fails, the impact will be lessened or lost. At each step, quality in the performance is a critical factor. For screening colonoscopy, quality benchmarks correlate directly with the frequency of interval cancers. The good news is that interval cancers following average risk screening colonoscopy occurs at a rate of about 1/1000 exams. The bad news is that 5% of the cancers are missed. The interval cancer rate is even greater in the high risk post-polypectomy patients (1/200), and is related most often (70%) to missed lesions and incomplete polypectomy. Clearly, quality performance is required. When the "simple" FOBT card was introduced in

the 1970s, there was no quality control. A quality control window was added later but interpretation was often inaccurate. Quality performance is also critical for FIT since a false positive triggers off an unnecessary colonoscopy, and a false negative has other consequences. Newer tests such as CTC and stool DNA testing have their own unique quality performance considerations.

With the field of CRC screening moving dramatically from its early rudimentary stage to the present widespread high technology stage, we need to be certain that maximum effectiveness is achieved by high quality performance at each step. In this book an experienced and thoughtful group of leaders in CRC screening have identified the key issues in quality performance. The authors have cast a wide net in this area, with comprehensive presentations for every screening modality. In addition, issues related to surveillance, sedation, pathology, medical-legal aspects, and cost-effectiveness have been addressed. Concrete examples of various programs and initiatives provide excellent "nuts and bolts" tools for guidance in this increasingly complex field.

It has become clear that we need to step back and take stock of how we are to move forward in CRC screening. The latest data indicates that there has been a progressively downward trend in CRC incidence and mortality in recent decades. The annual "Report to the Nation" demonstrated that a major factor in this trend is screening. In the USA it is "opportunistic" rather than within the framework of a nationally organized program, which makes quality performance programs more compelling. The US screening rate is the highest in the world and the incidence/mortality reduction is also the highest worldwide. A campaign has been initiated nationally by the ACS and CDC to further increase the US screening rate to 80% by 2018 and to help eliminate the current racial disparities. This accelerated screening needs to be accompanied by quality performance in order to achieve maximum effectiveness. Each man and woman who accepts screening should be offered a test of the highest quality that provides the greatest probability to have CRC diagnosed at an early stage, or even to have CRC prevented altogether. Everyone who has been touched by cancer in a loved one understands the human tragedy that can be averted. We need to screen. Any test is better than none, and the best test is the one that gets done, and done well! This book tells us how to do it and what gaps there are to be filled in the future. It is a state-of-the-art treatise on quality performance of the entire range of screening and surveillance and their related issues. It is a must read for everyone engaged in this effort.

Sidney J. Winawer, MD

Paul Sherlock Chair in Medicine Gastroenterology and Nutrition Service
Department of Medicine Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College
Cornell University

Preface

Colorectal cancer (CRC) is the third most common cancer in men and women, and the second leading cause of cancer-related death in the USA. Screening is highly effective in reducing the risk of developing and dying from CRC. There is a menu of screening options that includes tests that detect cancers (stool-based tests, imaging) and tests that detect both cancers and precancerous lesions with the option of concurrent removal and thus cancer prevention (colonoscopy). Regardless of modality, the most effective screening program is one that is high quality, safe, cost-effective, readily accessible, highly acceptable, and actually performed. Establishing quality metrics and benchmarks for all types of CRC screening and surveillance tests is important for delivering high value care.

This textbook will provide a comprehensive overview of quality metrics and methods used to improve quality for all major modalities of CRC screening. It will introduce the readers to the evidence of effectiveness behind various CRC screening modalities: stool-based tests (Fecal Occult Blood, Fecal Immunochemical and Fecal DNA tests), flexible sigmoidoscopy, colonoscopy, and CT colonography. It will review the latest guidelines for CRC screening, compare differences among the five major national guidelines and highlight the need for valid quality and cost indicators. The main focus will be colonoscopy since most quality indicators and analyses have focused on this modality of screening and surveillance, but one chapter will be devoted to quality indicators of other screening modalities. Differences between process and outcome measures will be highlighted and a small but valid set of recommended national measures will be listed.

Contents

Contributors

David A. Ahlquist Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Dennis J. Ahnen Department of Medicine, University of Colorado School of Medicine, Denver, CO, USA

John I. Allen Department of Medicine, Yale University School of Medicine, New Haven, CT, USA

James E. Allison Department of Internal Medicine/Gastroenterology, University of California San Francisco, San Francisco, CA, USA

Kenneth P. Batts Minnesota Gastroenterology, Minneapolis, MN, USA

Sarah Faye Blankstein Seattle, WA, USA

Joel V. Brill Predictive Health LLC, Paradise Valley, AZ, USA

Lawrence J. Burgart Minnesota Gastroenterology, University of Minnesota College of Medicine, Minneapolis, MN, USA

Abraham H. Dachman Department of Radiology, The University of Chicago Medical Center, Chicago, IL, USA

Jason A. Daniels Minnesota Gastroenterology, Minneapolis, MN, USA

H. Parry Dilworth Department of Pathology, Hospital Pathology Associates, Allina Health, Minnesota Gastroenterology, Minneapolis, MN, USA

Andrew D. Feld Department of Gastroenterology, University of Washington, Group Health Cooperative, Seattle, WA, USA

Kayla Allison Feld Seattle, WA, USA

Callum G. Fraser Centre for Research into Cancer Prevention and Screening, University of Dundee, Dundee, Scotland

Michael Frist Atlanta Gastroenterology Associates, LLC, Atlanta, GA, USA

Ziad F. Gellad Division of Gastroenterology, Duke University Medical Center & Durham Veterans Affairs Medical Center, Durham, NC, USA

Victoria Gómez Department of Gastroenterology, Mayo Clinic, Jacksonville, FL, USA

Stephen P. Halloran Clinical Biochemistry, Royal Surrey County Hospital, University of Surrey, Guildford, Surrey, UK

John M Inadomi Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

John B. Kisiel Department of Internal Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Paul Martin Knechtges Department of Radiology, Medical College of Wisconsin, Milwaukee, WI, USA

Elizabeth G. McFarland Department of Radiology, SSM St. Joseph West Medical Center, Lake St. Louis, MO, USA

Steven J. Morris Atlanta Gastroenterology Associates, LLC, Atlanta, GA, USA

Patrick M. O'Reilly Minnesota Gastroenterology, PA, St. Paul, MN, USA

Swati G. Patel Department of Internal Medicine, Division of Gastroenterology, University of Michigan, Ann Arbor, MI, USA

Douglas K. Rex Department of Gastroenterology/Hepatology, Indiana School of Medicine, IU Hospital, Indianapolis, IN, USA

chuyler O. Sanderson Minnesota Gastroenterology, Minneapolis, MN, USA

Marc Sonenshine Atlanta Gastroenterology Associates, LLC, Atlanta, GA, USA

Ashish K. Tiwari Department of Internal Medicine, Michigan State University (MSU), East Lansing, MI, USA

Michael Bradley Wallace Department of Gastroenterology and Hepatology, Mayo Clinic Florida, Jacksonville, FL, USA

Karen J Wernli Group Health Research Institute, Seattle, WA, USA

Judy Yee Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA

Graeme P. Young Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, SA, Australia

Ann G. Zauber Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

About the Editors

Dr. Shaukat is a gastroenterologist and a clinical researcher. She received her medical degree at The Aga Khan University Medical College in Pakistan. She then matriculated to Johns Hopkins School of Public Health where she received an M.P.H. in International Health and Epidemiology. She conducted a gastroenterology fellowship at Emory University School of Medicine. She is currently Associate Professor in the Department of Medicine, Division of Gastroenterology at the University of Minnesota and Section Chief of Gastroenterology at the Minneapolis Veterans Affairs Healthcare system.

Dr. Shaukat has numerous publications on epidemiology, molecular markers and outcomes of colorectal cancer, quality of colonoscopy and colon cancer screening. She is an invited speaker at national and international scientific meetings on quality of colonoscopy and benefits of colon cancer screening. Dr. Shaukat has an active research program through federal funding, and continues to study colon cancer screening and prevention.

Dr. Allen grew up in New Jersey, upstate New York and Albuquerque, New Mexico. He graduated from Rice University in 1973 and the University Of New Mexico School Of Medicine 1977. He completed internship, residency in Internal Medicine and Gastroenterology Specialty training at the University of Minnesota (Minneapolis). He then spent 10 years on the Academic Faculty in the Department of Medicine in Minnesota attaining the rank of Associate Professor of Medicine while conducting clinical and laboratory research in the fields of alcoholic hepatitis and colon cancer. In 1991 he was recruited to be Associate Director of the Virginia Piper Cancer Center at Abbott Northwestern Hospital (Minneapolis) and joined a private gastroenterology practice. From 1991–2013 Dr. Allen helped build this single specialty GI practice into Minnesota Gastroenterology, one of the largest GI practices in the country and helped develop their nationally known Quality Improvement program. He also worked closely with leadership in Allina Health, a large Integrated Delivery System in the Twin Cities. He currently Chairs the Quality Committee of Allina Health and is on their Board of Directors. In April 2013, he left community practice to become Clinical Chief of Digestive Diseases and Professor of Medicine at Yale University School of Medicine.

For the last decade, Dr. Allen has worked in a leadership position with the American Gastroenterological Association (AGA). He was selected to Chair the Clinical Practice and Quality Management Committee of the AGA and led development of clinical quality measures for gastroenterology. He has written extensively on quality improvement in GI and has chaired or co-chaired Task Forces that created many of the GI measures currently in Medicare's Physician Quality Reporting System. He has published and spoken widely about the impact of health care reform on the specialty of gastroenterology and continues to publish about evaluation and management of inherited colon cancer syndromes. In 2014 he became President of the AGA Institute.

Chapter 1
History and Overview of the National Quality Strategy

John I. Allen

Introduction

In March 2011, the Agency for Health Care Research and Quality (AHRQ) published a report detailing a "National Quality Strategy" (NQS) for US health care, as mandated by the Patient Protection and Affordable Care Act (ACA). NQS provides an official blueprint for achieving a high-value health-care system. This blueprint has profound implications for all medical providers and health-care systems in this country and physicians need to understand the basic elements of the strategy and their role in the evolving world of health-care delivery. This chapter provides a background on the history of quality improvement (QI) efforts in medicine, the development of the NQS, and elements that impact the practice of gastroenterology, especially colonoscopy and colorectal cancer (CRC) prevention.

Some of the best medical care in the world is available in USA, yet there is a growing body of evidence that our commitment to deliver coordinated, effective health care to all citizens is below the standards of many other developed countries. The USA spends more per capita than all other countries, yet we lack universal health care and we lag behind other developed countries in terms of life expectancy and many major health outcome measures [1]. Our "healthy life expectancy" (a measure of overall population health accounting for both length of life and levels of ill health) places us 26th among developed countries, a testament to our lack of a national coordinated system of disease and preventive care [1].

To enhance national discussions about coordinating USA's health-care delivery, the Commonwealth Fund established a Commission on High Performance Health Systems in 2005. The commission [2–4], composed of 16 nationally recognized health-care leaders, issued a series of reports beginning in 2006 that defined a

J. I. Allen (✉)
Section of Digestive Disease, Department of Medicine, Yale University School of Medicine, 40 Temple Street, Suite1A, New Haven, CT 06510, USA
e-mail: john.i.allen@yale.edu

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_1

framework for a high-performing health-care system, a series of organizing principles and finally a "roadmap" for reforming health insurance to achieve universal medical coverage.

In their initial report, the commissioners provided background on how we misallocate resources, fail to provide universal medical care, and fall short of delivering maximum value (defined as health outcomes per unit cost). The overarching recommendations from this report include (1) a commitment to a defined national strategy for achieving highest value, (2) a process to implement and refine that strategy, (3) proposals for care delivery through systems that emphasize clinical coordination, and (4) a movement to value-based reimbursement based on metrics that reflect health outcomes, quality of care, access to care, population-based disparities, and efficiency [2–4].

These reports, among many others, provided a foundation for discussions about restructuring health-care delivery in the USA and accelerated the commitment toward a "National Quality Strategy" that was ultimately codified within the ACA signed into law by President Barack Obama in March 2010. With passage of the ACA, the demand for providers and health systems to produce performance and health outcomes measures that are understandable to the lay public, readily available and tied to reimbursement has finally been woven into the core fabric of US medicine.

History of QI in Medicine

A brief history of the QI movement within US medicine is instructive and will help the reader understand current initiatives contained within the ACA, especially the NQS and the "value-based modifier" (VBM) that will form the basis of reimbursement by the Centers for Medicare and Medicaid (CMS), State Medicaid agencies, and many commercial health plans. While innumerable individual initiatives have provided a basis for this QI movement, five key events are highlighted in this chapter.

Ernest Amory Codman

Ernest Codman (1869–1940) was a surgeon at the Massachusetts General Hospital (MGH), a prolific author and the first vocal advocate of the "End Result" system of measuring the quality of medical care (in 1910). His colleagues described him as "maniacally obsessed" with the simple idea that every hospital should follow every patient long enough to determine whether or not their treatment was successful and if not why not [5]. He became so disliked because of his insistence on end result analysis that he resigned from MGH and opened the Codman Hospital (literally down the street). He also advocated analysis of treatment effectiveness (clinical effectiveness analysis or CEA) and recommended tying a surgeon's pay

to outcomes (the original VBM). He even developed the first surgical outcomes registry focused on osteosarcomas based on standardized definitions of disease and containing long-term data on entered cases. His concepts concerning registries helped launch similar efforts in Europe but even today, the concept of registries linking treatment to outcomes remains relatively rare in the USA compared to other developed countries.

Avedis Donabedian

Unlike Codmen, Avedis Donabedian (1919–2000) found a more receptive audience for proposals concerning health outcomes research in the 1960s. An extensive review of his original works was published in the Milbank Quarterly in 2005 [6]. He is credited with founding studies of quality in health-care and medical outcomes research based on the "Donabedian Model" of care. This model described three boxes containing (a) structure, (b) process, and (c) outcome measures and linked by a unidirectional arrow. Health-care systems of any size use this conceptual framework to modify structures and processes to enhance health outcomes. During the 1970s, the Donabedian Model became one of the intellectual cornerstones leading to the rise of evidence-based medicine (EBM) and development of clinical guidelines and care algorithms so prevalent in today's health-care world.

Institute of Medicine

The committee on quality of health care, commissioned by the Institute of Medicine, released seminal reports in 2000, 2001, and 2007 in which they described the importance of medical errors, the dysfunctional health-care system in the USA, and a plan of a "learning health-care system" going forward [7–9]. These reports documented the cost and patient impact of medical errors, elevated the concept of patient safety to national attention, illustrated how our dysfunctional delivery systems add to this toll, and more recently provided a description of a high-value (learning) health-care delivery system. Each of these reports became important in shaping national health-care policy, re-emphasizing the original concepts of Ernest Codman of accountability, performance metrics, and outcomes measurement.

Donald Berwick and the IHI

In the late 1980s, Donald Berwick MD and a group of visionary leaders founded the Institute for Healthcare Improvement (IHI) to promote a systematic, scientifically rigorous approach improving outcomes in medical care. Their most important contribution may be defining the "Triple Aim" of medicine: enhancing patient experi-

ence, increasing the health of a population, and reducing medical costs [10]. IHI has become an influential force in developing health policy and a source of education about process improvement for the USA and many other countries.

CMS Programs and the ACA

CMS has long sought to alter current fee for service (FFS) reimbursement to one based on health outcomes. To that end, CMS created the Physician Quality Reporting System (PQRS: originally called the Physician Quality Reporting Initiative or PQRI) in 2007. PQRS now consists of more than 200 performance measures, mostly of recommended clinical processes, prevention, and care coordination [11]. PQRS is described in more detail later in this chapter and it is tied to the VBM. In the 6 years of existence, less than 30% of eligible providers have participated in PQRS despite reimbursement incentives and various methods of data entry (web interfaces, registries, and administrative claims). As detailed below, CMS can adopt specific measures on a time-limited basis but will sunset measures that do not go through the rigorous definition and vetting process set up by the National Quality Forum (NQF).

Finally, with passage of the ACA, the NQS was mandated by legislation and subsequently codified. It is based on a rich history of QI work as summarized above and has set the nation on a path of public transparency (both quality and cost) and provider accountability. With reimbursement tied to outcomes through both the VBM (direct CMS reimbursement to individual providers) and creation of accountable care organizations (ACO) described below, the need for providers to focus on measurement of their performance has been cemented into our everyday practice of medicine.

National Quality Strategy

The NQS (officially known as the "National Strategy for Quality Improvement in Health Care") is intended to align priorities and efforts of both government and private sector stakeholders to enhance the value of care provided in the USA [12]. NQS was initially published in March 2011 as a result of a legislative mandate included in the ACA and is overseen by the secretary of US Department of Health and Human Services (HHS). It was the culmination of many years of collective work by multiple stakeholders including the NQF, which the HHS enlisted to recommend goals and key measures for each of the six NQS domains. NQF is an independent nonprofit organization that calls for, refines, and endorses standards and measures of health-care quality through a sophisticated consensus approach based on scrutiny of consumers of health care, payers, purchasers, and content experts. Further discussion about the NQF can be found below.

The six domains (priorities) of the NQS include the following:

1. Safer care by reducing harm caused in the delivery of care
2. Engaging patients and family in care decisions
3. Promoting effective communication and coordination of care
4. Promoting effective prevention and treatment practices for leading causes of morbidity and mortality
5. Working with communities to promote healthy living
6. Making care affordable

The NQS's three overarching aims are essentially the "Triple Aim" described above: (a) better individual care, (b) healthier populations, and (c) affordability. A key objective of the strategy is to build a national consensus on how to measure quality so that alignment can occur throughout the health-care industry. To that end, HHS works with CMS reporting initiatives to be sure that data collection is simple, the number of measures is parsimonious, and programs such as PQRS and meaningful use (that defines electronic medical record or EMR standards) can crosswalk. More information about the evolving NQS is available at the www.ahrq.gov/workingforquality website [13].

NQF Contributions to the NQS: National Priorities Partnership and Measures Application Partnership

While the secretary of HHS oversees the NQS, it is shaped, owned, and implemented through the National Priorities Partnership (NPP), an organization with 52 partners from all aspects of the health-care industry. NPP is co-chaired by Bernard Rosof of the Physician Consortium for Performance Improvement (PCPI—a physician-led organization that helps develop performance measures and was convened by the American Medical Association) and Susan Frampton, president of Planetree (a company based in Derby Connecticut, founded in 1978 and organized to study patient needs in health care). Membership can be obtained at http://www.qualityforum.org/Setting_Priorities/NPP/NPP_Partner_Organizations.aspx. NPP provides annual input to the secretary of HHS and is a forum for multiple stakeholders to discuss practical implementation of the NQS. It collaborates with CMS as this agency rolls out multiple federal quality initiatives. Detailed information about NPP can be found in its Field Guide of Resources at www.qualityforum.org/Field_Guide.

The MAP is a public–private partnership convened by NQF created to review performance measures for potential use in federal public reporting and performance-based payment programs and to align measures across multiple federal, state, and private entities. MAP is the first entity of its kind developed to give input to the federal government prior to final rulemaking decisions for programs that affect clinical care measurement. This process is similar to the Relative Value Scale Update Committee that gives input to CMS prior to its final rulemaking decisions about payments for medical services. It is led by a Coordinating Committee and

has four main workgroups including (a) Hospital Workgroup, (b) Clinician Workgroup, (c) Post-Acute Care and Long-Term Care Workgroup, and (d) Dual Eligible Beneficiaries Workgroup.

The workgroups advise the Coordinating Committee on areas of needed measures and the Committee then develops time-limited Task Forces to call for measures. On December 1, 2013, MAP received from HHS a list of 234 measures then currently under consideration for use in 20 federal programs, a variety of public reporting and payment-based reporting programs that cover clinicians, hospitals, and post-acute/long-term care settings. MAP is in the process of aligning all these measures and reducing redundancy across all incentive programs. The MAP Clinician Workgroup specifically is tasked to provide input on measures for PQRS and whether these or other measures will be used in the Physician Compare and VBM initiatives.

Actual measure development occurs through the NQF's Consensus Development Process. Performance measures can be proposed after a call for measures (for a specific topic) is published by NQF. Any recognized medical society, agency, nonprofit, or for-profit company or health system can propose a measure or measure set. The Consensus Development Process involves eight principle steps as follows:

1. Call for Nominations (of measures)
2. Call for Candidate Standards
3. Candidate Consensus Standard Review
4. Public and Member Comment
5. Member Voting
6. Consensus Standards Approval Committee (CSAC) Decision
7. Board Ratification
8. Appeals

Endorsement by NQF now is required for measures to remain in PQRS, Physician Compare, and the VBM program.

Medicare Programs

Currently, there are a variety of CMS programs that are intended to move federal health-care reimbursement away from volume-based payment (FFS) to value-based payment. These include programs at a health system level, hospital level, and provider level. Examples of Medicare programs with measures evaluated by MAP are provided in Table 1.1

Table 1.1 includes examples of gastroenterology (GI)-related measures that might be useful to practices or implemented at a health system or ACO level and used to assess quality in a GI practice. Additional measures under consideration within this process include rate of repeat colonoscopy for poor preps, appropriate age for CRC screening colonoscopy, and several measures related to bundled payment for a colonoscopy episode. Recently, the American Gastroenterological

Table 1.1 Federal and state programs used to migrate to value-based payment

Level of accountability	Name	Description	Examples of GI measures in program
Health system	Medicare Shared Savings Program	Measures ACO care coordination	CG-CAHPS
	Medicare Advantage 5 Star Quality Rating System	Health plan quality incentive program	Rate of CRC screening among plan members
	Medicaid Adult Core Measure Set	Basic quality metrics for Medicaid patients	Flu shots, BMI, CG-CAHPS, monitoring of persistent medications
	Quality Rating System for Qualified Health Plans for Insurance Exchanges	Monitors health plans for meeting ACA standards	CAHPS, Access to specialists, cultural competency, CRC screening, weight management
Clinician performance	PQRS	1.5–2 % reduction in Medicare payments beginning 2015	CAHPS, CRC screening, polyp surveillance interval normal exam, surveillance interval in patients with prior adenoma. Adenoma detection rate added in 2014 (not NQF endorsed as yet)
	Meaningful Use	Penalties begin in 2015 and will continue	Stage 1, 2, and 3 with increasing standards for communication
	Physician Compare	Public reporting website on individual physicians—2014	Process and experience patient outcomes, Meaningful Use, PQRS participation
	VBM	Pay for performance—2017 for all. Composite of quality (NQF endorsed) and cost measures	CAHPS, CRC screening, polyp surveillance interval normal exam, surveillance interval in patients with prior adenoma. Adenoma detection rate not currently endorsed
Hospital performance	Hospital Compare	Public reporting and pay for performance	GI as part of a larger group

PQRS Physician Quality Reporting System, *VBM* value-based modifier, *ACO* accountable care organizations, *ACA* Affordable Care Act, *NQF* National Quality Forum, *GI* gastroenterology, *CG-CAHPS* Consumer Assessment of Healthcare Providers and Systems (CAHPS ®) Clinician & Group, CRC colonoscopy and colorectal cancer, *BMI* body mass index

Association Institute (AGA) published a framework to develop a colonoscopy bundle and CMS has expressed interest in testing payments tied to such a bundle [14].

There is new information about PQRS as it relates to GI as of 2014. Of note, the adenoma detection rate is included in the 2014 PQRS but as yet is not endorsed by NQF. CMS is going to retire a number of claims-based measures (such as those related to hepatitis C) in order to encourage more use of a qualified registry. It is also increasing the number of measures that need to be reported from three to nine in many cases. As of 2014, CMS is offering a new "qualified clinical data registry" (QCDR) reporting option requiring nine measures across three NQF domains and including at least one outcomes measure. These specific measures can contain a combination of PQRS and non-PQRS measures. CMS announced recently that there are two registries pertinent to gastroenterologists that will be "qualified". These include the Digestive Health Outcomes Registry (DHRP) maintained by the AGA and the GI Quality Improvement Consortium (GIQuIC) a registry maintained by the American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy (ASGE). Reporting through a QCDR into PQRS can only be done at an individual level and must include more than 50% of eligible Medicare patients seen by a provider.

In summary, the following are current colonoscopy-related measures that are either endorsed or under consideration for use in a qualified registry (as a non-PQRS inclusion):

- Endoscopy/Polyp Surveillance: Colonoscopy Interval for Patients with a History of Adenomatous Polyps—Avoidance of Inappropriate Use (PQRS 185 NQF 0659)
- Endoscopy/Polyp Surveillance: Appropriate Follow-Up Interval for Normal Colonoscopy in Average Risk Patients (PQRS 320/NQF 0658)
- Screening Colonoscopy Adenoma Detection Rate (PQRS 343)
- Colonoscopy Assessment (Procedure adequacy)—Assessment of Bowel Preparation (non-PQRS measure)
- Colonoscopy Assessment (Cecum reached)—Cecal Intubation/ Depth of Intubation (non-PQRS measure)
- Unnecessary Screening Colonoscopy in Older Adults (non-PQRS measure)

Building a QI Program in Your Practice

Physicians who decide to build a QI program within their practices should understand clearly that performance is to be measured by their peers, compared to optimal practices, opportunities for improvement will be identified, and they will be held accountable for actively participating in these initiatives. When improvement opportunities are found, practices can follow the Donabedian Model described above to alter processes or structure and improve health outcomes. Several basic references are provided to help kick-start a QI program [15–18].

Variation in colonoscopy quality and outcomes exists and will likely continue until process and outcome measures for all colonoscopy examinations are either mandated (see later discussion) or become a routine part of practice for both gastroenterologists and nongastroenterologists who perform screening colonoscopy. The current FFS system of reimbursement, where payment is disconnected from health outcomes, will likely end in the near future. Current systems of credentialing occur at a facility level (a situation with inherent economic conflicts of interest) so factors other than quality and patient-centered health outcomes continue to be powerful influences in the community. Recent CMS efforts to begin identifying outliers within ambulatory surgical centers will continue and increase in intensity.

Recognizing variation in colonoscopy practice, physicians should feel compelled to demonstrate their own value as they perform colonoscopy and other endoscopic procedures. Uniform data collection and interpretation requires that measures be predefined and consensus gained on developing practice transparency and a commitment to improving. While measures used for federal or commercial incentive programs are rigidly standardized, those used for submission via registries or for practice (or ACO) improvement efforts can be less complex and more intuitive.

Optimal metrics should correlate with important clinical outcomes, be evidence based, reproducible, and easy to collect. Significant investments in infrastructure, staff time, and expertise are required for larger improvement efforts and fulfilling national expectations for performance and data submission. For short-term ad hoc improvement projects, manual data tracking and display are typically sufficient. Automated data accrual is helpful for larger settings and the repetitive nature of gastrointestinal endoscopy simplifies documentation if data can be collected using electronic report generators.

Every practice has opportunities for improvement in safety, efficiency, clinical outcomes, cost, or service. The capacity to undertake QI initiatives is usually constrained so practices should prioritize their efforts to (a) gaps in care that pose direct risk to patient safety or procedural outcomes, (b) measures required to ensure full reimbursement, (c) issues related to patient dissatisfaction, and (d) quality measures mandated regulatory agencies. Additional QI opportunities can be identified by attention to “near miss,” “never,” or sentinel events (all of which warrant investigation for structural or process failures); patient complaints; and employee or referring physician surveys.

Many practice changes can be addressed administratively, but substantive improvement or redesign in care processes usually requires a more formal process such as Lean or Six Sigma methodology. Here, process improvement is accomplished by assembling a team of responsible individuals who define a plan with clearly delineated goals, use of established techniques, and a timeline. Improvement teams should include both staff and managers with responsibility for the process or outcome being addressed, and individuals with skills and experience with database queries, data acquisition, statistical assessment, and process control charting.

Benchmarking is a method for comparing one’s performance and outcomes against those from similar individuals or institutions. External benchmarking can be accomplished by participation in a “registry” that typically provides comparison

against aggregate data from many groups. Risk adjustment for differences in populations and services can enable comparison between disparate groups. A prime motivation for participating in national registries for endoscopy or other focused practice areas within clinical GI (hepatitis and IBD care) is to facilitate automated submission of performance data on quality measures to CMS although current changes in CMS programs (see above) need to be considered as practices commit to a registry.

GIQuIC is a nonprofit national registry established by the ASGE and the ACG. This program provides comparative results on facility and physician-level quality measures pertaining to endoscopy. Measures of interest are electronically submitted following either manual abstraction or automated retrieval from an electronic endoscopic report generator. To date, this registry does not contain any PQRS measures, and through the QCDR process it must be reported at an individual level as summarized above.

DHRP developed by the AGA is actually two registries using differing data entry processes. Practices have the option of submitting measures to satisfy PQRS via the Group Measures process for either the inflammatory bowel disease or hepatitis C measures that are part of the "Group Measures" within PQRS. In this format, 20 consecutive patients with an IBD or hepatitis C are used for data extraction and submission using a web-based tool (at least half must be Medicare if used for PQRS submission). DHRP is currently available for IBD and hepatitis C practices and is linked to Bridges to Excellence recognition. A module is in development for colon cancer prevention. For more information, see www.gastro.org/practice/quality-initiatives/aga-digestive-health-recognition-program. In addition to the Group Measures process, DHRP also is a recognized QCDR so practices can submit using that format on 50 % of their Medicare patients. In this process, a colon cancer prevention (colonoscopy) set of measures is available.

Conclusion

What are the implications of all of these initiatives for national colonoscopy improvement efforts? Bluntly stated, the commitment of the USA to CRC prevention is huge and gastroenterologists who provide screening examinations will be held accountable for their outcomes. A commitment to enhancing value means a commitment to improving quality (known to be variable) and reducing total cost of care. Because we (gastroenterologists) led the effort to mandate population-based CRC screening with colonoscopy, we have an ethical commitment to be vigilant about our results and accountable for outcomes.

Gastroenterologists who understand future reimbursement and health-care trends are preparing their practices to meet new challenges of transparency and bundled payments. Pressures from large purchases of medical care (both employers and the federal government) will be sufficient to drive change. Robust measurement and public reporting of results both are firmly embedded in many regions of the country

and will become universal as we move to value-based reimbursement. The path is clear for those who study these issues, monitor process measures for internal improvement, push resource efficiency, connect to national registries to demonstrate quality externally, and constantly try to provide a service with the highest health value.

References

1. Murray CJL, Abraham J, Mohammed KA, Alvarado M, et al. (US Burden of Disease Collaborators). The state of US Health, 1990–2010 burden of diseases, injuries and risk factors. JAMA. 2013;310:591–608.
2. Framework for a high performance health system for the United States. The Commonwealth Fund. August 2006. http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/2006/Aug/Framework%20for%20a%20High%20Performance%20Health%20System%20for%20the%20United%20States/Commission_framework_high_performance_943 %20pdf.pdf. Accessed 9 Apr 2014.
3. Shih A, Davis K, Schoenbaum SC, Gauthier A, Nuzum R, McCarthy D. Organizing the US Health Care Delivery system for high performance. The Commonwealth Fund. August 2008. http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/2008/Aug/Organizing%20the%20U%20S%20 %20Health%20Care%20Delivery%20System%20for%20High%20Performance/Shih_organizingushltcaredeliverysys_1155 %20pdf.pdf. Accessed 9 Apr 2014.
4. Collins SR, Shoen C, Davis K, Gauthier AK, Schoenbaum SC. A roadmap to health insurance for all: principles for reform. The Commonwealth Fund. October 2007. http://www.commonwealthfund.org/~/media/Files/Publications/Fund%20Report/2007/Oct/A%20Roadmap%20to%20Health%20Insurance%20for%20All%20 %20Principles%20for%20Reform/Collins_roadmaphltinsforall_1066 %20pdf.pdf. Accessed 9 Apr 2014.
5. Brand RA. Ernest Amory Codman, MD, 1869–1940. Clin Orthop. 2009;467:2763–65.
6. Donabedian A. Evaluating the quality of medical care. Milbank Q. 2005;83:691–729.
7. National Research Council. To err is human: building a safer health system. Washington, DC: National Academies Press; 2000.
8. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press; 2001.
9. Institute of Medicine (IOM). The learning healthcare system: workshop summary. Washington, DC: National Academies Press; 2007.
10. Berwick DM, James B, Coye MJ. Connections between quality measurement and improvement. Med Care. 2003;41:130–8.
11. Kaye DR, Berenson RA. Grading a physician's value—the misapplication of performance measurement. NEJM. 2013;369:2079–81.
12. US Department of Health and Human Services. 2012 Annual progress report to congress: national strategy for quality improvement in health care. 2012. http://www.ahrq.gov/workingforquality/nqs/nqs2012annlrpt.pdf. Accessed 10 Apr 2014.
13. National Quality Forum. MAP 2014 recommendations on measures for more than 20 federal programs (final report January 2014). National Quality Forum. 2014. https://www.qualityforum.org/Setting_Priorities/Partnership/Measure_Applications_Partnership.aspx. Accessed 10 Apr 2014.
14. Brill JV, Jain R, Margolis PS, Kosinski LR et al. A bundled payment framework for colonoscopy performed for colorectal cancer screening or surveillance. Gastroenterology. 2014;146:849–53.

15. Allen JI. Gastroenterologists and the triple aim: how to become accountable. Gastrointest Endosc Clin N Am. 2012;22:85–96.
16. Allen JI. Maximizing the value of colonoscopy in community practice. Gastrointest Endosc Clin N Am. 2010;20:771–81.
17. Kappleman MD, Dorn SD, Peterson E, Runge T, Allen JI. Quality of care for gastrointestinal conditions: a primer for gastroenterologists. Am J Gastroenterol. 2011;106:1182–7.
18. Allen JI. Quality assurance for gastrointestinal endoscopy. Curr Opin Gastroenterol. 2012;28:442–50.

Chapter 2
Current Screening and Surveillance Guidelines

Swati G. Patel and Dennis J. Ahnen

Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality in the world. In 2008, there were more than 1.2 million new cases and approximately 610,000 deaths from CRC worldwide, making CRC the third most common cancer and the fourth leading cause of cancer-related death in the world [1]. Similarly, in the USA, CRC is the fourth most common malignancy and the second leading cause of cancer-related death; in 2013, there were an estimated 142,820 new cases and 50,830 deaths due to CRC [2]. An average-risk individual in the USA has a 4.8 % lifetime risk of developing CRC and a 2–3 % risk of death from CRC.

CRC mortality is stable or decreasing in most developed countries, but the USA is the only country in which both CRC incidence and mortality are steadily declining (about 2–3 % per year for the past 15 years). This decline is likely multifactorial (use of hormone replacement therapy among women, smoking cessation efforts, and widespread use of aspirin for cardiovascular health) and began well before screening was common in the USA (Fig. 2.1); however, reasonable estimates suggest that up to half of the recent trend can be attributed to CRC screening [3].

This chapter presents the historical basis for CRC screening, reviews the data available regarding current screening options for individuals at average and increased CRC risk, and reviews recommendations for surveillance after polyp removal; when possible, US and international guidelines will be compared. A detailed discussion of familial CRC syndromes or CRC associated with inflammatory bowel

D. J. Ahnen (✉)
Department of Medicine, University of Colorado School of Medicine, 5001 E 17th Ave Pkwy, Denver, CO 80220, USA
e-mail: dennis.ahnen@ucdenver.edu

S. G. Patel
Department of Internal Medicine, Division of Gastroenterology, University of Michigan, Ann Arbor, MI, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_2

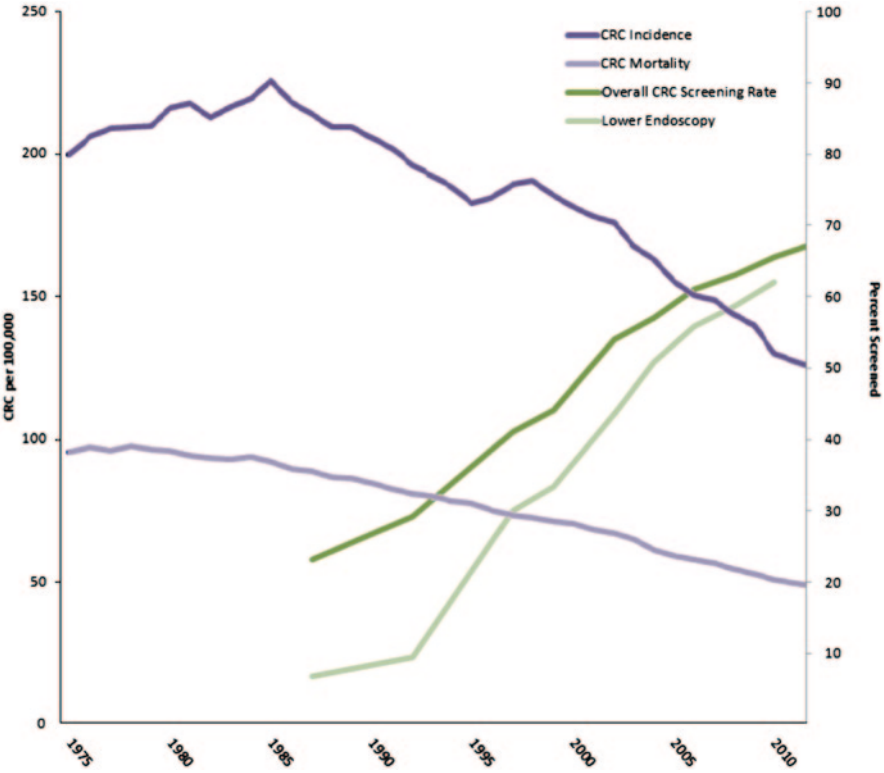

Fig. 2.1 Incidence/mortality of CRC and screening uptake rates over time. CRC incidence/mortality reported as rates among adults age 50 or older (Surveillance, Epidemiology and End Results database) to reflect the screening population. To cover the entire timeline, CRC screening test uptake rates derived from the National Health Information Survey were used for data before 1992 and Behavioral Risk Factor Surveillance System data were used for 1997–2010. The surveys did not differentiate between flexible sigmoidoscopy and colonoscopy for lower endoscopy; however, the sharp increase in lower endoscopy since 1995 is almost entirely the result of an increased use of colonoscopy.CRC colorectal cancer. (Adapted from Ref. [107]. With permission from Elsevier)

disease is outside the scope of this chapter; however, these topics are reviewed in detail elsewhere [4–6].

History and Rationale for CRC Screening

In the USA, screening for CRC has been promoted since the mid-1970s but the tools that are currently used for screening have a much longer history. Although the *Corpus Hippocraticum,* dating back to the fourth and fifth centuries BC, recorded the first rudimentary attempt at endoscopy with a rectal speculum, most historians credit Philipp Bozzini (Fig. 2.2a) as the creator of the first "modern" endoscope in 1806—the *Lichtleiter* or light conductor (Fig. 2.2b). The device was constructed

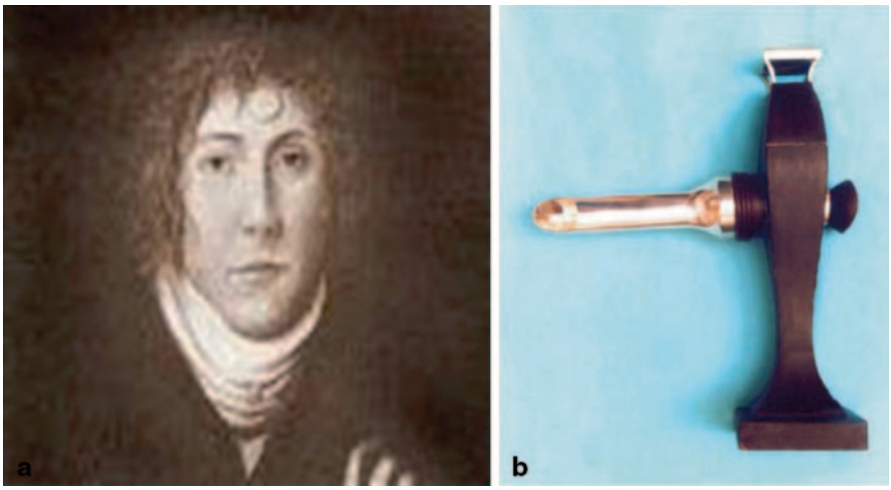

Fig. 2.2 **a** Philipp Bozzini (1773–1809) is credited with developing the first "modern" endoscope. **b** The *Lichtleiter* or light conductor. (Adapted from Ref. [108]. With permission from Nature Publishing Ltd.)

with double aluminum tubes (to be inserted in the body orifice being examined) and angled mirrors to project internal structures to the human eye, employing a single candle as a light source [7]. Rigid sigmoidoscopes have long been used diagnostically and screening sigmoidoscopy was developed in the 1950s [8].

Fecal occult blood testing (FOBT) also has a long history. In the 1850s, Christian Friedrich Schonbein first recognized the chemical reaction causing rapid bluing of guaiac (a resin from the West Indian gouyaca plant) when exposed to ozonized air [9]. Guaiac contains a phenolic compound that is oxidized to a quinone by hydrogen peroxide in a reaction catalyzed by peroxidases including hemoglobin. Von Deen developed a guaiac-based test for occult blood in 1863 [10]. Greegor stimulated widespread interest in FOBT when he reported, in 1967, that asymptomatic CRC could be detected by the presence of blood in the stool [11]. The immunologic tests to detect human hemoglobin were introduced in the 1970s [12], commercialized in the 1980s, and are now considered preferable to standard guaiac-based FOBT because of better performance characteristics (see below). Several FIT tests have now been approved by the US Food and Drug Administration (US-FDA).

As early as 1977, the American Cancer Society (ACS) recommended CRC screening with digital rectal exam and rigid proctoscopy as part of a *cancer-related health checkup* [13]. The rationale for screening was largely based on observations that patients with screen-detected CRCs had earlier stage disease and longer survival than those with symptomatic CRCs. Compelling evidence of the effectiveness of CRC screening emerged with the completion of large randomized screening trials beginning in the 1990s. On the basis of these trials, the US Preventive Services Task Force (USPSTF) initially recommended CRC screening with annual FOBT and/or sigmoidoscopy in 1995 with a grade B recommendation citing fair evidence of effectiveness [14]. In 2002, the USPSTF upgraded CRC screening to a grade A recommendation stating

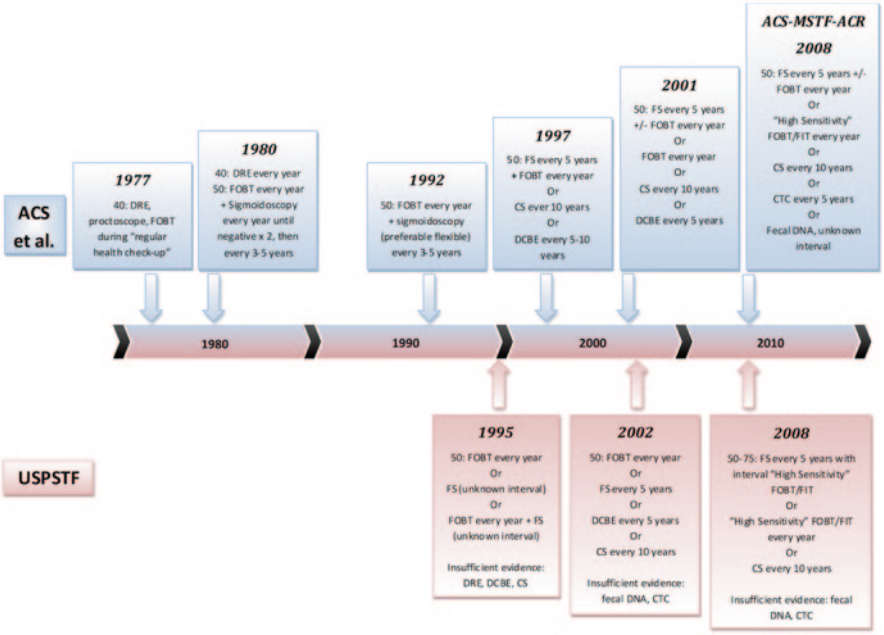

Fig. 2.3 Timeline of US colorectal cancer screening guidelines. ACS guidelines changed to ACS-MSTF-ACR guidelines in 2008. Prior to 2008, MSTF published independent guidelines [14, 35, 59, 109–111].ACS American Cancer Society, ACS-MSTF-ACR American Cancer Society-Multi Society Task Force-American College of Radiology. (Adapted from Ref. [108]. With permission from Springer Verlag)

that the USPSTF "strongly recommends that clinicians screen men and women aged 50 and older who are at average risk for colorectal cancer."In 2004,CRC screening became a Healthcare Effectiveness Data and Information Set (HEDIS) performance measure, essentially establishing that CRC screening is an accepted standard of care in the USA (HEDIS measures are used by more than 90% of US health plans to measure performance). CRC screening guidelines in the USA have evolved over time (Fig. 2.3), largely based on the results of the trials that are described in this chapter.

Average-Risk Screening Options

Current CRC screening options can be categorized into stool-based testing and structural radiographic or endoscopic imaging. Stool-based tests detect the consequences of colonic neoplasia (bleeding or shedding of neoplastic cells into the stool) and, as a one-time test, are better at detecting cancers than precancerous colonic polyps, while imaging modalities (endoscopy, radiology) can directly visualize both colonic polyps and cancers. The advantages, disadvantages, and performance characteristics of these tests are compared in Table 2.1.

Table 2.1 Summary of colorectal cancer Screening Modalities (Adapted from Ref. [108]. With permission from Springer Verlag)

Test	Advantages	Disadvantages	Sensitivity	Specificity	Screening interval	Guideline support	Cost per test
Imaging tests							
CS	Can visualize entire colon Performed every 10 years Can remove/biopsy lesions Can diagnose other diseases Single-step diagnostic and treatment Minimal patient discomfort	Invasive Sedation required, patient must be accompanied Time-consuming Expensive Full bowel preparation required Risk of bleeding, perforation Operator dependent, bowel preparation dependent	*Generally considered* "gold standard" 90 % (when using CTC as standard) for adenoma 5 mm, 97 % for advanced adenoma[a]	*Generally considered* "gold standard"	10 years	ACG ACS-MSTF-ACR USPSTF ASGE WGO	US$ > 1000[c]
FS	Simpler bowel preparation than CS Sedation not required Quick Performed every 5 years Does not require specialist or physician Lower risk than CS	Does not visualize entire colon Patient discomfort Risk of bleeding, perforation Two-step test Operator dependent, bowel preparation dependent	60–70 % for "clinically significant neoplasia"[b]	Equivalent to CS for region visualized	5 years	ACG ACS-MSTF-ACR USPSTF ASGE WGO CCA/CAN	US$150–300[c]
DCBE	Can visualize entire colon No sedation required Performed every 5 years Lower risk than CS	Insensitive for lesions 1 cm Less training for technicians/radiologists administering and interpreting exam Full bowel preparation required Two-step test	50 % for adenomas 1 cm 39 % for all polyps	96 % for adenomas > 10 mm	5 years	ACS-MSTF-ACR	US$300–400[c]

Table 2.1 (continued)

Test	Advantages	Disadvantages	Sensitivity	Specificity	Screening interval	Guideline support	Cost per test
CTC	Can visualize entire colon Less time consuming than endoscopy No sedation required Performed every 5 years Lower risk than CS	Can miss polpys 1 cm Full bowel preparation required Unclear how to follow extra-colonic findings Expensive Two-step test Radiation exposure Variability in performance	6–9 mm: 23–86 % /=10 mm: 52–92 %	86–95 %	5 years	ACG ACS-MSTF-ACR USPSTF WGO	US $>1000[c]
Stool-based tests							
gFOBT	Low risk, noninvasive Widely available No bowel preparation Inexpensive Home testing	High false-positive rate Insensitive for adenomatous lesions Requires frequent testing Two-step test Pretest dietary limitations	For CRC: Single test: 30 % Multiple nonrehydrated: 50–60 % Multiple rehydrated: 80–90 %	For CRC: 87–98 %	1 year	ACG ACS-MSTF-ACR USPSTF ASGE EU WGO CCA/CAN BSG/ACPGBI	US$ 13 [115]
FIT/iFOBT	Low risk, noninvasive Widely available No bowel preparation Inexpensive Home testing No dietary restrictions More specific to lower GI bleeding Detects human globin	High false-positive rate Insensitive for adenomatous lesions Requires frequent testing Two-step test	81.9–94.1 % for CRC 25–27 % for advanced adenoma 67 % for “clinically significant neoplasia”	87.5 % for CRC97–93 % for advanced adenoma 91.4 % for “clinically significant neoplasia”	1 year	ACG ACS-MSTF-ACR USPSTF ASGE WGO CCA/CAN BSG/ACPGBI	US$ 20 [115]

Table 2.1 (continued)

Test	Advantages	Disadvantages	Sensitivity	Specificity	Screening interval	Guideline support	Cost per test
Stool DNA	Low risk, noninvasive No bowel preparation Home testing No dietary restrictions Higher sensitivity than other stool tests	Need to collect an entire stool sample More expensive than other stool tests Unclear how to manage false-positive results Uncertain surveillance interval Two-step test	25–51 % for CRC 20–41 % for advanced adenomas+CRC	94–96 % for CRC	Unknown ACG recommends 3 years	ACG ACS-MSTF-ACR WGO	US$ 350[c]

FS flexible sigmoidoscopy, *CS* colonoscopy, *DCBE* double contrast barium enema, *CTC* computerized tomography colonography, *gFOBT* guaiac fecal occult blood testing, *FIT* fecal immunochemical testing, *iFOBT* immunochemical fecal occult blood testing, *ACG* American College of Gastroenterology, *ASGE* American Society for Gastrointestinal Endoscopy, *ACS-MSTF-ACR* American Cancer Society-Multi Society Task Force-American College of Radiology, *USPSTF* United States Preventative Services Task Force, *EU* European guidelines for quality assurance in CRC screening and diagnosis, *WGO* World Gastroenterology Organization, *CCA/ACN* Cancer Council Australia/Australian Cancer Network, *BSG/ACPGBI* British Society of Gastroenterology/Association of Coloproctology for Great Britain and Ireland

[a] Advanced adenoma: significant villous features (>25 %), size of 1.0 cm or more, high-grade dysplasia, or early invasive cancer

[b] Clinically significant neoplasia advanced adenoma or CRC

[c] American Cancer Society Colorectal Cancer Facts & Figs. 2008–2010

Stool-Based Tests

Stool-based CRC screening tests include guaiac-based and immunochemical FOBTs, and more recently, stool DNA tests. The concept of stool testing is based on the observation that colonic neoplasms can both bleed and shed cells into the stool. FOBT is the most widely used CRC screening modality in the world [15] and has been the most rigorously evaluated (see Table 2.2).

Guaiac FOBT

Guaiac-based tests detect heme in the stool by the presence of a peroxidase reaction, which turns the guaiac-impregnated paper blue. Most screening protocols require collecting stool samples from three consecutive bowel movements at home to optimize sensitivity. Patients are typically instructed to avoid aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) for 7 days and vitamin C, red meat, poultry, fish, and raw vegetables for 3 days prior to testing to improve specificity. However, a systematic review indicated that a recommended restricted diet did not decrease FOBT false-positivity rates, but did decrease compliance to testing [16]. There are a variety of commercial FOBTs available. The initial tests such as Hemoccult and Hemoccult-II have been shown to be effective in large prospective screening trials (Table 2.2) and are the standard by which subsequent FOBTs have been compared, but they have substantially lower sensitivity for CRC than Hemoccult SENSA (see below).

Performance Characteristics

The performance characteristics of guaiac FOBTs (gFOBTs) can be assessed as a one-time test for the detection of CRC or adenomas of the colon but gFOBTs are recommended to be repeated every 1–2 years, so the performance of a program of gFOBT testing is also important (this distinction highlights the critical importance of ongoing compliance as an issue for stool testing). The performance characteristics of gFOBTs vary with the prevalence of CRC and the age of the population screened and there is even greater performance variability among the types of gFOBTs [17–21]. Of all of the commercial kits available, Hemoccult SENSA has the highest one-time sensitivity for CRC (64–80%), but a lower specificity (87–90%) than the other gFOBTs (sensitivity <50%; specificity ~95%) [22].

Efficacy

The clinical efficacy of FOBT has been established by controlled trials using the lower sensitivity Hemoccult or Hemoccult II tests. The first trial, reported by Man-

Table 2.2 Summary of randomized controlled trials for fecal occult blood testing (FOBT) (Adapted from Ref. [108]. With permission from Springer Verlag)

Trial	Screening	Follow-up (years)	Testing	Participants	Attendance (first screen‖at least 1‖subsequent rounds)	Sensitivity[a]	PPV[b] CRC	PPV adenoma	CRC incidence	CRC mortality[c]	All-cause mortality
Minnesota [23], [112]	Annual (A) and biennial (B)	18	Hemoccult Rehydrated	46,551	– ‖ 75% ann, 78% bi ‖ –	92.2%	0.9–6.1%	6–11%	A: 0.8 (0.73–0.94, p 0.001) B: 0.83 (0.73–0.94, $p=0.002$)	A: 0.67 (0.51–0.83, p 0.05) B: 0.79, 0.62–0.97, p 0.05)	342 (334–350)[d] A: 340 (333–348) B: 343 (336–351) *NS*
Nottingham [24]	Biennial	11.7	Hemoccult Not rehydrated	152,303	53.4% ‖ 59.6% ‖ –	57.2%	9.9–17.1%	42.8–54.5%	1.51 versus 1.53/1000 person yr *NS*	0.87 (0.78–0.97, $p=0.010$)	1.01 (0.96–1.05) *NS*
Funen [21]	Biennial	17	Hemoccult II Not rehydrated	61,939	66.8% ‖ – ‖ 91–94%	55%	5.2–18.7%	14.6–38.3%	1.02 (0.93–1.12) *NS*	0.84 (0.73–0.96, $p<0.05$)	0.99 (0.97–1.02) *NS*
Goteborg [25]	Biennial[e]	15.75	Hemoccult II Rehydrated	23,916	63% ‖ 70% ‖ 60%	82%	4.8%	14%	0.96 (0.86–1.06)	0.84 (0.71–0.99, $p<0.05$)	1.02 (0.99–1.06) *NS*

NS non-significant results

[a] Proportion of all CRC that were detected by screening, where "all CRC" was the sum of screen-detected cancers (TP) and interval cancers within 1 or 2 years of screening (FN)

[b] Positive predictive value

[c] Reported as odd ratio with 95% confidence interval

[d] Mortality per 1000

[e] Three cohorts: all screened for initial prevalence, cohort 1 and 2 rescreened at 21–24 months, cohort 3 rescreened at 1 year and 2 year after initial screening. Cohort 1 rescreened at approximately 10 years

del et al. [23] from the University of Minnesota, randomized 46,551 patients to annual FOBT, biennial FOBT, or a control arm. Mortality due to CRC was decreased by 33% at 13 years in the annual screening group and 21% at 18 years in the biennial screening group when compared to the control arm. Subsequently, three European trials also demonstrated a CRC mortality benefit ranging from 13 to 16% using biennial screening [21, 24, 25]. Longer-term follow-up of the US study showed that gFOBT screening led to a 17–20% lower incidence of CRC [23] (Table 2.2) and that the mortality benefits have been maintained through 30 years of follow-up [26].

There is no direct evidence that screening with FOBT decreases all-cause mortality (Table 2.2). Although none of the trials were powered to assess an effect on all-cause mortality, a meta-analysis of the three major controlled trials [27] found that screening was associated with a significant decrease in CRC mortality, a significant increase in non-CRC mortality and no impact on overall mortality.

Fecal Immunochemical Tests

Immunochemical tests for blood in the stool have several advantages over gFOBTs. Fecal immunochemical tests (FITs) specifically detect human globin so they do not require dietary restriction of meat or peroxidase-rich food and FITs typically require one to two stool samples rather than the three recommended for gFOBTs. Not surprisingly, participation rates have been reported to be significantly higher for FIT than gFOBT; 61.5 versus 49.5% in a study by Hol et al. [28]. In addition, globin protein is digested in the stomach and proximal small bowel so FIT should be more specific for bleeding from the colon than gFOBTs. There are multiple FDA-approved FIT kits commercially available; the major technical differences among the tests are whether they can report quantitative as well as qualitative results and whether they can be performed in an individual laboratory or require central processing. The analysis of reported data with FITs is complicated by the fact that the level of sensitivity can be adjusted and the number of tests recommended is not uniform; the performance characteristics of the tests vary substantially by adjusting either or both of these parameters. FIT is typically more expensive than gFOBT but, for a single test, both are substantially less expensive than the imaging modalities described below.

Performance Characteristics

FIT is thought to have a similar sensitivity for CRCs and advanced adenomas (≥10 mm, presence of high-grade dysplasia or villous features) as Hemoccult SENSA and both have improved sensitivity over other gFOBTs like Hemoccult II. Allison et al. [18] reported that FIT sensitivity was higher than Hemoccult SENSA for distal CRCs (81.9 vs. 64.3%) but lower for advanced adenomas (29.4 vs. 41.3%). Hundt et al. [29] found great variability in the performance of six FIT kits for detec-

tion of adenomas; the two best performing tests (immoCARE-C (CARE diagnostica, Voerde, Germany) and FOB advanced (ulti med, Ahrensburg, Germany)) had sensitivities for the detection of advanced adenomas of 25 and 27 % with specificities of 97 and 93 %, respectively.

Efficacy

There are no long-term data regarding the impact of screening with FIT on CRC mortality or incidence; however, there are several trials underway with results expected in the 2020s. Results from the initial round of screening of one of the trials comparing colonoscopy with FIT (hemoglobin threshold of 75 ng/mL) showed higher compliance with the FIT arm, higher adenoma detection in the colonoscopy arm, and, after one round of FIT testing, no difference in CRC detection rates [30].

Fecal DNA Testing

Fecal DNA testing is a new and evolving stool-based screening test based on the observation that colonic neoplasms have altered DNA compared to normal cells, that colonic neoplasms shed cells into the stool, and that their DNA can be detected in stool. Fecal DNA testing has the theoretical advantage of identifying a marker thought to be in the causal pathway to CRC (mutations or mutation-like events) rather than the less specific finding of blood in the stool. Typically, an entire bowel movement is collected and shipped to a laboratory for the fecal DNA tests.

Performance Characteristics

Fecal DNA testing is a very active area of ongoing research and there are numerous studies reporting high sensitivity and specificity of various stool DNA tests in selected patient populations. In two studies using colonoscopy as a standard, a fecal DNA test (PreGen Plus®; no longer commercially available) had a sensitivity of 25–51 % for CRC and 20–41 % for clinically significant neoplasia (CRC plus advanced adenomas) with specificities of 94–96 % [31, 32]. A combination stool DNA/FIT assay (Cologuard®) was recently reported to have a 92 and 42 % sensitivity for CRC and advanced adenomas, respectively, with a specificity of 86 % [33]. This test has been submitted to the FDA for premarketing approval.

Efficacy

There are no long-term data available upon which to draw conclusions regarding the efficacy of fecal DNA testing on CRC mortality or incidence.

Blood Tests

A reliable blood test for colon cancer screening would have substantial advantages over stool collections. A large prospective study of methylated septin 9 in patients scheduled for screening colonoscopy demonstrated that a CRC marker can be detected in blood; the assay had a 48% sensitivity for CRC [34]. A septin 9 CRC screening assay (ColoVantage®) has been submitted to the FDA for premarketing approval.

Structural Tests

Colonic imaging tests used for screening include radiologic (barium enema and CT colonography) as well as endoscopic (flexible sigmoidoscopy (FS) and colonoscopy) tests. Although barium enema is still supported as a screening modality in the multi-society guidelines [35], there are no studies evaluating its effectiveness in CRC screening and it is rarely used for screening.

Computerized Tomography Colonography

Computerized tomography colonography (CTC) emerged as a CRC screening tool in the mid-1990s, and the technology has rapidly evolved since. CTC is an attractive screening approach in that, like colonoscopy, it visualizes polyps as well as cancer throughout the colon but it does not require sedation, it takes less time, and is associated with a lower complication rate than colonoscopy. Current protocols require patients to undergo a standard bowel preparation and the colon is inflated using a rectal catheter prior to imaging, which can cause discomfort.

Performance Characteristics

Defining the sensitivity and specificity for CTC is more complicated than for any of the other screening modalities since the current radiologic practice is to not report polyps less than 5 mm in size. The reported sensitivity for polyps sized 6–9 mm has ranged from 23 to 86% and from 52 to 92% for polyps > 10 mm and 75–100% for CRC [36–39]. This wide variability has been attributed to differences in technology and operator experience and training.

There is a concern that operator dependence could be even a bigger issue in the general community than that reported in the controlled trials. The trials reporting the best CTC performance [36, 39] went to great lengths to ensure that their study radiologists were highly trained and experienced with CTC. Thus, these study results may not be generalizable to the community.

Despite these concerns, the best CTC studies reported sensitivities for cancer and for polyps larger than 10 mm of 94 and 90 %, respectively, with specificites for polyps > 10 mm of 86–95 % [36–38].

Barriers to the widespread use of CTC screening include residual angst about the ability of CRC to detect diminutive and flat polyps. Even though only a small percentage of polyps less than 5 mm have advanced histology (only 1 of 966 diminutive polyps found in Pickhardt's trial had villous features), it is unclear if leaving these polyps undetected and unremoved is acceptable to patients and their providers. There are little data about the performance of CTC for the detection of flat lesions in the colon which are increasingly reported as having a substantial cancer risk [40]. Small flat lesions are also missed frequently by endoscopy, however, and the overall sensitivity of CTC and colonoscopy for polyps > 6 mm is similar [41].

CTC is less expensive than colonoscopy but there are conflicting data regarding the cost-effectiveness of CTC compared with colonoscopy [36, 42–45]. Most of these modeling studies assumed that patients would only be referred for colonoscopy if polyps greater than 10 mm were found. In practice, Shah et al. [46] found that both patients and physicians preferred to follow even small polyps with colonoscopic examination. If all detected polyps led to colonoscopy, the cost of primary CTC screening would increase substantially.

Efficacy

There are no long-term data available to assess CTC screening on CRC mortality.

Flexible Sigmoidoscopy

FS is generally performed with a 60-cm sigmoidoscope, which typically allows visualization to the descending colon or splenic flexure (less than half of the colonic length). The bowel preparation for FS is usually enemas alone; although simpler, the preparation may not be as good as with the more extensive preparations used for CTC or colonoscopy. FS typically does not require sedation and can be performed by nonphysicians (nurses, mid-levels), but it causes more patient discomfort than sedated procedures.

Performance Characteristics

The sensitivity of FS for advanced adenomas and CRC of the entire colon is approximately 60–70 % (when compared to colonoscopy as gold standard) if colonoscopy is recommended for any adenoma detected in the distal colon [47]. Provided that the bowel preparation is good, the sensitivity and specificity for detecting lesions in the distal bowel is thought to be equivalent to colonoscopy.

Efficacy

Although earlier studies had been conflicting, three recent large controlled trials from the UK [48], Italy [49], and the USA [50] (Table 2.3) reported decreases in both incidence (18–23%) and mortality (22–31%) in patients randomized to FS. The benefit of FS was due to a decrease in left-sided CRCs with no significant effect on right-sided CRCs. None of the FS trials has found a statistically significant reduction in overall mortality.

Colonoscopy

Colonoscopy is thought by many to be the most effective CRC screening test available given its ability to both visualize and remove/sample lesions throughout the entire colon. There are, however, no controlled trials to establish the effect of colonoscopy on CRC incidence and mortality. It is important to recognize that colonoscopy quality is highly operator dependent and varies greatly due, in large part, to differences in the training, experience, and skill of the endoscopist and the quality of the endoscopic equipment and the prep. In one study of endoscopists at an academic medical center, adenoma detection rates (ADRs) varied almost threefold (17–47%) and serrated polyp detection rate varied even more (1–18%) [51]. Cecal intubation rates, withdrawal times (WTs), and ADRs are accepted measures of colonoscopy quality [52], the goal of colonoscopy is to prevent CRC. Longer WTs are generally associated with higher ADRs and two studies [53, 54] have shown that higher ADRs are associated with lower interval (post-colonoscopy) CRC rates.

Colonoscopy is the most expensive and highest risk CRC screening test with a perforation rate of about 0.6 per 1000 (higher in patients undergoing polypectomy) and a bleeding risk as high as 8.7 per 1000 procedures in which a polypectomy is performed [55]. Bowel preparation is critically important for colonoscopy and typically includes clear liquids the day prior to the procedure and ingestion of a large volume of a polyethylene containing liquid with half the dose the night before and the other half the morning of the exam. The exam is generally performed with conscious sedation or anesthesia, which provides an amnesic benefit so that most patients report that the preparation is the most unpleasant part of the procedure.

Performance Characteristics

Because colonoscopy has been viewed as the gold standard in CRC screening, there are no robust estimates of test characteristics in terms of sensitivity and specificity. Initially, tandem colonoscopy studies (two complete colonoscopies by different endoscopists during the same session) [41] estimated miss rates of 2% for adenomas 10 mm or greater, 13% for adenomas 5–10 mm, and 25% for adenomas less than 5 mm, with a 22% overall miss rate for all polyps. Studies performing both CTC and colonoscopy estimate that the miss rate for colonoscopy is substantially higher

Table 2.3 Summary of randomized controlled trials for flexible sigmoidoscopy: CRC incidence, mortality, and all-cause mortality (Adapted from Ref. [108]. With permission from Springer Verlag)

Trial	Participants	Follow-up (years)	CRC incidence (RR[b] or number)	CRC mortality (RR[b])	All-cause mortality (RR or number)
Telemark [113] Norway	799	13	0.2 (95 % CI, 0.03–0.95)[a]	No patients died of CRC in either arm	1.57 (95 % CI, 1.03–2.4)[a]
NorCCaP[c] [114] Norway	55,736	7	134.5 versus 131.9/100,000 person yr	0.73 (95 % CI, 0.47–1.13) ITT[d] 0.41 (95 % CI, 0.21–0.82) per protocol[a]	1.02 (95 % CI, 0.98–1.07)
UK FS trial [48]	113,195	11.2	0.77 (95 % CI, 0.70–0.84) ITT[a] 0.67 (95 % CI, 0.60–0.76) per protocol[a]	0.69 (95 % CI, 0.59–0.82) ITT[a] 0.57 (95 % CI, 0.45–0.72) per protocol[a]	0.97 (95 % CI, 0.94–1.0)
SCORE[e] Trial [49]	34,272	11.4	0.82 (95 % CI, 0.69–0.96) ITT[a] 0.69 (95 % CI, 0.56–0.86) per protocol[a]	0.78 (95 % CI, 0.56–1.08) ITT 0.62 (95 % CI, 0.40–0.96) per protocol[a]	660.3 verus 641.0/100,000 person yr
PLCO[f] Trial [50] US	77,445	11.9	0.79 (95 % CI 0.72–0.85)[a]	0.74 (95 % CI 0.63 to 0.87)[a]	0.98 (95 % CI, 0.96–1.01)

CI confidence interval, *CRC* colorectal cancer, *RR* relative risk

[a] Denotes statistically significant

[b] Relative risk

[c] Norwegian Colorectal Cancer Prevention

[d] Intention to treat

[e] Sigmoidoscopy in colorectal cancer screening working group

[f] Prostate Lung Colorectal Ovarian Cancer Screening Trial

(12 % miss rate for polyps greater than or equal to 10 mm) [36]. Reports of the range of ADRs among endoscopists [53] suggest the average endoscopist may miss up to half of patients with adenomas.

Efficacy

There have been no randomized controlled trials of colonoscopic screening with CRC incidence or mortality endpoints, but there is substantial indirect evidence to support its use as a screening tool. The efficacy of colonoscopic polypectomy was initially highlighted by the National Polyp Study (NPS) which estimated a 76–90 % reduction in incidence of CRC after polyp removal compared to historic controls [17]. Similarly, a veterans affair (VA)-based case–control study by Muller et al. [56] reported that having had a lower endoscopy within the previous 6 years was associated with a 60 % reduced CRC mortality (odds ratio (OR) 0.41, 95 % confidence interval (CI) 0.33–0.50). Efficacy can also be extrapolated from randomized controlled trials performed for other screening modalities that eventually referred patients for colonoscopy. The reduction in CRC incidence in the FOBT trials [26] is attributable to the colonoscopy and polypectomy performed for positive FOBT results.

It seems intuitive that colonoscopy would be a better screening test than sigmoidoscopy since it can visualize the entire colon. Recent studies, however, have called into question the ability of colonoscopy to prevent CRC throughout the entire colon. Case–control studies from Canada and Germany [57] reported that colonoscopy resulted in a significant decrease in CRC mortality (OR 0.33, CI 0.28–0.39) and in metachronous advanced adenoma rates in the left colon but neither found a risk reduction in the right colon. A US case–control study [58] using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database found a protective effect of colonoscopy for CRC; the magnitude of the benefit was substantially greater for left- than right-sided CRC (OR 0.24 (95 % CI, 0.21–0.27) vs. 0.58 (95 % CI, 0.53–0.64). These marked regional differences could reflect a different biology of right-sided tumors, a higher proportion of flat and indistinct lesions, and/or a higher likelihood of poor bowel preparation in the right colon, among other reasons.

At least three randomized controlled trials are currently underway to directly examine the efficacy of colonoscopy in reducing CRC incidence and mortality. Both the US Department of Veterans Affairs CONFIRM (Colonoscopy vs. Fecal Immunochemical Test in Reducing Mortality from Colorectal Cancer) trial and a Spanish trial [30] will be comparing colonoscopy to FIT, while the Nordic-European Initiative on CRC will compare colonoscopy to no screening. These trials are expected to take another decade to complete.

PillCam Colon

There are little published data on the use of the colonic capsule endoscopy for CRC screening in the USA. PillCam Colon® has received FDA approval for use in pa-

tients with incomplete optical colonoscopy but not yet for screening and it has not been incorporated into any CRC screening guidelines.

Guidelines for Average-Risk Screening

The most frequently cited colon screening guidelines in the USA are those developed by the USPSTF which focus on average-risk screening [59], those developed jointly by the ACS, the American College of Radiology, the US Multi-Society Task Force (MSTF; includes the American Gastroenterology Association Institute, the American College of Gastroenterology (ACG), and the American Society for Gastrointestinal Endoscopy) [35], and the National Comprehensive Cancer Network (NCCN), which include screening recommendations for average- and high-risk groups (see Table 2.4) and polyp/cancer surveillance recommendations [60]. The British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) published guidelines in 2010 [61] that update recommendations on screening, polyp surveillance, and cancer surveillance. The guidelines published by the European Commission [15] and the Australian guidelines [62] focus their recommendations on screening.

Diet and Lifestyle

There is little mention of diet or lifestyle modifications for the prevention of CRC in the US and European guidelines. The MSTF, ACG, NCCN, European Union (EU), and UK guidelines do not mention these interventions at all whereas the USPSTF guidelines point out that interventions such as avoidance of red meat and alcohol or consumption of a high-fiber diet have not been substantiated in trials, therefore cannot be recommended. In contrast, the Australian guidelines "strongly recommend" limiting alcohol consumption and restricting caloric intake, "recommend" engaging in physical activity, maintaining healthy body mass index, avoiding tobacco smoke, and restricting dietary fat to prevent CRC.

Average-Risk Screening

All guidelines define the "average risk" population as asymptomatic adults age 50 years or older without a personal or family history of colonic neoplasia or inflammatory bowel disease. There is a stark contrast in the approach to screening average-risk individuals in the US guidelines versus the non-US guidelines. In the USA, the general approach has been to support offering a variety of options, acknowledging differences in patient preferences and variable access to the different modalities. In the European and Australian guidelines, there is more of an emphasis

Table 2.4 Summary of US screening guidelines

		USPSTF	ACS/MSTF/ACR	ACG	NCCN
Average risk (no family history)	Age to screen	50–75 75–85: suggest stopping 85: stop screening	50-Individualized	50-Not specified	50-Not specified
	Test(s) (interval)	HS FOBT (annual) FS (q 5 year) + interval FOBT CS (q 10 year)	HS FOBT (annual) FS (q 5 year) CS (q 10 year)	CS preferred (q 10 year)	CS preferred (q 10 year)
FDR with early onset CRC (or adenoma)	Specifications	N/A	1 FDR with CRC or any adenoma age <60 or 2 or more FDR with CRC or any adenoma at any age	1 FDR with CRC or *advanced* adenoma age <60 or 2 or more FDR with CRC or any adenoma at any age	1 FDR with CRC age <50 or 2 or more FDR with CRC at any age
	Age to screen	N/A	40 or 10 years before CRC	40 or 10 years before CRC	40 or 10 years before CRC
	Test(s) (interval)	N/A	CS (q 5 years)	CS (q 5 years)	CS (q 3–5 years)
FDR with CRC (or adenoma) any age	Specifications	N/A	1 FDR with CRC or adenoma at any age	1 FDR with CRC or advanced adenoma at any age	1 FDR with CRC > 50
	Age to screen	N/A	40	50	50 or 10 years before CRC
	Test(s) (interval)	N/A	Any (average-risk interval)	CS (q 10 years)	CS (q 5 years)
SDR with CRC	Specifications	N/A	2 SDRs with CRC at any age	N/A	1 SDR with CRC < 50
	Age to screen	N/A	40	N/A	50
	Test(s) (interval)	N/A	Any (average-risk interval)	N/A	Per colonoscopy findings

USPSTF US Preventative Services Task Force, *ACS/MSTF/ACR* American Cancer Society/Multi Society Task Force/American College of Radiology, *ACG* American College of Gastroenterology, *NCCN* National Comprehensive Cancer Network, *HS FOBT* high sensitivity fecal occult blood test, *FS* flexible sigmoidoscopy, *CS* colonoscopy, *FDR* first-degree relative, *CRC* colorectal cancer, *SDR* second-degree relative

on participation in a "screening program" with a single option or limited options offered through their national health services.

The modalities supported by the ACS/MSTF/ACR guidelines include annual high sensitivity FOBT (HemeSensa or FIT) or stool DNA (the interval for stool DNA is not clearly specified). In terms of structural exams, the MSTF supports FS every 5 years, colonoscopy every 10 years, double-contrast barium enema (DCBE) every 5 years, or CTC every 5 years. The USPSTF does not recommend DCBE and concludes that there is insufficient evidence to support CTC or fecal DNA testing for routine screening but endorses annual HS-FOBT, FS every 5 years preferably with an interval high-sensitivity FOBT or colonoscopy every 10 years. Although the ACG supported the MSTF guidelines, they stated their updated society guidelines [63] that colonoscopy is the "preferred strategy," and lists FS (every 5–10 years), CTC (every 5 years), FOBT (annual), and fecal DNA (every 3 years) as acceptable alternatives. The NCCN also lists colonoscopy as a preferred option if it is available with annual FOBT, sigmoidoscopy (every 5 years), or the combination as alternatives.

FOBT every 2 years is the primary screening test recommended by the EU guidelines, the UK Bowel Screening Program, and the Australian guidelines. The Australian guidelines also include the option of adding FS every 5 years to an FOBT program. The non-US guidelines also emphasize quality metrics for overall screening programs such as invitation coverage, uptake rates, timeliness of testing/results, and compliance with colonoscopy after positive test.

The USPSTF guidelines do not recommend routine screening for individuals 75–85 years of age and explicitly recommend against routine screening in individuals older than 85. The MSTF advises that in older individuals, decisions about screening should be individualized balancing risk, benefits, and comorbidities. The other guidelines do not specifically address when to stop screening.

High-Risk Screening

Family History

Rationale

Approximately 30% of all CRCs have some familial component [64]. Two meta-analyses [65, 66] on this issue have reported a strikingly similar result with about a twofold increase in the risk of CRC in individuals with a single first-degree relative (FDR) with CRC and about a fourfold increased risk for those with at least two affected FDRs. The relative risk also increased as the age of the CRC in the relative decreased.

It is less clear if FDRs of individuals with adenomatous polyps are at a significantly increased risk of CRC. In the meta-analysis cited above [65], the relative risk

of CRC in FDRs of people with adenomatous polyps was increased (1.99; 95% CI 1.55–2.55) but these studies have been criticized as being flawed in design [67]. Since adenomas are so common, it seems unlikely that FDRs of anyone with an adenoma is at a substantially increased CRC risk but risk does appear to be increased in relatives of individuals with large or histologically advanced adenomas [68].

Data to Support Screening

There are no controlled studies available establishing the impact of screening individuals with a family history of CRC or adenomas on CRC incidence or mortality.

Guidelines

The USPSTF [59] does not make specific recommendations for screening in high-risk populations. The ACS/MSTF/ACR guidelines [35] categorize several groups as "high risk" based on family history. This group recommends that individuals with an FDR with either CRC or an adenomatous polyp before the age of 60 start CRC screening with colonoscopy at age 40 (or 10 years before the CRC diagnosis in their FDR) and the interval for follow-up should be every 5 years. Individuals with an FDR with CRC or an adenoma greater than age 60 or two second-degree relatives with CRC or adenomas are advised to initiate screening at age 40 using any MSTF recommended screening modality at standard intervals.

In contrast, the ACG [63] recommends that individuals with a single FDR older than 60 with CRC or adenomas undergo average-risk screening. For those with a single FDR with CRC or an *advanced* adenoma diagnosed under the age of 60 or two FDRs with CRC or advanced adenomas, the ACG recommends colonoscopy screening at age 40 (or 10 years younger than the youngest affected family member) with a 5-year surveillance interval. Additionally, the ACG identifies African Americans as a high-risk group and recommends initiating screening at age 45. The NCCN guidelines [60] are similar to those of the ACG except the age cutoff for high risk is CRC in a relative is 50 rather than 60 years.

The UK guidelines [61] differ substantially from the US guidelines. For individuals with one FDR with CRC diagnosed younger than age 50 or two FDRs diagnosed after age 60, the UK guidelines recommend colonoscopy once at age 55 and if normal, no follow-up. For those with two FDRs diagnosed with CRC younger than 60 or three FDRs diagnosed with CRC at any age, the UK guidelines recommend colonoscopy at age 50 and surveillance every 5 years.

The Australian guidelines recommend average-risk screening for individuals with a single FDR with CRC diagnosed after the age of 55. For individuals with one FDR diagnosed with CRC younger than 55, or two first- or second-degree relatives with CRC at any age, the Australian recommendation is to perform colonoscopy at the age of 50 or 10 years before the youngest family member's diagnosis at an interval of every 5 years.

Polyp Surveillance

Rationale

Individuals with colonic adenomas are at increased risk for developing metachronous adenomas or cancer compared with individuals without adenomas.

Data to Support Surveillance

Surveillance intervals should ideally be based on data demonstrating an impact on CRC incidence and mortality but the majority of data supporting surveillance focuses on findings of adenomas and advanced adenomas at follow-up examinations. Saini et al. [69] performed a meta-analysis of five studies and identified baseline colonoscopy findings associated with increased risk of advanced adenomas at follow-up. Individuals with three or more adenomas at baseline (when compared to those with one to two adenomas at baseline) and those with high-grade dysplasia (compared to those with low grade dysplasia at baseline) had an increased risk of advanced adenoma at follow-up (2.52; 95% CI, 1.07–5.97 and 1.84; 95% CI, 1.06–3.19, respectively). A pooled analysis [70] of eight prospective studies including 9167 patients with adenomas at baseline and follow-up colonoscopy within 3–5 years also found that the number of adenomatous polyps at baseline is associated with increasing risk of advanced adenoma at follow-up (one adenoma—8.6%, two adenomas—12.7%, three adenomas—15.3%, four adenomas—19.6%, 5+adenomas—24.1%, trend <0.001). Size of the largest adenoma at baseline (for polyps ≥20 mm OR 2.99; 95% CI, 2.24–4.00), presence of proximal adenoma (OR 1.68; 95% CI, 1.43–1.96), and baseline villous histology (1.28; 95% CI 1.07–1.52) were also independent risk factors for advanced adenomas at follow-up.

Although the data are limited, detection of an advanced adenoma on surveillance is a consistent risk factor for finding an advanced adenoma on the next examination, regardless of findings on index examination. After an index exam showing a "high-risk adenoma" (HRA; three or more adenomas, adenoma ≥10 mm, with villous features or high-grade dysplasia), "low-risk adenoma" (LRA; 1–2 tubular adenomas<10 mm), or no adenoma and a follow-up exam showing AA in each case, Pinsky et al. [71] reported a 19.3, 15.6, and 11.5% incidence of AA on second surveillance, respectively. In contrast, if both the baseline and surveillance colonoscopy showed no HRAs, the risk of advanced adenoma on the next surveillance examination was very low (3.1%) [71]. Laiyemo et al. [72] and Robertson et al. [73] reported similar results.

Sessile serrated polyps (SSPs; synonymous with sessile serrated adenomas (SSAs)) are increasingly being recognized as important malignant precursors. Approximately 20–30% of CRCs arise through the CPG island methylator phenotype (CIMP) pathway in which SSPs are thought to be the precursors [74]. CIMP-posi-

tive tumors account for a disproportionate percentage of interval cancers (cancers arising at or before next scheduled surveillance examination), particularly in the right colon [75]. Endoscopic features, such as bland color, flat contour, and poorly defined borders have rendered SSPs more difficult to detect and completely resect than conventional adenomas [76].

Schreiner et al. [77] demonstrated that patients with at least one nondysplastic serrated polyp in the proximal colon carried a significantly higher risk of synchronous advanced neoplasia (OR 1.90, 95% CI 1.33–2.70) and those with a serrated lesion ≥10 mm carried a 3.37 (95% CI 1.71–6.65) odds of synchronous advanced neoplasia. In addition, those with proximal nondysplastic serrated polyps at baseline were more likely to have advanced neoplasia at surveillance 5.5 years from the index exam (2.17, 95% CI 1.03–4.59).

Guidelines

The ACS/MSTF updated guidelines for colonoscopy surveillance in 2012 [78] and included, for the first time, guidelines for serrated polyps. The ACS/MSTF guidelines recommend a 5–10-year follow-up interval for individuals with one to two small (<10 mm) tubular adenomas at baseline. For individuals with three to ten small tubular adenomas at baseline or at least one adenoma ≥10 mm or an adenoma with villous features or high-grade dysplasia, the recommended surveillance interval is 3 years; those with more than ten adenomas are advised to have surveillance in less than 3 years and be evaluated for the possibility of a polyposis syndrome. The recommendation for patients with SSP(s) <10 mm with no dysplasia is to repeat colonoscopy in 5 years and those with SSP(s) ≥10 mm, those with dysplasia or any traditional serrated adenomas should undergo surveillance at 3 years. In terms of follow-up after initial surveillance, the MSTF recommends that patients with an LRA at baseline and HRA, LRA, or no adenoma at surveillance should undergo second surveillance at 3, 5, and 10 years, respectively. Those with HRA at baseline and HRA, LRA, or no adenoma at surveillance should undergo second surveillance at 3, 5, and 5 years, respectively. The NCCN surveillance guidelines are similar to those of the ACS/MSTF.

In contrast to the US guidelines for polyp surveillance summarized above (see Fig. 2.4), the BSG divides baseline findings into "low risk" (one to two adenomas <10 mm), "intermediate risk" (three to four adenomas <10 mm or at least one adenoma ≥10 mm), and "high risk" (≥5 adenomas <10 mm or ≥3 adenomas with at least 1 ≥10 mm) findings. The guidelines recommend that individuals with low-risk findings undergo either no surveillance or a repeat examination in 5 years, individuals with intermediate risk findings undergo surveillance at 3 years, and those with high-risk findings undergo surveillance in 1 year.

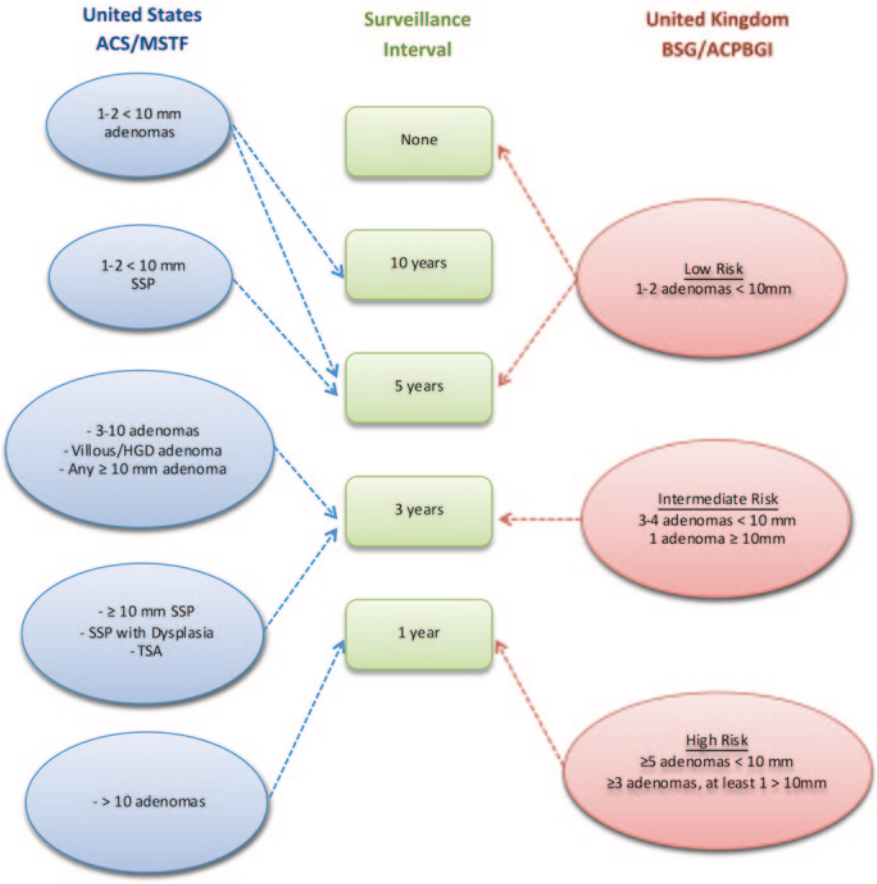

Fig. 2.4 Comparison of the US and UK polyp surveillance guidelines. Recommended colonoscopy surveillance interval based on findings on index colonoscopy

Cancer Surveillance

Rationale

Synchronous cancer (two or more simultaneous primary tumors not due to direct extension/metastasis) occurs in 2–5% of patients diagnosed with CRC [79, 80] and synchronous adenomas are present in at least 30% of these patients. Metachronous lesions (nonanastomotic new lesions developing at least 6 months after initial diagnosis) develop in 1.5–3% of patients in the first 3–5 years after surgical resection [79, 81–88]. More than half of these lesions arise within the first 2 years post resection [82, 84, 86], suggesting that they may have been missed synchronous cancers. Anastomotic recurrence occurs in 2–4% of patients with CRC, with higher rates of

recurrence in patients with rectal cancer [82, 84, 89–93]. More than 80% of anastomotic recurrences occur within the first 2.5 years post resection [84, 85].

Data for Surveillance

There is a clear benefit for colonoscopy surveillance post-cancer resection for detecting metachronous cancers and adenomas. The majority of metachronous cancers detected by surveillance are early stage (65% are Dukes stage A or B) [82, 84–86, 94–97], asymptomatic (56%) [82, 84, 85, 90, 94, 98, 99], and potentially surgically curable (87%) [84, 85, 89, 90, 94–98].

On the other hand, neither prospective randomized trials [82, 89, 100] nor meta-analyses [101] have found a benefit of shorter colonoscopic surveillance intervals (1 year) compared to longer intervals (3–5 years) for CRC recurrence after resection. This is likely because anastomotic recurrences are uncommon and most patients with anastomotic recurrence also have other sites of metastatic disease.

Guidelines

The ACS/MSTF published guidelines for colonoscopy surveillance after cancer resection in 2006 [102]. These guidelines recommend "clearing colonoscopy" preoperatively if possible or within a few months of resection. Colonoscopy should subsequently be performed 1 year post resection then 3 years later then every 3–5 years depending whether adenomas are found. Given the higher risk of recurrence in rectal cancer, rectal surveillance (usually via sigmoidoscopy) should be performed every 3–6 months for the first 2–3 years post resection. The NCCN guidelines are similar to those of the ACS/MSTF except that they recommend another annual colonoscopy if an advanced adenoma is found at the 1 year postresection colonoscopy.

In contrast, the UK guidelines recommend colonoscopic surveillance 5 years after surgery and every 5 years thereafter.

Current Screening Practices Around the World

The approach to screening in the USA is very different from approaches in the rest of the world. Screening in Europe and Australia is usually included as part of a national health program which typically offers a single or limited screening strategy, in most cases FOBT. In the USA, a variety of options are included in national guidelines with an emphasis on individualizing the screening approach based on local expertise, access to specialty care, and patient preference. Despite these options, about 80% of all screening in the USA is done by colonoscopy, in part because

there are substantial incentives for colonoscopic screening for both the primary care provider (PCP) and endoscopist. Colonoscopy is the one screening test that examines the entire colon and allows polypectomy during the same procedure and many PCPs believe that it is superior to the other CRC screening approaches [103]. If colonoscopy is negative, no further CRC screening is needed for 10 years and the responsibility for follow-up is shared with the endoscopist. There are strong financial incentives for the endoscopist to offer colonoscopic screening since screening colonoscopies are covered by almost all insurance plans in the USA and they are well reimbursed. Colonoscopy accounts for a large proportion of the average US gastroenterologist's revenue stream.

In contrast, there are few disincentives to colonoscopy screening in the USA. One would think that cost would be a major issue; however, cost-effectiveness models have argued that the increased cost of colonoscopy is justified by its estimated increased effectiveness. There are, however, a number of trends in the use of colonoscopy that are impacting its cost-effectiveness in a negative manner. The increase in ADRs will identify a larger portion of the screened population that will require more frequent surveillance and increase the pathology costs associated with colonoscopy. The tendency of endoscopists to schedule follow-up colonoscopies at intervals substantially shorter than the guidelines recommend [104] and the increasing use of monitored anesthesia care for routine colonoscopies also increases overall cost. Interestingly, all screening and preventive approaches look more attractive [105] and even cost-effective [106] as the cost of CRC treatment with the addition of biologics has skyrocketed.

Conclusions

Colon screening is arguably one of the greatest cancer prevention success stories of the past 25 years. Although CRC mortality is falling in many Western countries, the USA is the only country in which both incidence and mortality have been steadily falling for the past 30 years and much of this is likely due to screening. Screening rates are currently more than 60% in the USA and are continuing to increase (Fig 2.1). Conceptually, the field appears to be moving from early detection of CRC to identification and removal of precancerous colonic polyps. There is robust evidence to support FOBT and FS as primary screening modalities and indirect evidence to support colonoscopic screening. International guidelines focus on a screening program as a whole and generally support a single screening strategy (FOBT in most cases) while US guidelines support a variety of options including stool-based tests (FOBT, FIT, fecal DNA) and structural tests (DCBE, CTC, FS, colonoscopy). Colonoscopic screening has become the dominant screening modality in the USA. There are several trials underway to investigate the efficacy of colonoscopy but will not be completed for at least another 10 years. Despite drawing on the same evidence, the US guidelines tend to be more aggressive in screening and surveillance when compared to international guidelines.

References

1. Center MM, Jemal A, Smith RA, et al. Worldwide variations in colorectal cancer. CA Cancer J Clin. 2009;59:366–78.
2. National Institutes of Health. Colon and rectal cancer. In: Institute NC, editor. Cancer topics. Volume 2013. 2013. http://www.cancer.gov/cancertopics/types/colon-and-rectal. Accessed 23 Sep 2014.
3. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116:544–73.
4. Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. Curr Gastroenterol Rep. 2012;14:428–38.
5. Farraye FA, Odze RD, Eaden J, et al. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010;138:746–74, 774 e1–4; quiz e12–3.
6. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and familial colon cancer. Gastroenterology. 2010;138:2044–58.
7. Natalin RA, Landman J. Where next for the endoscope? Nat Rev Urol. 2009;6:622–8.
8. Hertz RE, Deddish MR, Day E. Value of periodic examinations in detecting cancer of the rectum and colon. Postgrad Med. 1960;27:290–4.
9. Fruton JS. Proteins, enzymes, genes: the interplay of chemistry and biology. New Haven: Yale University; 1999.
10. University H, Editor. Boston medical and surgical journal. vol 157. Boston: Massachusetts Medical Society, New England Surgical Society; 1907. pp. 170–4.
11. Greegor DH. Diagnosis of large-bowel cancer in the asymptomatic patient. JAMA. 1967;201:943–5.
12. Adams EC, Layman KM. Immunochemical confirmation of gastrointestinal bleeding. Ann Clin Lab Sci. 1974;4:343–9.
13. Eddy D. ACS report on the cancer-related health checkup. CA Cancer J Clin. 1980;30:193–240.
14. USPSTF. Guide to clinical preventive services. 2nd ed. In Force UPST, editor. Department of Health and Human Services, 1995.
15. Von Karsa LAA, Ronco G, Ponti A, Malila N, Arbyn M, Segnan N, Castillo-Beltran M, Boniol M, Ferlay J, Hery C, Sauvaget C, Voti L, Autier P. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening—first report. In: IAfRo, editor. Cancer. Luxembourg: European Commission; 2008.
16. Pignone M, Campbell MK, Carr C, et al. Meta-analysis of dietary restriction during fecal occult blood testing. Eff Clin Pract. 2001;4:150–6.
17. Winawer SJ, Flehinger BJ, Schottenfeld D, et al. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. J Natl Cancer Inst. 1993;85:1311–8.
18. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst. 2007;99:1462–70.
19. Allison JE, Tekawa IS, Ransom LJ, et al. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med. 1996;334:155–9.
20. Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol. 2008;103:1541–9.
21. Kronborg O, Jorgensen OD, Fenger C, et al. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol. 2004;39:846–51.

22. Whitlock EP, Lin JS, Liles E, et al. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149:638–58.
23. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. 2000;343:1603–7.
24. Scholefield JH, Moss S, Sufi F, et al. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut. 2002;50:840–4.
25. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg. 2008;95:1029–36.
26. Shaukat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369:1106–14.
27. Moayyedi P, Achkar E. Does fecal occult blood testing really reduce mortality? A reanalysis of systematic review data. Am J Gastroenterol. 2006;101:380–4.
28. Hol L, de Jonge V, van Leerdam ME, et al. Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. Eur J Cancer. 2010;46:2059–66.
29. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med. 2009;150:162–9.
30. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med. 2012;366:697–706.
31. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med. 2004;351:2704–14.
32. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med. 2008;149:441–50, W81.
33. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370:1287–97.
34. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut. 2014;63:317–25.
35. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;134:1570–95.
36. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med. 2003;349:2191–200.
37. Cotton PB, Durkalski VL, Pineau BC, et al. Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. JAMA. 2004;291:1713–9.
38. Rockey DC, Paulson E, Niedzwiecki D, et al. Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. Lancet. 2005;365:305–11.
39. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med. 2008;359:1207–17.
40. Soetikno R, Kaltenbach T. High-quality CT colonography can detect nonpolypoid colorectal neoplasm (NP-CRN)-science or rhetoric? Acad Radiol. 2010;17:1317; author reply 1317–8.
41. van Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006;101:343–50.
42. Ladabaum U, Song K, Fendrick AM. Colorectal neoplasia screening with virtual colonoscopy: when, at what cost, and with what national impact? Clin Gastroenterol Hepatol. 2004;2:554–63.
43. Hassan C, Zullo A, Laghi A, et al. Colon cancer prevention in Italy: cost-effectiveness analysis with CT colonography and endoscopy. Dig Liver Dis. 2007;39:242–50.
44. Vijan S, Hwang I, Inadomi J, et al. The cost-effectiveness of CT colonography in screening for colorectal neoplasia. Am J Gastroenterol. 2007;102:380–90.

45. Hur C, Chung DC, Schoen RE, et al. The management of small polyps found by virtual colonoscopy: results of a decision analysis. Clin Gastroenterol Hepatol. 2007;5:237–44.
46. Shah JP, Hynan LS, Rockey DC. Management of small polyps detected by screening CT colonography: patient and physician preferences. Am J Med. 2009;122:687 e1–9.
47. Imperiale TF, Wagner DR, Lin CY, et al. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med. 2000;343:169–74.
48. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375:1624–33.
49. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial–SCORE. J Natl Cancer Inst. 2011;103:1310–22.
50. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366:2345–57.
51. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol. 2011;9:42–6.
52. Rex DK, Petrini JL, Baron TH, et al. Quality indicators for colonoscopy. Am J Gastroenterol. 2006;101:873–85.
53. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370:1298–306.
54. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med. 2010;362:1795–803.
55. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. Ann Intern Med. 2009;150:849–57, W152.
56. Muller AD, Sonnenberg A. Protection by endoscopy against death from colorectal cancer. A case-control study among veterans. Arch Intern Med. 1995;155:1741–8.
57. Baxter NN, Sutradhar R, Forbes SS, et al. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. Gastroenterology. 2011;140:65–72.
58. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol. 2012;30:2664–9.
59. USPSTF. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149:627–37.
60. NCCN. NCCN clinical practice guidelines in oncology: colorectal cancer screening. Volume 2014. 2013. http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Accessed 12 Jan 2014.
61. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59:666–89.
62. Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. In: Australian National Health & Medical Research Council. Cancer Council Australia ACN, editor. 2005.
63. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104:739–50.
64. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343:78–85.
65. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001;96:2992–3003.
66. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer. 2006;42:216–27.
67. Imperiale TF, Ransohoff DF. Risk for colorectal cancer in persons with a family history of adenomatous polyps: a systematic review. Ann Intern Med. 2012;156:703–9.

68. Austin GL, Goldstein JI, Peters SL, et al. Are colorectal cancer screening recommendations for first-degree relatives of patients with adenomas too aggressive? Clin Gastroenterol Hepatol. 2011;9:308–13.
69. Saini SD, Kim HM, Schoenfeld P. Incidence of advanced adenomas at surveillance colonoscopy in patients with a personal history of colon adenomas: a meta-analysis and systematic review. Gastrointest Endosc. 2006;64:614–26.
70. Martinez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology. 2009;136:832–41.
71. Pinsky PF, Schoen RE, Weissfeld JL, et al. The yield of surveillance colonoscopy by adenoma history and time to examination. Clin Gastroenterol Hepatol. 2009;7:86–92.
72. Laiyemo AO, Pinsky PF, Marcus PM, et al. Utilization and yield of surveillance colonoscopy in the continued follow-up study of the polyp prevention trial. Clin Gastroenterol Hepatol. 2009;7:562–7; quiz 497.
73. Robertson DJ, Burke CA, Welch HG, et al. Using the results of a baseline and a surveillance colonoscopy to predict recurrent adenomas with high-risk characteristics. Ann Intern Med. 2009;151:103–9.
74. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138:2088–100.
75. Arain MA, Sawhney M, Sheikh S, et al. CIMP status of interval colon cancers: another piece to the puzzle. Am J Gastroenterol. 2010;105:1189–95.
76. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy-results of the complete adenoma resection (CARE) study. Gastroenterology. 2013;144:74–80 e1.
77. Schreiner MA, Weiss DG, Lieberman DA. Proximal and large hyperplastic and nondysplastic serrated polyps detected by colonoscopy are associated with neoplasia. Gastroenterology. 2010;139:1497–502.
78. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844–57.
79. Ringland CL, Arkenau HT, O'Connell DL, et al. Second primary colorectal cancers (SPCRCs): experiences from a large Australian Cancer Registry. Ann Oncol. 2010;21:92–7.
80. Passman MA, Pommier RF, Vetto JT. Synchronous colon primaries have the same prognosis as solitary colon cancers. Dis Colon Rectum. 1996;39:329–34.
81. Bruinvels DJ, Stiggelbout AM, Kievit J, et al. Follow-up of patients with colorectal cancer. A meta-analysis. Ann Surg. 1994;219:174–82.
82. Schoemaker D, Black R, Giles L, et al. Yearly colonoscopy, liver CT, and chest radiography do not influence 5-year survival of colorectal cancer patients. Gastroenterology. 1998;114:7–14.
83. Safi F, Beyer HG. The value of follow-up after curative surgery of colorectal carcinoma. Cancer Detect Prev. 1993;17:417–24.
84. Barillari P, Ramacciato G, Manetti G, et al. Surveillance of colorectal cancer: effectiveness of early detection of intraluminal recurrences on prognosis and survival of patients treated for cure. Dis Colon Rectum. 1996;39:388–93.
85. Juhl G, Larson GM, Mullins R, et al. Six-year results of annual colonoscopy after resection of colorectal cancer. World J Surg. 1990;14:255–60; discussion 260–1.
86. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. Ann Intern Med. 2002;136:261–9.
87. Mulder SA, Kranse R, Damhuis RA, et al. The incidence and risk factors of metachronous colorectal cancer: an indication for follow-up. Dis Colon Rectum. 2012;55:522–31.
88. Cali RL, Pitsch RM, Thorson AG, et al. Cumulative incidence of metachronous colorectal cancer. Dis Colon Rectum. 1993;36:388–93.
89. Makela JT, Laitinen SO, Kairaluoma MI. Five-year follow-up after radical surgery for colorectal cancer. Results of a prospective randomized trial. Arch Surg. 1995;130:1062–7.

90. Kjeldsen BJ, Kronborg O, Fenger C, et al. A prospective randomized study of follow-up after radical surgery for colorectal cancer. Br J Surg. 1997;84:666–9.
91. Pietra N, Sarli L, Costi R, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. Dis Colon Rectum. 1998;41:1127–33.
92. Castells A, Bessa X, Daniels M, et al. Value of postoperative surveillance after radical surgery for colorectal cancer: results of a cohort study. Dis Colon Rectum. 1998;41:714–23; discussion 723–4.
93. Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. Dis Colon Rectum. 1997;40:15–24.
94. Granqvist S, Karlsson T. Postoperative follow-up of patients with colorectal carcinoma by colonoscopy. Eur J Surg. 1992;158:307–12.
95. Kronborg O, Hage E, Deichgraeber E. The remaining colon after radical surgery for colorectal cancer. The first three years of a prospective study. Dis Colon Rectum. 1983;26:172–6.
96. Togashi K, Konishi F, Ozawa A, et al. Predictive factors for detecting colorectal carcinomas in surveillance colonoscopy after colorectal cancer surgery. Dis Colon Rectum. 2000;43:S47–53.
97. Weber CA, Deveney KE, Pellegrini CA, et al. Routine colonoscopy in the management of colorectal carcinoma. Am J Surg. 1986;152:87–92.
98. Chen F, Stuart M. Colonoscopic follow-up of colorectal carcinoma. Dis Colon Rectum. 1994;37:568–72.
99. Patchett SE, Mulcahy HE, O'Donoghue DP. Colonoscopic surveillance after curative resection for colorectal cancer. Br J Surg. 1993;80:1330–2.
100. Ohlsson B, Breland U, Ekberg H, et al. Follow-up after curative surgery for colorectal carcinoma. Randomized comparison with no follow-up. Dis Colon Rectum. 1995;38:619–26.
101. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2002;1CD002200. doi.10.1002/14651858.CD002200
102. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2006;130:1865–71.
103. McQueen A, Bartholomew LK, Greisinger AJ, et al. Behind closed doors: physician-patient discussions about colorectal cancer screening. J Gen Intern Med. 2009;24:1228–35.
104. Walker AS, Nelson DW, Fowler JJ, et al. An evaluation of colonoscopy surveillance guidelines: are we actually adhering to the guidelines? Am J Surg. 2013;205:618–22; discussion 622.
105. Luo Z, Bradley CJ, Dahman BA, et al. Colon cancer treatment costs for Medicare and dually eligible beneficiaries. Health Care Financ Rev. 2010;31:35–50.
106. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev. 2011;33:88–100.
107. Patel SG, Ahnen DJ. Prevention of interval colorectal cancers: what every clinician needs to know. Clin Gastroenterol Hepatol. 2014;12(1):7–15.
108. Patel S, Ahnen D. Screening for colon polyps and cancer. In: Miller AB, editor. Epidemiologic studies in cancer prevention and screening, vol 79. New York: Springer; 2013. pp. 233–61.
109. Levin B, Murphy GP. Revision in American Cancer Society recommendations for the early detection of colorectal cancer. CA Cancer J Clin. 1992;42:296–9.
110. Byers T, Levin B, Rothenberger D, et al. American Cancer Society guidelines for screening and surveillance for early detection of colorectal polyps and cancer: update 1997. American cancer society detection and treatment advisory group on colorectal cancer. CA Cancer J Clin. 1997;47:154–60.
111. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001–testing for early lung cancer detection. CA Cancer J Clin. 2001;51:38–75; quiz 77–80.

112. Mandel JS, Church TR, Ederer F, et al. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999;91:434–7.
113. Thiis-Evensen E, Hoff GS, Sauar J, et al. Flexible sigmoidoscopy or colonoscopy as a screening modality for colorectal adenomas in older age groups? Findings in a cohort of the normal population aged 63-72 years. Gut 1999;45:834–9.
114. Hoff G, Grotmol T, Skovlund E, et al. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338:b1846.
115. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007;146:244–55.

Chapter 3
Comparative Effectiveness and Cost-Effectiveness of Current CRC Screening Modalities

Ann G. Zauber

Introduction

The natural history of colorectal cancer (CRC), with a detectable precursor lesion (the adenoma), favors a screening intervention which is able to identify and possibly remove advanced adenomas and early-stage cancers. Screening has been credited in achieving a 53 % reduction in CRC mortality rates since 1975 [1, 2]. We now have multiple types of CRC screening tests. In this chapter, we discuss how to compare different CRC screening tests with respect to effectiveness, comparative effectiveness, and cost-effectiveness [3]. Examples of these types of comparisons are given.

The current US guidelines and recommendations for CRC screening [4–6] now include a choice of options for screening tests, with varying degrees of evidence for their effectiveness to reduce CRC mortality. In this chapter, we consider the screening tests of stool-based tests, flexible sigmoidoscopy, colonoscopy (with strong direct and indirect evidence for their effectiveness), as well as newer tests of computed tomography colonography (CTC) and stool DNA. We discuss how to evaluate CRC screening tests with respect to comparative effectiveness. The question addressed is how to compare these different tests in a program of screening in terms of benefits to the patient relative to the resources required and available to deliver such benefits.

The Institute of Medicine (IOM) committee [7] has broadly defined *comparative effectiveness analysis* as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of comparative effectiveness analysis is to assist consumers, clinicians, purchasers, and policy

A. G. Zauber (✉)
Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 307 East 63 Street, Room 357, New York, NY 10065, USA
e-mail: zaubera@mskcc.org

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_3

makers to make informed decisions that will improve health care at both the individual and population levels." Risk relative to benefit is an essential component of comparative effectiveness with the goal to determine test strategies that provide the best balance of benefit to risk. As noted by Tunis, Benner, and McClellan in 2010 [8], the primary purpose of comparative effectiveness analysis is to help health-care decision makers make informed clinical and health policy decisions.

One commonly used component of comparative effectiveness is cost-effectiveness analysis which relates the cost of the process of screening to the benefits achieved. However, effectiveness and more recently comparative effectiveness, rather than cost-effectiveness analyses, have been used to date in setting clinical guidelines for CRC screening in the USA. Cost per se is not included in evaluations by the US Preventive Services Task Force (USPSTF) or for Patient-Centered Outcomes Research Institute (PCORI). Cost-effectiveness analyses are more commonly considered in assessing coverage or reimbursement levels for a given test. However, an understanding of cost-effectiveness techniques provides insight to the balance of risk and benefits that are required in current medical practice.

This chapter is integral to the attributes of quality of health care as given by Donabedian [9] in 1992 as (1) *effectiveness* being the ability to attain the greatest improvements in health now achievable by the best care, (2) *efficiency* as the ability to lower the cost of care without diminishing attainable improvements in health, (3) *optimality* as balancing of costs against the effects of care on health (or on the benefits of health care, meaning the monetary value of improvements in health) so as to attain the most advantageous balance, (4) *acceptability* as conformity to the wishes, desires, and expectations of patients and responsible members of their families, (5) *legitimacy* as conformity to societal preferences as expressed in ethical principles, values, norms, laws, and regulations, and (6) *equity* as conformity to a principle that determines what is just or fair in the distribution of health care and of its benefits among the members of the population.

Background on History of Comparative Effectiveness for CRC Screening

In 1997, Winawer et al. [10] published the multisociety guidelines for CRC screening based on the best evidence available from randomized controlled trials (RCTs) on fecal occult blood testing (FOBT) showing a CRC mortality reduction [11–13] and from observational data such as from case-control studies [14–16]. They presented CRC screening guidelines to include a panel of choices of annual FOBT, flexible sigmoidoscopy every 5 years, flexible sigmoidoscopy with FOBT, double contrast barium enema every 5–10 years, and colonoscopy every 10 years. However, they also addressed the question of whether all new CRC screening tests required a long-term RCT to assess whether the new test reduced CRC mortality relative to

usual care to be considered effective for CRC screening. They foresaw that new CRC screening tests were on the horizon and others would follow. They suggested that a new test could be considered for inclusion in the panel of screening recommendations if there was convincing evidence that the new test had "(1) comparable performance with respect to sensitivity and specificity, (2) is equally acceptable to patients [ie patients are adherent to this screening test] and (3) has comparable or lower complication rates and costs." They concluded that under these circumstances "it would not be necessary to submit each new technology to the original standard of proof, i.e., a RCT with death from CRC as an outcome measure." The inclusion of the fecal immunochemical test (FIT) in the multisociety guidelines and American Cancer Society Guidelines for CRC screening [5, 17] was based on this type of comparison [10] of FIT characteristics with that of guaiac-based FOBT (gFOBT).

These prescriptives of comparisons [10] were forerunners to those of the IOM [7] in 2009 for comparative effectiveness. We note that this comparison of new and old tests could require that the new test be superior, equivalent, or noninferior [18] to the older test with respect to test parameters of sensitivity, specificity, or adherence. Assessment of effectiveness alone required a test to be better than no screening.

Effectiveness Analysis

The original randomized controlled screening trials for FOBT [11–13] and for flexible sigmoidoscopy [19–22] all compared the CRC screening test to usual care (when such care implied little or no screening). Such trials allowed an assessment of the effectiveness of the screening test compared to no screening. They evaluated whether or not the screening test works, i.e., does it reduce CRC mortality relative to not screening. Long-term RCTs for colonoscopy are currently underway with the endpoints of CRC incidence and mortality reduction but will not be reported out until 2020 or beyond. These are COLONPREV trial in Spain [23] (ClinicalTrials.gov NCT00906997), the CONFIRM trial in the US Veterans Administration (VA) setting (ClinicalTrials.gov NCT01239082), and the NordICC trial in Northern Europe [24] (ClinicalTrials.gov NCT00883792). However, only the NordICC trial is an effectiveness trial comparing screening colonoscopy to usual care.

Comparative Effectiveness Analysis for CRC Screening Tests

Recent evaluations of new tests compare the test characteristics of the new test with those of an established test. As noted, this practice is based on recommendations from the multisociety guidelines of 1997 [10].

Comparison of gFOBT and FITs Performance for Sensitivity, Specificity, and Adherence

The three RCTs of FOBT [11–13] with a CRC mortality endpoint used the guaiac-based Hemoccult II test (gFOBT). This test requires two specimens from each of the three stool samples, dietary restrictions for red meat and cruciferous vegetables, and provides a qualitative assessment of blood in the stool. A higher-sensitive guaiac test, Hemoccult SENSA, has also been developed, but its higher sensitivity for CRC is associated with lower specificity. There is a wide range of FITs using different laboratory methodologies to detect human hemoglobin in the feces. An advantage of FIT is there is no dietary restriction. Both qualitative and quantitative FIT tests are available.

Allison [25–28] has conducted a number of comparative studies of "head-to-head" comparisons of gFOBT and FIT and concluded that the FIT had higher sensitivity and higher specificity for distal CRC than the sensitive guaiac test. Systematic reviews also have concluded that FIT is more sensitive in detecting CRC and advanced adenomas than gFOBT [29].

Studies in the Netherlands demonstrated a higher adherence to FIT than gFOBT testing and a higher detection rate for advanced adenomas or cancer [30, 31]. Consequently, both adherence and test performance values were higher for FITs than the gFOBT. These evaluations of "head-to-head" comparisons are consistent with the recommendations set down by the 1997 multisociety [10].

Raginel and colleagues [32] in 2013 compared two quantitative FITS (OC Sensor and Magstream) as well as gFOBT for diagnostic accuracy in a screening population of 1224. OC Sensor identified CRC with greater accuracy than Magstream.

Comparison of Different FITs and Different Programs of FIT

FIT is becoming more commonly recommended for stool sampling tests than the gFOBT [5, 17]. A quantitative meta-analysis by Lee [33] assessed the diagnostic accuracy (sensitivity and specificity) of 8 FITs for CRC from 19 studies and concluded that FIT is moderately sensitive, highly specific, and has high overall diagnostic accuracy for detecting CRC. The overall pooled estimate of sensitivity for CRC was 79% and the estimate for specificity was 94% (The role of FIT to detect advanced adenomas was not addressed in this overview). The eight tests included qualitative and quantitative measures. The analysis also demonstrated that the cutoff for a positive test affected the diagnostic performance of FIT. Lee concluded that "Overall, no single commercial FIT brand seemed to perform markedly better or worse than others for CRC detection, but this finding should be interpreted cautiously because most studies did not include 'head-to-head' comparisons." Heterogeneity for sensitivity and specificity estimates was decreased if discontinued FITs were excluded. Heterogeneity of effects was also due to different cutoffs for a positive test result between studies.

gFOBT Versus Colonoscopy

Brenner and colleagues [34] recently assessed the performance of gFOBT under routine screening conditions relative to screening colonoscopy in a state-wide analysis from Bavaria and concluded that gFOBT has poor diagnostic performance, especially with respect to detection of adenomas. They suggested that better noninvasive CRC screening tests than gFOBT are needed.

Flexible Sigmoidoscopy Versus FIT

Both flexible sigmoidoscopy [19–22] and a program of repeat FOBT [11–13] have been shown in RCTs to reduce CRC in comparison to usual care of no screening. Holme and colleagues have conducted a Cochrane review of how well these two strategies reduce CRC mortality [35]. They used five trials comparing flexible sigmoidoscopy to no screening with a meta-analysis of relative risk (RR) of 0.72, and four trials comparing programmatic FOBT to no screening with a meta-analysis RR of 0.87. Given that there were no trials that compared the two tests "head-to head," they used a Bayesian approach of a contrast-based network meta-analysis for indirect analyses and presented the results as posterior median RR of 0.85 with 95% credibility intervals of 0.72–1.01 for flexible sigmoidoscopy with the conclusion that both tests reduce CRC mortality but there was insufficient data whether flexible sigmoidoscopy or programmatic FOBT reduced CRC mortality more than the other.

Colonoscopy Versus Fecal Immunochemical Tests

Two of the three large-scale current RCTs on colonoscopy with a mortality endpoint are comparative effectiveness analyses of screening colonoscopy versus a program of FIT with biennial FIT testing for the COLONPREV trial in Spain [23] (ClinicalTrials.gov NCT00906997) and annual FIT testing for the VA trial (VA) (ClinicalTrials.gov NCT01239082). The Spanish COLONPREV trial [23] is a noninferiority trial whereas the CONFIRM trial in the US VA population is a superiority trial of colonoscopy over a program of annual FIT. NordICC, the third large trial evaluating colonoscopy, is a classic effectiveness trial [24] comparing colonoscopy with usual care to assess whether colonoscopy has reduced CRC mortality compared to usual care.

To date, the COLOPREV (Spanish) trial has reported higher baseline adherence for FIT (34%) than for colonoscopy (25%) $P < 0.001$, comparable detection of CRC, and lower detection of advanced adenomas for the FIT arm (0.9%) compared to the colonoscopy arm (1.9%). Of note, their initial publication in 2012 compared the adherence and clinical findings based on only one round of FIT but the full protocol is for five rounds of FIT screening. A single round of FIT has never been

recommended as a sufficient screening test for long-term prevention. Incidence and mortality outcomes will not be available for 10 years. The US VA trial (CONFIRM) is currently enrolling subjects. The NordICC trial has closed enrollment as of June 2014.

A smaller randomized trial by Gupta [36] compared adherence to screening with colonoscopy (25%), FIT (41%), and usual care (12%) in an underserved population receiving care at Dallas hospital in a program for medical assistance for uninsured residents in the Dallas county area. Adherence and level of detection of neoplasia were higher for FIT and colonoscopy than for usual care; outreach for screening was higher for a one-time FIT than for colonoscopy (ClinicalTrials.gov NCT01191411).

Inadomi and colleagues [37] conducted a RCTs on how choice of FOBT or colonoscopy affected adherence to these screening tests. Patients were randomized to recommendation of screening of FOBT, colonoscopy, or choice of FOBT or colonoscopy. Overall, 58% of subjects completed the CRC screening test that was assigned or that they chose. However, only 38% of those assigned to colonoscopy completed the test, whereas 67% of those assigned to FOBT completed the test. The authors suggest that patient preference should be considered when making CRC screening recommendations.

CTC Versus Optical Colonoscopy

Two large trials compared CTC and subsequent findings on optical colonoscopy in series of patients having same-day screening colonoscopy [38, 39]. The Department of Defense Study (DOD) [39] accrued 1233 subjects. The per-adenoma test characteristics were 92% sensitivity of CTC for adenomas 10 mm or larger detected by optical colonoscopy and 86% sensitivity for adenomas 6 mm or larger. Specificity was 96% for patients with adenomas 10 mm or larger and 80% for patients with adenomas 6 mm or larger. CTC results were not reported for lesions measuring less than 6 mm. Extracolonic findings deemed to be of high clinical importance were found in 4.5% of subjects. The National CT Colonography Trial (NCTC) sponsored by the American College of Radiology Imaging Network (ACRIN 6664) [38] accrued 2600 asymptomatic subjects for same-day CTC and optical colonoscopy. The per-adenoma sensitivity of CTC for adenomas or CRC 10 mm or larger as detected by colonoscopy was 84%, which was slightly lower than the estimate from the Department of Defense study (92%). Sensitivity for adenomas 6 mm or larger was 70%. Specificity was 86% for patients with adenomas 10 mm or larger and 88% for patients with adenomas 6 mm or larger. Extracolonic findings were observed in 66% of subjects, but only 16% were considered of clinical importance requiring either additional evaluation or urgent care.

In the Netherlands, Stoop [40] reported on a randomized trial of colonoscopy versus noncathartic CTC to assess participation (adherence) and neoplastic/diag-

nostic yield in subjects in Amsterdam and Rotterdam. Adherence was significantly higher for CTC (34%) than for colonoscopy (22%) (RR = 1.56, $P < 0.001$) but diagnostic yield for advanced neoplasia was higher for colonoscopy than for CTC (RR = 1.46, $P < 0.02$). Serious adverse events were rare (two post-polypectomy bleeds for colonoscopy and three for CTC). Participation was higher for CTC, diagnostic yield for advanced neoplasia was higher for colonoscopy, and adverse events were comparable.

Stool DNA Versus FOBT with Colonoscopy Evaluation for All

Imperiale has led two clinical trials [41, 42] evaluating a stool DNA test. In his first trial, the stool DNA test (PreGenPlus) was compared to the Hemoccult II test which was the test assessed originally in RCTs of CRC screening. All patients were subsequently evaluated by screening colonoscopy [42]. Sensitivity of the stool DNA test PreGenPlus for CRC was low (52%) but exceeded that of Hemoccult II with 12% CRC sensitivity. The PreGenPlus test was reevaluated internally for its lower-than-anticipated sensitivity for CRC.

A new multitargeted stool DNA (Cologuard; [41]) has been developed which is a multitargeted test including a fecal immunochemical test to detect hemoglobin as well as tests to detect mutations associated with CRC in the DNA of cells shed by advanced adenomas or CRC. Based on a new clinical trial (ClinicalTrials.gov NCT01397747) of 10,023 subjects who were having screening colonoscopy, Cologuard had 92% sensitivity for CRC and 42% sensitivity for advanced adenomas. The subjects also completed a commercially available FIT (OC-Sensor) which had 74% sensitivity for CRC and 42% sensitivity for advanced adenomas. However, Cologuard had lower specificity (87%) for CRC or advanced adenomas than the FIT (OC-Sensor) with 95% specificity. The Cologuard test has been approved by the Food and Drug Administration (FDA) and has been proposed for coverage by Centers for Medicare and Medicaid Services (CMS).

Comparative Effectiveness Studies from the PROSPR Underway

The National Cancer Institute (NCI) has organized a program for Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR) for grants on comparative effectiveness on the process of screening for CRC, cervical cancer, and breast cancer. For CRC, the goal is to understand the process of screening across initial participation, high-quality testing, appropriate and timely referral to diagnostic colonoscopy after a positive test, appropriate surveillance, and appropriate treatment. The purpose is to understand where in the screening processes there could be improvements.

Comparative Effectiveness of Quality of Colonoscopy to Reduce CRC Interval Cancers

PROSPR investigators from Kaiser Permanente in Northern California demonstrated that the comparative effectiveness of quality of colonoscopy, as measured by the adenoma detection rate, was inversely related to subsequent interval cancer. For each percentage increase in the adenomas detection, there was 3% decrease in the risk of interval CRC [43]. Cost-effectiveness analysis of these results is underway. Further work from this collaboration is expected to inform our understanding of how best to deliver CRC screening care in the future.

Cost-Effectiveness Analysis of CRC Screening Programs

Cost-effectiveness analysis is a special type of comparative effectiveness which includes cost in the comparison of the effectiveness of different strategies. Cost is used as a synthesis of resource use and adverse events to relate to outcomes such as life-years gained (LYG) with screening. Cost-effectiveness analysis provides a tool to determine which CRC screening programs to implement based on their costs to deliver a given screening program [44]. The amount of money (cost) a society or payer is willing to pay for an additional quality-adjusted life year (QALY) gained provides a threshold of costs that can be used to choose scenarios which provide benefit within the confines of resources available or in consideration with other medical and societal needs [3]. A cost of US$ 50,000 for an intervention that provides for an additional year of quality-adjusted life is considered acceptable in many industrialized countries but a cost of US$ 100,000 per LYG is often used in the USA [44, 45]. More recently, Neuman et al. [45] suggested using US$ 50,000 per QALY as a lower boundary, and US$ 100,000 and US$ 15,000 per QALY as upper boundaries when "outside the context of an explicit resource constraint." Cost-effectiveness analysis cannot necessarily determine the optimal intervention but does focus on what intervention will provide the greatest health benefits, given the decision maker's or society's willingness to pay for a unit of benefit. Furthermore, the incremental cost-effectiveness ratio (ICER) of increase in cost (risk) in relationship to QALY saved (benefit) for one scenario to another provides for a measure of when the risk to benefit ratio is best balanced or optimized. A summary table for risks and benefits is also frequently a part of an assessment of cost-effectiveness analyses [46].

Reviews of Cost-Effectiveness for CRC Screening Tests

Pignone [47] led a review of cost-effectiveness analysis for CRC screening tests in 2002 as part of a systematic review of evidence for the USPSTF [48]. They

concluded that CRC screening is effective as compared with no screening for all tests considered, but no single test strategy was consistently found to be the most effective or to be preferred for a given willingness to pay per LYG across the different cost-effectiveness analyses. A more recent comprehensive review of these issues led by Lansdorp-Vogelaar [49] found similar findings as the Pignone report. All studies found that CRC screening was cost-effective, and at times cost-saving compared with no screening. However, the studies differed with respect to which screening test or strategy was most effective or had the best incremental cost-effectiveness ratio for a given willingness to pay per LYG. They also noted the lack of consistency in perspective population, time horizon and discount rate, and the heterogeneity [50, 51] of results for different cost-effectiveness analyses. An even more recent review of cost-effectiveness analyses for CRC screening by Cruzado et al. [52] again found that there is no single CRC screening test that has been clearly identified as the most cost-effective. There was consensus [44, 49, 52] that newer technologies of CTC, stool DNA (based on the earlier PreGenPlus test), and capsule endoscopy were not yet cost-effective compared with the established screening options.

Given that no CRC screening strategy emerged across different analyses as being the most effective or having the best incremental cost-effectiveness ratio for a given willingness to pay per LYG, Lansdorp-Vogelaar suggested that willingness to be screened (i.e., adherence) should be considered in choosing a best strategy [44]. The prior cost-effectiveness analyses had focused on 100% adherence in the population screened. Lansdorp-Vogelaar invoked the saying that the "best test is the test that gets done" and even more so "the best test is the test that gets done *well*." The prior cost-effectiveness analyses had been based on efficacy of the tests for those willing to be screened. On a population level, the acceptability of a given screening test must be included in a choice of a test; this is consistent with the original recommendations by Donabedian [9] and the Multi-Society Task Force [10].

Cost-Effective CRC Screening Tests if There Would be Higher Use of New Expensive Chemotherapies for Advanced Disease

Landsdorp-Vogelaar also assessed cost-effective strategies for CRC screening when there would be widespread use of the new expensive chemotherapies for treating later-stage disease [50, 51]. She considered annual gFOBT, annual FIT, 5-year flexible colonoscopy, colonoscopy every 10 years, and a combination of sigmoidosopy every 5 years with a gFOBT annually and assessed scenarios with older chemotherapy and newer, more expensive chemotherapy for treatment of those with advanced disease. Compared with no screening, the treatment savings from preventing advanced CRC deaths by screening more than doubled with the widespread use of new chemotherapies. The lifetime average treatment savings were larger than the lifetime average screening costs. Although colonoscopy was the one screening test considered that did not become cost saving when newer chemotherapy drugs were used, net costs were reduced by 78% and were close to cost savings. These results

suggest that with the increase in chemotherapy costs for advanced CRC, most CRC screening tests become cost saving. Screening not only reduces CRC incidence and mortality but also lowers the cost of cancer treatment in the population.

Use of Microsimulation Models to Assess Long-Term Effects for Cost-Effectiveness Analysis

Components of a Cost-Effectiveness Analysis

Microsimulation modeling has been used for cost-effectiveness analysis for CRC screening tests to include the outcome of LYG (or quality LYG) in comparison to lifetime costs accrued to this screening strategy. In general, a cost-effectiveness analysis comparing multiple strategies includes the following components:

- Is a test strategy effective? That is, does the screening test provide LYG relative to no screening?
- What is the average cost-effectiveness ratio (ACER)? This is the discounted (3%) cost of the screening strategy relative to no screening divided by the LYG with screening. The ACER is derived without regard to comparison to other screening alternatives [53]. It shows whether the net benefits of the strategy are a good value for the resources required among individuals who would not be screened at all without the availability of that strategy. Note that costs include treatment costs for those developing CRC. Consequently, there are costs associated with no screening as well as for with screening.
- Is the ACER (cost per LYG relative to no screening) below the society's willingness to pay threshold of US$ 50,000, 100,000, or 150,000 per quality LYG?
- Determine which strategies provide the least cost for a given level of effectiveness.
  - We assess the relative performance of each economically efficient (i.e., nondominated) strategy using the ICER which is the additional cost of a strategy divided by its additional clinical benefit compared with the next less-expensive nondominated strategy. Dominated strategies include those that are more costly and less effective than a competing option (strongly dominated strategies) and those that had a higher incremental cost per LYG compared to a more costly strategy (i.e., weakly dominated strategies) [54].
- Derive an efficiency frontier for the dominant strategies.
  - All nondominated strategies represent the set of potentially cost-effective (depending on the willingness to pay for an LYG) or cost-efficient options. When the discounted total costs and the discounted LYG associated with each strategy are plotted on a graph, the line connecting the subset of efficient strategies is called the efficient frontier [55].

- Sensitivity analyses for the impact on the effectiveness and cost outcomes given other assumptions of test parameters are required.

In this chapter, we use the results from the *Mic*rosimulation *Sc*reening *An*alysis (MISCAN) microsimulation model, from the Cancer Intervention and Surveillance Modeling Network (CISNET) of the NCI to provide two examples of using cost-effectiveness analysis to address issues in CRC screening. Our cost estimates are based on CMS reimbursement rates for screening tests, complications of screening, and cancer treatment.

Threshold Analysis for Cost of CTC

Example of Cost-Effectiveness Analysis in Assessing a Reimbursement Level for a New Test

In 2009, the CMS considered whether to provide coverage for a new test, CTC, for CRC screening for Medicare enrollees [46, 54, 56]. The CRC CISNET modelers conducted a cost-effectiveness analysis to inform CMS, should CTC be approved for coverage by CMS. We assumed that a CTC test which detected a polyp of size 6 mm or larger would be followed up by a diagnostic colonoscopy to remove the polyp for pathological analysis; furthermore, the CTC examination would be repeated at 5-year intervals provided no adenomas of CRC were detected. In a chapter for a prior publication [56], we described the methods we used for the microsimulation modeling, the assumptions for the microsimulation model, the CMS reimbursement cost assumptions, and the derivation of an efficient frontier of CRC screening tests of gFOBT, FIT, flexible sigmoidoscopy with and without FOBT, and colonoscopy. The original analysis was also published [54]. Harris advocated for a formal risk and benefit table for inclusion with cost-effectiveness analyses in an editorial [46] on this work [54].

Given that CTC was being considered for CMS coverage, there was no established national CMS payment for screening CTC. We used as the CMS reimbursement for CTC the sum of the national average CMS payments for abdominal and pelvic computed tomography (CT) without contrast plus the national average CMS payments for image processing on an independent workstation as a placeholder for CTC in our original analysis. This cost was US$ 488 per CTC test which is only slightly lower than the cost of a colonoscopy without polypectomy (US$ 498) from CMS rate of 2008. We considered the test parameters for CTC from two studies—that of the DoD [39] and that of NCTC [38].

The discounted LYGs (on the *y*-axis) plotted against the discounted costs (on the *x*-axis) for each of the 14 strategies provide descriptive and quantitative measures of the comparisons of risk to benefit (Fig. 3.1). The higher the point, the more effective the screening strategy [55]. All strategies except Hemoccult II and sigmoidoscopy alone have relatively high LYGs. The more to the left, the lower is the cost.

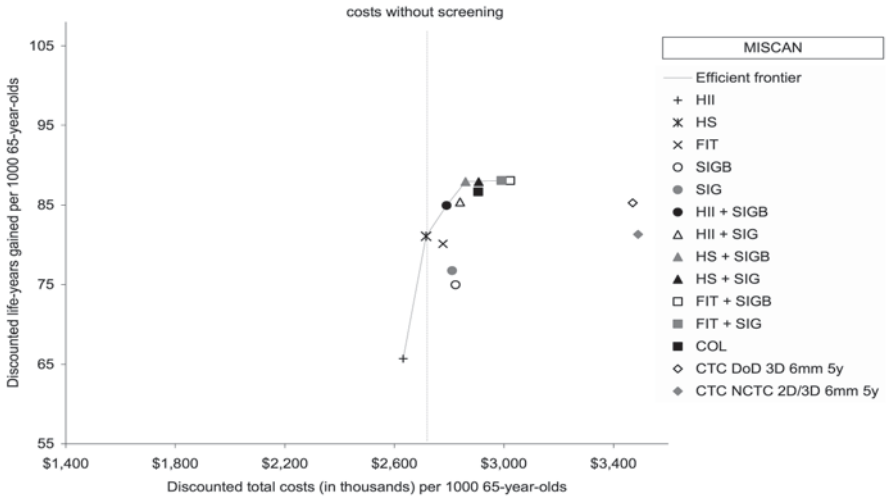

Fig. 3.1 Discounted costs and discounted life-years gained per 1000 65-year-olds for 14 CRC screening strategies including two strategies for CT-colonography (CTC)* and the efficient frontier connecting the efficient strategies—*Mic*rosimulation *Sc*reening *An*alysis (MISCAN) model. (*The two CTC strategies are not competing options; they represent a range of estimates of CTC test characteristics. They are shown here together for comparison purposes only. The incremental cost-effectiveness ratios (ICERs) are assessed separately using each CTC strategy in turn)

The more to the right, the more expensive is the screening strategy. The strategies towards the upper left-hand corner are those with the higher LYGs relative to lower costs per LYG. Costs for strategies that include endoscopy are more expensive than those using FOBTs only. However, the highest cost strategy is CTC when per test CTC cost is US$ 488.

For a quantitative comparison of LYGs per cost for multiple strategies, we ranked the screening strategies by increasing effectiveness (i.e., discounted number of LYGs compared with no screening) from annual Hemoccult II with the lowest life years saved to flexible sigmoidoscopy with biopsy every 5 years plus annual FIT and compared their life years saved relative to the cost of the strategy. In Fig. 3.1, for the plot of costs versus LYGs, the black line links the strategies with the most LYGs relative to a given level of costs and is called the efficient frontier. These strategies represent the set of efficient options and include Hemoccult II, Hemoccult SENSA, flexible sigmoidoscopy with biopsy and annual Hemoccult SENSA, and flexible sigmoidoscopy with biopsy and annual FIT. Strategies which are more costly and less effective (fewer LYGs) than another strategy are below the efficient frontier and are considered dominated by the more efficient strategies. These dominated strategies include FIT, sigmoidoscopy alone, four of the flexible sigmoidoscopy and FOBT combinations, colonoscopy, and CTC. However, the only strategies relatively far off the efficient frontier (i.e., a dominated strategy) are flexible sigmoidoscopy alone and two strategies for CTC. The other dominated strate-

gies (including colonoscopy) are close to that of the efficient frontier and could be considered in the set of acceptable cost-effective screening options. Based on this analysis, Hemoccult II and flexible sigmoidoscopy are less attractive screening options because of the lower LYGs with Hemoccult II and the lower LYGs as well as the higher costs per LYG than other options with flexible sigmoidoscopy. CTC also is a less attractive strategy with higher costs than other strategies which provide comparable or higher LYGs at lower costs (when the CTC cost is at US$ 488 per test as initially considered).

This cost-effective analysis is also used to visualize and quantify the increase in costs per LYG when moving from one efficient strategy to the next highest strategy. The slope of the efficient frontier changes markedly going from Hemoccult II to the Hemoccult SENSA strategy. Then there is a relatively flat line with only slight increase in life years saved relative to increasing costs for the remaining strategies. The inverse of the slope is used as the measure of the relative performance of the efficient strategies and is the ICER, defined as the additional cost of a specific strategy, divided by its additional clinical benefit, compared with the next least-expensive strategy. Those strategies on the flat of the efficient frontier curve represent diminishing returns of effectiveness per expenditure [55].

The two strategies (DoD and ACRIN) for CTC are far from the efficient frontier in Fig. 3.1 when using a cost of US$ 488 per scan (i.e., when the CTC cost was just below that used for colonoscopy without polypectomy (US$ 498)). Knudsen used threshold analysis to determine that the cost for CTC would need to be US$ 108 (for NCTC) and US$ 122 (for DoD) per test in the 65-year old cohort to place the CTC strategy on the efficient frontier of strategies (i.e., thus cost-effective) relative to the LYGs with the CTC strategy [54, 56]. In a previous analysis using slightly different CTC test characteristics, Lansdorp-Vogelaar [57] determined that CTC would need to be at a cost approximately 40% lower per scan than colonoscopy procedure with referral of CTC lesions 6 mm or larger and repeat CTC every 5 years to be cost-effective (and on the efficient frontier). These results are largely consistent with that of Knudsen [54].

In an alternative analysis, Knudsen [54] showed if individuals who would not be screened otherwise would agree to be screened with CTC, the threshold costs for CTC would be US$ 204 (for NCTC) and US$ 293 (DoD) for a 10% increase in relative adherence for CRC screening and would be US$ 435 (NCTC) and US$ 547 (DoD) for a 25% relative increase for CRC screening.

Example of Decision Analysis for Choice of Age to End CRC Screening Strategies in the Elderly

Original Decision Analysis for CRC Screening for the USPSTF in 2008

In 2008, the USPSTF requested a decision analysis to evaluate a range of CRC screening tests with respect to age to begin, age to end, and intervals of screening

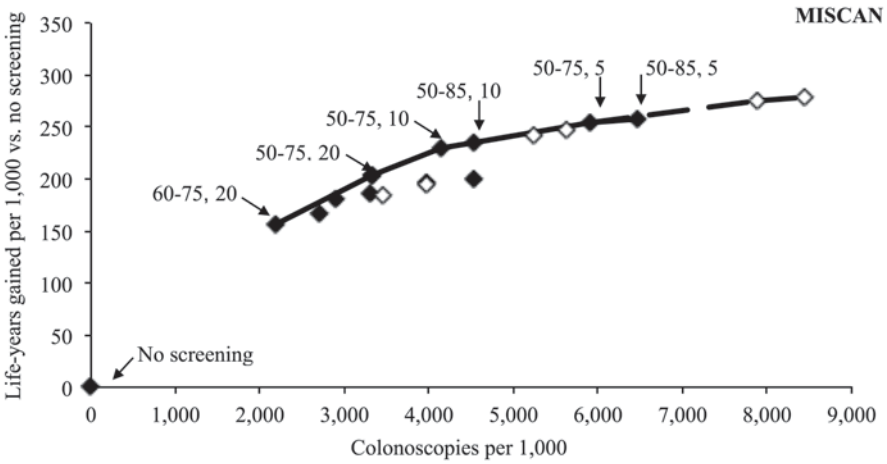

Fig. 3.2 Life years gained per 1000 screened with different strategies of colonoscopy by number of colonoscopies per 1000 required per strategy. Results from the MISCAN model. (Based on data from Ref. [58])

to inform their decision of which screening tests and which screening scenarios to recommend. Long-term outcomes were LYGs with different screening strategies as obtained from the microsimulation modeling groups of the NCI-sponsored CISNET. These LYGs compared to no screening (the benefit) were balanced against the number of colonoscopies required per strategy. The number of colonoscopies required per scenario represents both resource use and risk of complications of colonoscopy of perforation or major bleeds requiring hospitalization in an asymptomatic average-risk population. In the average-risk population, the screening strategies considered were three ages to begin screening (40, 50, and 60), two ages to end screening (75 and 85), and three intervals of rescreening for those with no prior findings (5, 10, 20 years for endoscopy and 1, 2, 3 years for FOBTs). Tests considered were colonoscopy, flexible sigmoidoscopy with and without a FOBT, and gFOBT alone and FIT alone [58].

The results from the MISCAN CISNET model for the colonoscopy strategies are given in Fig. 3.2 [58]. The LYGs are plotted on the *y*-axis against the number of colonoscopies (screening and surveillance) required for each scenario on the *x*-axis. LYGs increase with increasing colonoscopy resource use. However, there is an inflection point between a strategy of beginning screening at age 50 and stopping at age 75 with a 10-year interval and that of beginning at age 50 but stopping at age 85 with a 10-year interval. This inflection point represented where additional resource use (colonoscopy) did not provide for an appreciable benefit of more LYGs. It is this kind of analysis that can provide an understanding of how to balance the benefits compared to the risks.

Based on consistent findings for the small increase in LYGs with extending screening to age 85 rather than stopping at age 75 for the strategies of colonoscopy, FIT, gFOBT, and flexible sigmoidoscopy with an FOBT, the USPSTF recommended

that CRC screening should be conducted in the average risk population from age 50 to 75. However, the USPSTF recommended against routine screening to continue in persons older than 75 years with an adequate screening history because the benefits of continuing screening from age 50 to 85 instead of 75 years do not justify the additional colonoscopies required [4]. However, this USPSTF recommendation to stop routine screening in those with consistent screening with negative findings was misunderstood by many to mean stop at age 75 regardless of past screening history or lack thereof [59].

Decision Analysis for What Age to End CRC Screening in the Elderly in Those with no Prior Screening

To address this issue, a recent microsimulation modeling study assessed up to what age (76–90) CRC screening should be considered in elderly persons without previous screening and to determine which screening test—colonoscopy, sigmoidoscopy, or FIT—applied just at one time would be indicated and at what age [60]. The study first determined that the effectiveness of CRC screening in unscreened elderly persons declined with increasing age, and by age 90, there was net harm (loss of QALYS) in screening. Furthermore, the cost-effectiveness of screening versus no screening increased rapidly with increasing age. The next step was to assess theACER as to when the screening strategy exceeded a threshold of US$ 100,000 per QALY which used the assumption that a benefit costing less than US$ 100,000 per QALY was acceptable to society.

The optimal strategy of choice of screening test was that screening test strategy that was the most effective (i.e., most LYGs) and still cost-effective within the US$ 100,000 threshold (Table 3.1). This was determined for each age 76 and older and for each comorbidity level. The age to which screening should be considered declined by comorbidity status—up to age 86 for those with no comorbidity, up to age 83 with moderate comorbidities, and only up to age 80 for those with severe comorbidities. Also colonoscopy, as the screening test of choice, would stop 3 years earlier than the maximum stopping per comorbidity; i.e., stop any CRC screening at age 86 for those with no comorbidities but colonoscopy would be the screening test of choice only up to age 83.

Summary

Effectiveness, comparative effectiveness, and cost-effectiveness analyses are key components to Donabedian's vision for attributes of quality of health care as conceived in 1992 [9]. He advocated for *effectiveness* for improvements in health with the best care, *efficiency* to lower the cost without diminishing the improvements in health, *optimality* to balance costs against improvements in health, and *acceptability* that the treatment conforms to the desires of the patient. His last two advocacies are that such

Table 3.1 Summary of age to stop initiating colorectal cancer screening for elderly persons without prior screening by level of comorbidity and type of screening test (colonoscopy, flexible sigmoidoscopy, or fecal immunochemical test). (Reprinted from Ref. [60]. With permission from American College of Physicians)

Comorbidity status	Up to what age should CRC screening be considered?	Which screening strategy is indicated at what age?										
		Age										
		76	77	78	79	80	81	82	83	84	85	86
No comorbidity	86	COL	COL	COL	COL	COL	COL	COL	COL	SIG	FIT	FIT
Moderate comorbidity	83	COL	COL	COL	COL	COL	SIG	FIT	FIT			
Severe comorbidity	80	COL	COL	SIG	FIT	FIT						

The age to stop is based on the strategy which is the most effective and still cost effective within societal cost boundary of less than US$ 100,000 per quality life year gained

Persons are classified as having no comorbidity (none of the conditions below) or moderate comorbidity if they have an ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebrovascular disease, or a history of acute myocardial infarction; severe comorbidity if they have chronic obstructive pulmonary disease, congestive heart failure, moderate or severe liver disease, chronic renal failure, dementia, cirrhosis and chronic hepatitis, or AIDS

CRC colorectal cancer, *COL* once-only colonoscopy screening, *SIG* once-only sigmoidoscopy screening, *FIT* once-only fecal immunochemical test screening

health care have *legitimacy* for social preferences and ethical principles and finally that there be *equity* for all within our population. The Gastroenterology community (GI) community has been well versed in these principles. The original Multi-Society Task Force led by Winawer et al. in 1997 [10] recognized the need for comparative effectiveness which took into account acceptability to patient and improvement of tests. Now, more than 20 years later, the methodologies to achieve such analysis and examination of these issues are more robust and widely known and applied.

Eisenberg [61] in 1989 had connected clinical economics as first and foremost to be based on the use of medical services in the encounter between clinician and patient. He stated the a cost-effectiveness analysis incorporates both cost and effect and measures the net cost of providing a service (expenditures minus savings) as well as the outcomes obtained. The advantage of cost-effectiveness analysis is that it considers the possibility of improved outcomes in exchange for the use of more resources. Sox [62] in 2010 listed seven principles for comparative effectiveness research of (1) allowing decision makers to make informed decisions; (2) providing information on benefits, harms, costs, and logistics of different policies; (3) comparing across a broad range of interventions; (4) directly comparing tests "head-to-head"; (5) assessing patient-relevant outcomes as well as economic implications; (6) identifying patient characteristics of meaningful outcomes; and (7) including new and old data as well as systematic reviews of existing research.

In this chapter, we have provided current examples of studies of effectiveness, comparative effectiveness, and cost-effectiveness. Overall, the currently recommended CRC screening strategies of FIT, flexible sigmoidoscopy with FIT, and colonoscopy are all cost-effective strategies. CRC screening can also be cost saving as the use of biological increases for advanced disease [50]. We find that we must balance the effectiveness of screening tests with the resources required to deliver population-based screening with such tests. We also have presented examples of how using cost-effectiveness analysis with a common denominator of costs can be used to identify and quantify the balance between benefit and excess risk within the context of availability of screening resources. Given the large impact that CRC screening can have to reduce CRC mortality, it is imperative that we continue to assess what are the CRC screening options that can provide the greatest impact for the population and most efficiently use our medical resources.

Acknowledgments This work is supported in part from the following grants: U01 CA-152959, U01 CA-151736, U54 CA-163262, and R01 CA-079572.

References

1. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA: Cancer J Clin. 2014;64(2):104–17.
2. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116(3):544–73.

3. Cohen JP. Comparative-effectiveness research: does it matter? Clin Ther. 2013;35(4):371–9.
4. United States Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149(9):627–37.
5. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;134(5):1570–95.
6. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143(3):844–57.
7. Ratner R, Eden J, Wolman D, Greenfield S, Sox H. Institute of Medicine: Initial national priorities for comparative effectiveness research. Washington, DC: National Academic Press; 2009.
8. Tunis SR, Benner J, McClellan M. Comparative effectiveness research: policy context, methods development and research infrastructure. Stat Med. 2010;29(19):1963–76.
9. Donabedian A. The role of outcomes in quality assessment and assurance. QRB Qual Rev Bull. 1992;18(11):356–60.
10. Winawer SJ, Fletcher RH, Miller L, Godlee F, Stolar MH, Mulrow CD, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology. 1997;112(2):594–642.
11. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348(9040):1472–7.
12. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996;348(9040):1467–71.
13. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365–71.
14. Newcomb PA, Norfleet RG, Storer BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. J Natl Cancer Inst. 1992;84(20):1572–5.
15. Newcomb PA, Stover BE, Morimoto LM, A T, Potter JD. Long-term efficacy of sigmoidoscopy in the reduction of colorectal cancer incidence. J Natl Cancer Inst. 2003;95:622–5.
16. Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med. 1992;326(10):653–7.
17. Levin B, Brooks D, Smith RA, Stone A. Emerging technologies in screening for colorectal cancer: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. CA: Cancer J Clin. 2003;53(1):44–55.
18. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. J Gen Intern Med. 2011;26(2):192–6.
19. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624–33.
20. Holme O, Loberg M, Kalager M, Bretthauer M, Hernan MA, Aas E, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA. 2014;312(6):606–15.
21. Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366(25):2345–57.
22. Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial–SCORE. J Natl Cancer Inst. 2011;103(17):1310–22.
23. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med. 2012;366(8):697–706.

24. Kaminski MF, Bretthauer M, Zauber AG, Kuipers EJ, Adami HO, van Ballegooijen M, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. Endoscopy. 2012;44(7):695–702.
25. Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver. 2014;8(2):117–30.
26. Allison JE, Lawson M. Screening tests for colorectal cancer: a menu of options remains relevant. Curr Oncol Rep. 2006;8(6):492–8.
27. Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst. 2007;99(19):1462–70.
28. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med. 1996;334(3):155–9.
29. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the u.s. Preventive services task force. Ann Intern Med. 2008;149(9):638–58.
30. Hol L, van Leerdam ME, van Ballegooijen M, van Vuuren AJ, van Dekken H, Reijerink JC, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. GUT. 2010;59(1):62–8.
31. Hol L, Wilschut JA, van Ballegooijen M, van Vuuren AJ, van der Valk H, Reijerink JC, et al. Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Cancer. 2009;100(7):1103–10.
32. Raginel T, Puvinel J, Ferrand O, Bouvier V, Levillain R, Ruiz A, et al. A population-based comparison of immunochemical fecal occult blood tests for colorectal cancer screening. Gastroenterology. 2013;144(5):918–25.
33. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med. 2014;160(3):171.
34. Brenner H, Hoffmeister M, Birkner B, Stock C. Diagnostic performance of guaiac-based fecal occult blood test in routine screening: state-wide analysis from Bavaria, Germany. Am J Gastroenterol. 2014;109(3):427–35.
35. Holme O, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database Syst Rev. 2013;9:Cd009259.
36. Gupta S, Halm EA, Rockey DC, Hammons M, Koch M, Carter E, et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. JAMA Intern Med. 2013;173(18):1725–32.
37. Inadomi JM, Vijan S, Janz NK, Fagerlin A, Thomas JP, Lin YV, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med. 2012;172(7):575–82.
38. Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med. 2008;359(12):1207–17.
39. Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med. 2003;349(23):2191–200.
40. Stoop EM, de Haan MC, de Wijkerslooth TR, Bossuyt PM, van Ballegooijen M, Nio CY, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. Lancet Oncol. 2012;13(1):55–64.
41. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370(14):1287–97.

42. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med. 2004;351(26):2704–14.
43. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370(14):1298–306.
44. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening—an overview. Best Pract Res Clin Gastroenterol. 2010;24(4):439–49.
45. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $ 50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796–7.
46. Harris R. Speaking for the evidence: Colonoscopy vs Computed Tomographic Colonography. J Natl Cancer Inst. 2010;102(16):1–3.
47. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;137(2):132–41.
48. U.S. Preventive Services Task Force. Screening for colorectal cancer: recommendation and rationale. Ann Intern Med. 2002;137(2):129–31.
49. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev. 2011;33(1):88–100.
50. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. J Natl Cancer Inst. 2009;101(20):1412–1422.
51. Schrag D. The price tag on progress–chemotherapy for colorectal cancer. N Engl J Med. 2004;351(4):317–9.
52. Cruzado J, Sanchez FI, Abellan JM, Perez-Riquelme F, Carballo F. Economic evaluation of colorectal cancer (CRC) screening. Best Pract Res Clin Gastroenterol. 2013;27(6):867–80.
53. Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. 2nd ed. New York: Oxford University Press; 2000.
54. Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, Kuntz KM, et al. Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the medicare population. J Natl Cancer Inst. 2010;102(16):1238–52.
55. Mark DH. Visualizing cost-effectiveness analysis. JAMA. 2002;287(18):2428–9.
56. Zauber AG, Knudsen AB, Rutter CM, Lansdorp-Vogelaar I, Savarino JE, Van Ballegooijen M, et al. Cost-effectiveness of CT Colonography to screen for colorectal cancer. 2009. http://www.cms.gov/medicare-coverage-database/details/technology-assessments-details.aspx?TAId=58. Accessed: 11. Sept. 2014.
57. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Boer R, Wilschut J, Habbema JD. At what costs will screening with CT colonography be competitive? A cost-effectiveness approach. Int J Cancer. 2009;124(5):1161–8.
58. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):659–69.
59. Shellnut JK, Wasvary HJ, Grodsky MB, Boura JA, Priest SG. Evaluating the age distribution of patients with colorectal cancer: are the United States Preventative Services Task Force guidelines for colorectal cancer screening appropriate? Dis Colon Rectum. 2010;53(1):5–8.
60. van Hees F, Habbema JD, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG. Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. Ann Intern Med. 2014;160(11):750–9.
61. Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practices. JAMA. 1989;262(20):2879–86.
62. Sox HC, Helfand M, Grimshaw J, Dickersin K, Tovey D, Knottnerus JA, et al. Comparative effectiveness research: challenges for medical journals. J Clin Epidemiol. 2010;63(8):862–4.

Chapter 4
Quality Indicators and Benchmarks for Guideline-Recommended Fecal Occult Blood Tests

James E. Allison, Callum G. Fraser, Stephen P. Halloran and Graeme P. Young

Nonstandard Abbreviations

ACP	American College of Physicians
ACR	American College of Radiology
ACS	American Cancer Society
CDC	Centers for Disease Control
CRC	Colorectal cancer
EWG	Expert Working Group
FDA	Food and Drug Administration
FIT	Fecal immunochemical test for hemoglobin
FOBT	Fecal occult tests for blood: Traditional, low analytical sensitivity
FS	Flexible sigmoidoscopy
GMEC	Guildford Medical Device Evaluation Centre
gFOBT	Guaiac fecal occult blood test
sFOBT	Sensitive guaiac fecal occult blood test
f-Hb	Fecal hemoglobin concentration
Hb	Hemoglobin
MSTF	Multi-Society Task Force

J. E. Allison (✉)
Department of Internal Medicine/Gastroenterology, University of California San Francisco, SFGH Campus, 1001 Potrero Avenue, San Francisco, CA 94110, USA
e-mail: jallison@medsfgh.ucsf.edu

C. G. Fraser
Centre for Research into Cancer Prevention and Screening, University of Dundee, Dundee, Scotland

S. P. Halloran
Clinical Biochemistry, Royal Surrey County Hospital, University of Surrey, Guildford, Surrey, UK

G. P. Young
Flinders Centre for Innovation in Cancer, Flinders University, Adelaide, SA, Australia

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_4

POCT Point-of-care test
PPV Positive predictive value
WEO World Endoscopy Organization

Introduction

In 2008–2009, US national screening guidelines for colorectal cancer (CRC) changed and, for the first time, the traditional, low analytical sensitivity, guaiac fecal occult blood test (gFOBT) was no longer recommended. Two different fecal tests for blood, the sensitive guaiac test (sFOBT) and the fecal immunochemical test for hemoglobin (FIT), were recommended as replacements [1–3]. The evidence for the use of FIT was strong and, since 2008, this evidence has expanded exponentially so that, as of 2013, FIT are considered to be the best noninvasive fecal tests available as the first step of a two-step screening, where a positive FIT precedes a diagnostic structural examination such as colonoscopy. FIT have been shown to be well suited to large-scale population-based screening programs and are being widely adopted in new screening programs throughout the world. Many existing CRC screening programs which use gFOBT are moving to FIT [4–6].

Since FIT were reintroduced to the US market in 2003, the evidence for them being superior to gFOBT has become much stronger. It is the goal of this chapter to explain why attention to quality indicators and benchmarks has led to this conclusion and also to educate readers about the intricacies of, and differences in, FIT as compared with the traditional and sensitive FOBT. We will discuss in detail the need for standardizing FIT nomenclature and results and the reasons for recommending quantitative over qualitative FIT for population screening. This chapter allows readers to be able to evaluate FIT comparison studies and make informed decisions on which of the many available FIT is best for their purposes and provide resources for the information necessary to build a quality FIT-based testing program at a facility or program level.

The sFOBT

The change in guaiac-based tests recommended in the joint guideline from the American Cancer Society (ACS), the US Multi-Society Task Force (MSTF) on CRC, and the American College of Radiology (ACR) [1] was based on studies showing the application sensitivity of sFOBT was superior for both CRC and advanced adenomas than that of the traditional gFOBT. This evidence was good but limited to only a few studies [7–9]. The Committee deciding on which screening tests to recommend formulated what later became called the "50% rule." This rule was used for determining which fecal tests (blood and DNA) were eligible for recommendation in their guidelines. The rule stated that any fecal tests that had been shown in the published peer-reviewed literature to detect a majority (>50%) of prevalent CRC in an asymptomatic population was an acceptable option for screening in average-risk adults aged 50 years and older. The targeted, updated systematic

review for the US Preventive Services Task Force (2008) on CRC screening did not use the 50% rule, but used the same small number of studies used by the ACS, MSTF, and ACR and concluded that evidence in the literature was sufficient to make the sFOBT its recommended choice of available guaiac-based tests [2].

Only one study since 2008 has been reported on the performance characteristics of the sFOBT [10] in a large (>5000) average-risk patient population. The study was carried out in the Israeli population that consisted of 85% Jews and 15% Arabs. In addition to the problem of generalizing such results to more diverse ethnic populations, the results were estimated by long-term follow-up (4 years) and only the test-positive participants were further evaluated with colonoscopy. The authors admit to a "less-than-perfect" follow-up process. They very likely overestimated the positive predictive value (PPV) for advanced neoplasms by including small polyps (unlikely to bleed and be the source of a positive sFOBT) with advanced adenomas and cancers that are more likely to bleed and to be detected by fecal testing. An important finding was that the positivity rate was much lower than that reported in other studies [7–9, 11], but this difference could be attributable to different dietary habits and the very long time between fecal application to the test card and development (minimum of 1 week from application of the first sample, and often only after 10 days).

In 2008, a comparative study of a fecal DNA test with a gFOBT and a sFOBT was published: 3764 patients were assessed with all three tests and all were colonoscoped regardless of their fecal test results. Application sensitivity for "screen-relevant neoplasia" (advanced adenoma and cancer) in the participants screened with both guaiac-based tests was low–10% for the gFOBT and 18% for the sFOBT. This was because the investigators pooled the sensitivity for both cancers and advanced adenomas together in the term "screen-relevant neoplasia." Specificity was 98% for the gFOBT and 97% for the sFOBT. The calculated specificity for the sFOBT was higher than any prior report in the literature for this test [12].

Most screen-relevant neoplasms are advanced adenomas and not cancers. Thus, the application sensitivities for screen relevant neoplasia are low because the sFOBT has a lower sensitivity for advanced adenoma than for cancer [13]. It is important to remember that application sensitivity for advanced adenomas is less important than application sensitivity for cancers because advanced adenomas are not cancers and most will never develop into fatal cancers [14]. Furthermore, fecal tests for blood are recommended for use in a program of repeated screens where there is an ability to detect advanced adenomas long before they become cancer.

The differences in reported performance characteristics including positivity rate, specificity, and PPV for the sFOBT are likely due to the composition of the screened populations studied. Other factors include whether diet was restricted and/or there was a delay in the development of the test cards to allow for degradation of plant peroxidases, a significant confounder and speculated to be a contributor to poor specificity in patients not on diet restriction when tested. Even if conditions could be made similar, there are many reasons why the sFOBT is not an ideal selection for population screening, including that two samples from each of three feces are required to be collected, bleeding from the upper gastrointestinal tract is detected as well as from the colorectum, visual interpretation of the colors developed is not easy, the test development cannot be automated for use in large screening programs, and the cutoff concentrations (and therefore the clinical characteristics) are set by the manufacturer.

The Suitability and Effectiveness of FIT Over gFOBT for Population Screening

An extensive literature has been published on this subject since the 2008 publication of the still current US CRC screening guidelines. The main reasons for FIT being the best fecal test screening choice are as follows:

1. Better patient uptake and acceptance of FIT over gFOBT [15–21].
2. Dietary restriction is not required because an antibody is used in FIT that specifically recognizes the globin component of human hemoglobin.
3. Specificity for lower gastrointestinal tract bleeding.
4. Better clinical performance characteristics of FIT over gFOBT [7, 11, 19, 20, 22–30].
5. Higher-quality laboratory processing is available using automation to simultaneously analyze and report on large numbers of samples per hour.
6. Better sensitivity for advanced adenomas.

An excellent and comprehensive review of this subject was published in the *Canadian Journal of Gastroenterology* in 2012 [30]. Based on this accumulated knowledge on population screening with FIT, an editorial published in *Gut* in 2012 suggested that the use of gFOBT for CRC screening was a less-effective and obsolete strategy [31].

Proof of this premise that FIT are superior to any gFOBT requires that FIT be carefully characterized and evaluated to show this difference and to determine which FIT are best for programmatic population screening. The authors of this chapter have published widely on FIT and the following discussion draws heavily from our journal publications and what we have posted on the website of the interdisciplinary and intercountry Expert Working Group (EWG) on FIT for Screening formed by the Colorectal Cancer Screening Committee of the World Endoscopy Organization (WEO)–http://www.worldendo.org/weo-colorectal-cancer-screening-committee.html and http://www.worldendo.org/weo-crcsc-expert-working-group-fit-for-screening.html [6, 32–37]. Readers who desire more detailed information are encouraged to use these publications and the informative website as resources.

Quality standards and benchmarks are critical to FIT effectiveness and for evaluating the many FIT available. There is a need for FIT refinement and standardization to ensure traceability of analytical results, consistency in fecal sample mass evaluation, assessment of hemoglobin (Hb) stability, and common units for reporting Hb concentrations. We recommend a standardized approach to nomenclature, measurement of fecal Hb (f-Hb) concentrations, and results reporting as described below.

A Standardized Approach to FIT Nomenclature

FIT nomenclature is inconsistent and needs to be standardized so that published FIT studies are amenable to comparison [32]. We recommend that terms such as

immunological fecal occult blood test (iFOBT), immunohistochemical test, FIT 50, FIT 100, and high-sensitivity FOBT be dropped and replaced by the term "FIT" defined as the fecal immunochemical test for hemoglobin that identifies the measurement of f-Hb using an immunochemical method.

FIT come in two formats:

1. Qualitative (dichotomous, positive/negative) FIT express Hb cutoff concentration using a range of units and they have no requirement for commonality in methodological principles or standardization procedures. The quoted cutoff concentrations for a positive test result differ between products, are set by the manufacturer, and consequently are not necessarily comparable. Although these FIT are said to be easy to use and have integral quality monitoring, the color lines that develop are difficult to interpret, especially when faint, and the color development is very dependent on time from sample application. The interpretation of a positive result is subjective and there is evidence of a lot-to-lot variation in qualitative FIT leading to variation in cutoff f-Hb by individual readers and over time [38].
2. Quantitative (measured hemoglobin concentration) FIT provide a numerical result and the opportunity to assign one or more concentrations at which a result is designated "positive." In doing so, it determines the referral rate for colonoscopy and the clinical characteristics of the screening program. Currently, these all-important numerical values are not comparable across different FIT products and this limits the value of FIT research and carries the potential of misleading those who may not be aware of this problem.

We strongly recommend the use of quantitative over qualitative FIT for population screening but, as yet, the Food and Drug Administration (FDA) has not approved any for its use in the USA. All FIT screening in the USA is done with qualitative FIT although some of the approved methods do have the capability of providing high-quality measures of f-Hb concentrations. Results of quantitative FIT can show a direct correlation between mean f-Hb and degree of advanced neoplasia [28, 39, 40]. In a study by Ciatto et al., higher f-Hb concentration was associated significantly with size, presence of severe dysplasia, and presence of a villous component [41].

If quantitative FIT were available in the USA, they could be one of several recommended screening tests in a national screening program. Their major advantage over qualitative FIT is they allow selection of the cutoff f-Hb that enables the program to meet preset objectives for detecting advanced neoplasia. Moreover, instead of taking more than one sample or decreasing the interscreening interval, the cutoff f-Hb could be made lower to achieve the desirable outcome of increased sensitivity. Although quantitative FIT assays require automated analytical systems, they provide opportunities to individualize CRC screening, enhance risk stratification [42], better exploit endoscopy resources, and maximize clinical effectiveness. They have so many advantages compared with qualitative FIT [43] that they ought to be available everywhere, recommended in all CRC screening guidelines, and approved for use by all relevant regulatory bodies [36].

A Standardized Approach to Measurement and Results Reporting

We have covered this important section in a number of publications from the EWG, but some of the points made are worth emphasizing again [32, 34]. The many FIT available vary in several key aspects. For instance, manufacturers rarely describe their analytical specificity. We need confidence that they work with all Hb variants and we need to understand their cross-reactivity with partially degraded Hb present in feces, especially since Hb degrades rapidly both in vivo and in vitro. Hb has a number of common and rare variants that have the potential to affect analytical accuracy because the reagent antibodies may not recognize their binding sites. Manufacturers need to assess and report the performance of their assays with a range of Hb variants, not only with Hb from animal species.

While increased analytical specificity for Hb has the potential of missing bleeding in individuals with Hb variants, it also presents the opportunity to detect breakdown products of Hb (peptides derived from globin). If antibodies are developed that cross-react with human globin-derived peptides while avoiding cross-reaction with interfering molecules, then FIT could become more effective in detecting proximal lesions, less affected by samples' deterioration during mailing, and perhaps might even reduce the difference on detection rates observed between men and women which has been recently highlighted [33].

We can only compare studies with one another if the concentrations of Hb that FIT measure are consistently standardized. Consistency in reporting requires that FIT concentrations be expressed as the quantity of Hb present in feces (micrograms of Hb per gram of feces) not in the collection or measurement solution as has been the custom (nanograms of Hb per milliliter of buffer). If reported as nanograms of Hb per milliliter buffer, the results cannot be compared because they are unique to an individual product design, to its sample collection system, and in the ratio of the mass of feces collected to the volume of buffer used to try to preserve the sample.

A 2010 study in the *International Journal of Cancer* illustrates this point [32, 44]. The positivity rates, sensitivity, and specificity of six different FIT were reported using the manufacturers' quoted f-Hb cutoffs in nanograms of Hb per milliliter of buffer for six qualitative FIT (Table 4.1). Note that FIT A and FIT E have

Table 4.1 Positivity, sensitivity, and specificity for advanced neoplasia and manufacturers' quoted cutoff fecal hemoglobin concentrations (ng Hb/mL buffer) for six qualitative FIT [32, 44]

FIT	Positivity (%)	Sensitivity (%)	Specificity (%)	Manufacturers' quoted fecal hemoglobin cutoff (ng Hb/mL buffer)
A	6.4	29.8	96.7	50
B	11.0	30.5	92.9	40
C	22.3	53.2	81.8	10
D	24.1	56.0	82.0	40
E	35.0	59.6	70.2	50
F	46.8	73.4	58.8	25

FIT fecal immunochemical test

the same f-Hb cutoff yet their positivity, sensitivity, and specificity with identical fecal samples are very different. Similarly, it would be expected that a FIT with a low f-Hb cutoff would have a high sensitivity and a very low specificity, yet this is not the case for FIT C. A further study of nine FIT nicely reinforces the message that FIT are not all the same [45], although manufacturers of qualitative FIT can modify their product to render an f-Hb cutoff that meets the requirements of a screening program [46].

The problem illustrated above can be easily rectified by converting the data in previous publications expressed in nanograms of Hb per milliliter of buffer to the recommended units using the formula:

μg Hb per g feces = (ng Hb per mL × mL buffer)/(mg feces collected).

Illustrations of how this can be done are shown in Tables 4.2 and 4.3.

Hb is not stable and degrades from the time it is released into the gastrointestinal tract. The rate of degradation depends on the chemical and microbiological composition of the feces, temperature, effectiveness of stabilizing bactericidal preservatives in the specimen collection device, and the period of time from the blood loss to analysis. The stability of Hb in the specimen collection devices needs to be characterized in a standardized way so that products can be compared and judgments can be made on their suitability for screening in different environments and under different climatic conditions.

As pointed out in a recent review in *Gut and Liver* [33], FIT analysis depends on antibodies binding to globin of Hb; thus, FIT are more susceptible to false-negative results if samples are not adequately preserved. In 2009, the Australian Commonwealth government had to temporarily suspend participation in the National Bowel Cancer Screening Program after problems were found in the buffer of the FIT kits that had been distributed between December 2008 and May 2009. The buffer in the FIT specimen collection device was not sufficiently effective at minimizing Hb degradation at the high temperatures found in the country during the summer

Table 4.2 Fecal immunochemical test cutoff fecal hemoglobin concentration after unit standardization. (Courtesy of Jeffrey Lee, MD, Division of Gastroenterology, UCSF)

FIT brand	Cutoff fecal hemoglobin concentration reported in the literature or by manufacturer	Standardized fecal cutoff concentration hemoglobin (μg Hb/g feces)
SENTiFOB	100 ng/mL	17
OC-Sensor/Micro/Diana	100 ng/mL	20
OC-light	50 ng/mL	10
FOB gold	100 ng/mL	17
Magstream 1000/Hem Sp	20 ng/mL	67
Monohaem	0.02 mg/g	20
FlexSure OBT (Hemoccult ICT)	0.3 mg/g	300
Ridascreen hemoglobin	24.5 μg/g	24.5

This list represents a mix of qualitative and quantitative FIT and is not a complete list of available FIT

FIT fecal immunochemical test

Table 4.3 Data supplied by the manufacturers of the four FIT evaluated by GMEC [48] to enable conversion between ng Hb/mL buffer and μg Hb/g feces

Analytical system	Sample mass (mg)	Buffer volume (mL)	Conversion factor[a]
HM-JACKarc	2	2.0	1.00
NS-PLUS C15	10	1.9	0.19
OC-SENSOR DIANA	10	2.0	0.20
FOB Gold/BioMajesty	10	1.7	0.17

By multiplying hemoglobin concentrations expressed in ng Hb/mL of preservative buffer by the conversion factor given in Table 4.3, the reported concentration units are converted to μg Hb/g feces. These units are largely independent of the design features that are peculiar to individual devices. The factor is derived from the ratio of the mass of fecal specimen collected to the volume of stabilizing buffer in the collection device (both average-collected fecal mass and the buffer volume are provided by FIT manufacturers). No standardized method of determining "average collected fecal mass" has yet been agreed and, therefore, until we have a standardized method, the conversion factors carry a degree of uncertainty but will correct for gross difference between devices and facilitate comparison of outcomes in large studies or programs

FIT fecal immunochemical test, *GMEC* Guildford Medical Device Evaluation Centre

[a] Derivation and use of the conversion factor: Standardizing Hemoglobin Stability in FIT

period. As a result, the collection devices returned for analysis yielded a lower-than-expected proportion of positive results, with many participants receiving likely false-negative results. The potential for inaccurate FIT results during hot weather was investigated in a retrospective Italian study and showed f-Hb 17% higher in the winter, when 13% more cancers were detected [47]. Since 2011, companies have been actively enhancing the effectiveness of their preservative buffers, using antibacterial and stabilizing agents. An evaluation of quantitative FIT devices commissioned by the National Health Service (NHS) Bowel Cancer Screening Programme in England conducted in 2012/2013 showed that stability should now only present significant problems at very high ambient temperatures [48]. This report is supportive of recent product claims of increased stability. When product changes (enhancements) are introduced by manufacturers, it is important that customers are apprised of the changes and new product codes or designations are adopted to enable comparative clinical research to make valid observation about product performance over periods of time and in different countries.

Standards for FIT Processing and Development

FIT can be processed, developed, and interpreted at point-of-care (POC) by different types of health-care professionals or at centralized, automated, accredited laboratories by professionals in laboratory medicine experienced in using analytical systems and interpretation of numerical data. Most FIT in the USA are marketed for POC use. Automated analytical systems for FIT have many advantages [5, 49] over POC manual use and interpretation, including higher throughput and improved analytical accuracy and precision, while eliminating the potential for visual bias by observers. The person developing and interpreting manual tests often needs to

wait for a prescribed period of time specified by the manufacturer after application of the feces in solution to the test cassette or strip before reading the test. This is prone to difficulties in a busy clinical setting and accurate interpretation of results for manually developed and interpreted fecal tests requires training and supervision, especially when interpreting borderline results [50–52] (Fig. 4.1). These facts should discourage those who might recommend patients screen themselves with over-the-counter FIT and "at home" development. Another advantage of laboratory analysis is that the user can select the f-Hb cutoff that will initiate further investigation, usually colonoscopy. To enable high analytical quality, we recommend the use of automated FIT systems and interpretation in accredited laboratories in preference to that of POC testing. We strongly recommend the use of laboratories accredited to internationally accepted standards, such as "ISO 15189: Medical Laboratories–Particular Requirements for Quality and Competence." These will have comprehensive quality management systems in operation and will collect numerical quality indicators such as positivity rate, internal quality control data showing test result variation, imprecision and changes in bias over time, and performance in proficiency testing and external quality assessment.

If we recommend automated development and interpretation of FIT, we must be able to demonstrate the quality and accuracy of the recommended instruments for this task. To this end, the EWG has supported the evaluation of four quantitative FIT systems by the established Guildford Medical Device Evaluation Centre (GMEC) based in England [48]. At the commencement of the evaluation in December 2012,

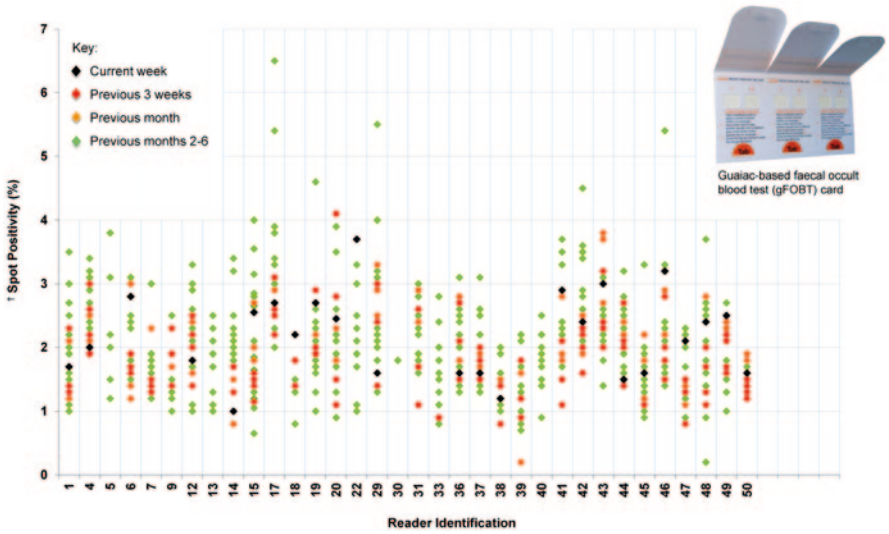

Fig. 4.1 Example of the variable spot positivity rate of well-trained, supervised, and monitored individuals reading guaiac-based fecal occult blood test (gFOBT) cards over a rolling 6-month period. († Spot positivity (%) calculated as (number of spots read as positive/number of spots read) for readers who have read at least 600 spots per week and where each "spot" is one of six windows (see card image))

all systems (specimen collection devices and associated measurement instruments) that met criteria prescribed by the NHS Bowel Cancer Screening Programme were included in the evaluation. The following criteria for evaluation were required for systems to be suitable for population-based CRC screening:

- The system provided a quantitative measurement of f-Hb.
- The analysis could be automated.
- The specimen collection device was suitable for home use.

For the evaluation, each manufacturer was asked to supply:

- The analyzer.
- Consumables and reagents, including calibrators and controls.
- Training for the study laboratory professionals, scientists, and colleagues.
- Ongoing technical support.

Four automated, quantitative FIT devices/analyzers were found to be eligible for evaluation, having met the simple criteria above:

- FOB Gold NG, Sentinel CH. SpA, Italy/Biomajesty, Sysmex, UK
- HM-JACKarc, Kyowa-Medex Co. Ltd, Japan
- NS-PLUS C15 Hb, Alfresa Pharma Corp, Italy
- OC-SENSOR DIANA, Eiken Chemical Co. Ltd, Japan

The evaluation assessed the suitability of the specimen collection device for use in a population-screening program, including that of sending it through a postal system, performing to a consistently high analytical quality including analytical precision, suitable measurement range, adequate linearity, appropriate reporting units, and other performance characteristics. The suitability of the specimen collection devices was assessed by a large panel of users and is summarized in the report.

Summary and Conclusions

The idea that fecal tests are inferior to structural examinations has been promoted by US gastroenterology and endoscopy societies since 2000 when two screening colonoscopy studies were published in *The New England Journal of Medicine* [53, 54]. It was reinforced in 2008 with the publication of the "Joint guidelines from the American Cancer Society, the US Multi-society Task Force on Colorectal Cancer, and the American College of Radiology" and with the publication in 2009 of the American College of Gastroenterology "Guidelines for colorectal cancer screening" [1, 3]. Since 2000, screening rates for CRC have increased, but as of 2012 [55]:

1. Only 65.1% of US adults were up to date with CRC screening and 27.7% had never been screened.
2. The proportion of respondents who had never been screened was greater among those without insurance (55.0%) and without a regular care provider (61.0%) than among those with health insurance (24.0%) and a regular care provider (23.5%).

This information has led the Centers for Disease Control (CDC) to recommend promoting both fecal test for blood and colonoscopy as viable screening test options to increase CRC screening rates and reduce health disparities. The ACS and the National Colorectal Cancer Roundtable have advised physicians that fecal tests have been shown to decrease both incidence of and mortality from CRC and are reasonable screening test choices [56]. Endoscopic journals have published articles on CRC screening where experts have said: "Colonoscopy remains the dominant CRC screening strategy in the USA but is less effective at preventing right sided CRC than previously thought" and, "FIT has emerged as an effective low cost alternative to colonoscopy and is considered by some an equivalent or superior approach to screening as compared to colonoscopy." [57] The American College of Physicians (ACP) in its Guidance Statement on Screening for CRC (2012) stated, "Shared decision making is important when selecting a screening test because the currently available colorectal cancer screening tests are believed to be similarly efficacious" [58]. Even a recently published *Journal of the American Medical Association* (*JAMA)* patient page on options for colorectal cancer screening states "Evidence does not yet support any one screening test over another, so in deciding which screening option is best for you, consider your personal health situation and talk with your doctor" [59].

This change in US institutional and professional society thinking about the value of screening tests other than optical colonoscopy is very welcome, although with acceptance comes responsibility. More well-designed and comparative, analytical, and clinical effectiveness studies must be government-funded. They are necessary to identify FIT products best qualified for population screening. Further standardization of the analytical and clinical performance characteristics of FIT is urgently needed. Those of us who promote the use of FIT for CRC screening must be sure that only the best FIT are chosen for population screening and that the conditions for collection and handling of samples, analysis, and interpretation of results are of the highest quality. We hope that publication of this chapter will help to achieve this goal.

Acknowledgement The authors thank Dr. Helen Seaman for her help in preparing this manuscript for publication.

References

1. Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US multi-society task force on colorectal cancer, and the American college of radiology. CA Cancer J Clin. 2008;58(3):130–60. doi:10.3322/ca.2007.0018. (Epub 2008/03/07).
2. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. preventive services task force. Ann Intern Med. 2008;149(9):638–58. doi:0000605-200811040-00245 [pii].

3. Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US multi-society task force on colorectal cancer. Gastroenterology. 2006;130(6):1865–71.
4. Imperiale TF. Noninvasive screening tests for colorectal cancer. Dig Dis. 2012;30(Suppl 2):16–26. doi:10.1159/000341884. (Epub 2012/12/12).
5. Halloran SP, Launoy G, Zappa M. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First edition faecal occult blood testing. Endoscopy. 2012;44(Suppl 03):SE65–87. doi:10.1055/s-0032-1309791.
6. Fraser CG, Halloran S, Allison J, Young G. Making colorectal cancer screening FITTER for purpose with quantitative faecal immunochemical tests for haemoglobin (FIT). Clin Chem Lab Med. 2013;51(11):2065–7. doi:10.1515/cclm-2013-0408.
7. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med. 1996;334(3):155–9. doi:10.1056/NEJM199601183340304. (Epub 1996/01/18).
8. Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. Dig Dis Sci. 1997;42(10):2064–71. doi:10.1023/a:1018866400973.
9. Rennert G, Rennert HS, Miron E, Peterburg Y. Population colorectal cancer screening with fecal occult blood test. Cancer Epidemiol Biomarkers Prev. 2001;10(11):1165–8.
10. Kershenbaum A, Flugelman A, Lejbkowicz F, Arad H, Rennert G. Excellent performance of Hemoccult Sensa in organised colorectal cancer screening. Eur J Cancer. 2013;49(4):923–30. doi:10.1016/j.ejca.2012.09.020. (Epub 2012/10/27).
11. Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst. 2007;99(19):1462–70. doi:10.1093/jnci/djm150. (Epub 2007/09/27).
12. Ahlquist DA, Sargent DJ, Loprinzi CL, Levin TR, Rex DK, Ahnen DJ, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med. 2008;149(7):441–50, W81. (Epub 2008/10/08).
13. Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for hemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer. 2006;107(9):2152–9. doi:10.1002/cncr.22230. (Epub 2006/09/26).
14. Allison JE, Meijer GA. Colonic polyps: the harm of overdiagnosis. Practical approaches to the diagnosis and treatment of colorectal cancer, Series 8. Prac Gastroenterol. 2012;XXXVI(11):25–38.
15. Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. Prev Med. 2012;55(2):87–92. doi:10.1016/j.ypmed.2012.05.006. (Epub 2012/05/29).
16. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen. 2003;10(3):117-22. doi:10.1258/096914103769011003.
17. Hoffman RM, Steel S, Yee EF, Massie L, Schrader RM, Murata GH. Colorectal cancer screening adherence is higher with fecal immunochemical tests than guaiac-based fecal occult blood tests: a randomized, controlled trial. Prev Med. 2010;50(5–6):297–9. doi:10.1016/j.ypmed.2010.03.010. (Epub 2010/03/24).
18. Hol L, van Leerdam ME, van Ballegooijen M, van Vuuren AJ, van Dekken H, Reijerink JC, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut. 2010;59(1):62–8. doi:10.1136/gut.2009.177089. (Epub 2009/08/13).
19. Hughes K, Leggett B, Del Mar C, Croese J, Fairley S, Masson J, et al. Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community. Aust NZ J Public Health. 2005;29(4):358–64. (Epub 2005/10/15).

20. van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135(1):82–90. doi:10.1053/j.gastro.2008.03.040. (Epub 2008/05/17).
21. Digby J, McDonald PJ, Strachan JA, Libby G, Steele RJ, Fraser CG. Use of a faecal immunochemical test narrows current gaps in uptake for sex, age and deprivation in a bowel cancer screening programme. J Med Screen. 2013;20(2):80–5. doi:10.1177/0969141313497197. (Epub 2013/09/07).
22. Williams JA, Hunter R, Smith M, Coles ME, Hubert TW, Thomas DW. Evaluation of an immunological test for occult bleeding from colorectal neoplasia. Aust N Z J Surg. 1982;52(6):617–21. (Epub 1982/12/01).
23. St John DJ, Young GP, Alexeyeff MA, Deacon MC, Cuthbertson AM, Macrae FA, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. Gastroenterology. 1993;104(6):1661–8. (Epub 1993/06/01).
24. Robinson MH, Marks CG, Farrands PA, Thomas WM, Hardcastle JD. Population screening for colorectal cancer: comparison between guaiac and immunological faecal occult blood tests. Br J Surg. 1994;81(3):448–51. (Epub 1994/03/01).
25. Rozen P, Knaani J, Papo N. Evaluation and comparison of an immunochemical and a guaiac faecal occult blood screening test for colorectal neoplasia. Eur J Cancer Prev. 1995;4(6):475–81. (Epub 1995/12/01).
26. Petrelli N, Michalek AM, Freedman A, Baroni M, Mink I, Rodriguez-Bigas M. Immunochemical versus guaiac occult blood stool tests: results of a community-based screening program. Surg Oncol. 1994;3(1):27–36. (Epub 1994/02/01).
27. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology. 2005;129(2):422–8. doi:10.1016/j.gastro.2005.05.056. (Epub 2005/08/09).
28. Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med. 2007;146(4):244–55. (Epub 2007/02/21).
29. Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol. 2010;105(9):2017–25. doi:10.1038/ajg.2010.179. (Epub 2010/05/27).
30. Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley A, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Cancer J Gastroenterol. 2012;26(3):131–47. (Epub 2012/03/13).
31. Young GP, Fraser CG, Halloran SP, Cole S. Guaiac based faecal occult blood testing for colorectal cancer screening: an obsolete strategy? Gut. 2012;61(7):959–60. doi:10.1136/gutjnl-2011-301810.
32. Allison JE, Fraser CG, Halloran SP, Young GP. Comparing fecal immunochemical tests: improved standardization is needed. Gastroenterology. 2012;142(3):422–4. doi:10.1053/j.gastro.2012.01.015. (Epub 2012/01/28).
33. Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means means getting FIT. The past, present, and future of colorectal cancer screening using FIT. Gut Liver. 2014;8(2):117–30.
34. Fraser CG, Allison JE, Halloran SP, Young GP. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. J Natl Cancer Inst. 2012;104(11):810–4. doi:10.1093/jnci/djs190. (Epub 2012/04/05).
35. Fraser CG, Allison JE, Young GP, Halloran S. Newer fecal tests: opportunities for professionals in laboratory medicine. Clin Chem. 2012;58(6):963–5. doi:10.1373/clinchem.2012.185025. (Epub 27 March 2012).

36. Fraser CG, Allison JE, Young GP, Halloran SP. Quantitation of hemoglobin improves fecal immunochemical tests for noninvasive screening. Clin Gastroenterol Hepatol. 2013;11(7):839–40. doi:10.1016/j.cgh.2013.02.031. (Epub 2013 Apr 13).
37. Fraser CG, Allison JE, Young GP, Halloran SP, Seaman HE. A Standard for Faecal Immunochemical Tests for haemoglobin evaluation reporting (FITTER) (Letter). Ann Clin Biochem. 2014;51:301–2.
38. McDonald PJ, Anderson CM, Fraser CG. Acceptance quality checks for qualitative fecal immunochemical tests ensure screening program consistency. Int J Cancer. 2011;128(1):247–8. author reply 248–9. doi:10.1002/ijc.25316. (Epub 2010/03/17).
39. Digby J, Fraser CG, Carey FA, McDonald PJ, Strachan JA, Diament RH, et al. Faecal haemoglobin concentration is related to severity of colorectal neoplasia. J Clin Pathol. 2013;66(5):415–9. doi:10.1136/jclinpath-2013-201445. (Epub 2013/02/19).
40. Liao C-S, Lin Y-M, Chang H-C, Chen Y-H, Chong L-W, Chen C-H, et al. Application of quantitative estimates of fecal hemoglobin concentration for risk prediction of colorectal neoplasia. World J Gastroenterol. 2013;19(45):8366–72.
41. Ciatto S, Martinelli F, Castiglione G, Mantellini P, Rubeca T, Grazzini G, et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer. 2007;96(2):218–21. doi:10.1038/sj.bjc.6603534. (Epub 2007/01/11).
42. Chen LS, Yen AM, Fraser CG, Chiu SY, Fann JC, Wang PE, et al. Impact of faecal haemoglobin concentration on colorectal cancer mortality and all-cause death. BMJ Open. 2013;3(11):e003740. doi:10.1136/bmjopen-2013-003740. (Epub 2013/11/10).
43. Fraser CG. A future for faecal haemoglobin measurements in the medical laboratory. Ann Clin Biochem. 2012;49(6):518–26. doi:10.1258/acb.2012.012065. (Epub 2012/09/06).
44. Brenner H, Haug U, Hundt S. Inter-test agreement and quantitative cross-validation of immunochromatographical fecal occult blood tests. Int J Cancer. 2010;127(7):1643–9. doi:10.1002/ijc.25154. (Epub 2010/01/06).
45. Tao S, Seiler CM, Ronellenfitsch U, Brenner H. Comparative evaluation of nine faecal immunochemical tests for the detection of colorectal cancer. Acta Oncol. 2013;52(8):1667–75. doi:10.3109/0284186x.2013.789141. (Epub 2013/04/27).
46. Tao S, Brenner H. Well adjusted qualitative immunochemical faecal occult blood tests could be a promising alternative for inexpensive, high-quality colorectal cancer screening. Eur J Cancer Prev. 2013;22(4):305–10. doi:10.1097/CEJ.0b013e32835b6991.
47. Grazzini G, Ventura L, Zappa M, Ciatto S, Confortini M, Rapi S, et al. Influence of seasonal variations in ambient temperatures on performance of immunochemical faecal occult blood test for colorectal cancer screening: observational study from the Florence district. Gut. 2010;59(11):1511–5. doi:10.1136/gut.2009.200873. (Epub 2010/07/07).
48. Carroll MRR, Piggott C, Pearson S, Seaman HE, Halloran SP. Evaluation of quantitative faecal immunochemical tests for haemoglobin. Guildford: Guildford Medical Device Evaluation Centre (GMEC). 2013. http://worldendo.org/assets/downloads/pdf/activities/fit_reports/gmec_fit_evaluation_report.pdf. Accessed 17 Sept 2014.
49. Fraser CG. Fecal occult blood tests. Life savers or outdated colorectal screening tools? Clin Lab News. 2011;37:8–10.
50. Niv Y. Fecal occult blood test–the importance of proper evaluation. J Clin Gastroenterol. 1990;12(4):393–5.
51. Fleisher M, Winawer SJ, Zauber AG, Smith C, Schwartz MK. Accuracy of fecal occult blood test interpretation. National Polyp Study Work Group. Ann Intern Med. 1991;114(10):875–6.
52. Selinger RR, Norman S, Dominitz JA. Failure of health care professionals to interpret fecal occult blood tests accurately. Am J Med. 2003;114(1):64–7. doi:S0002934302013505 [pii].
53. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med. 2000;343(3):162–8. doi:10.1056/nejm200007203430301. (Epub 2000/07/20).

54. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med. 2000;343(3):169–74. doi:10.1056/nejm200007203430302. (Epub 2000/07/20).
55. Centers for Disease Control and Prevention. Vital signs: colorectal cancer screening test use—United States, 2012. Centers for Disease Control and Prevention. 2013 (updated 8 Nov 2013; cited 62). http://www.cdc.gov/mmwr/pdf/wk/mm6244.pdf.
56. National Colorectal Cancer Roundtable. Tools & Resources—The New FOBT Clinician's Reference Resource. Updated 20 Dec 2013. http://nccrt.org/about/provider-education/fobt-clinicians-reference-resources.
57. Kahi CJ, Anderson JC, Rex DK. Screening and surveillance for colorectal cancer: state of the art. Gastrointest Endosc. 2013;77(3):335–50. doi:10.1016/j.gie.2013.01.002. (Epub 2013/02/16).
58. Qaseem A, Denberg TD, Hopkins RH, Humphrey LL, Levine J, Sweet DE, et al. Screening for colorectal cancer: a guidance statement from the American college of physicians. Ann Intern Med. 2012;156(5):378–86. doi:10.1059/0003-4819-156-5-201203060-00010.
59 Sugerman D. Options for colorectal cancer screening. JAMA. 2013;310(6):658. doi:10.1001/jama.2013.57593.

Chapter 5
Quality Indicators for CT Colonography

Elizabeth G. McFarland, Judy Yee, Abraham H. Dachman and Paul M. Knechtges

Introduction

Computed tomography (CT) colonography (CTC) was initially implemented as a minimally invasive examination for the detection of polyps and colorectal cancer in the mid-1990s. In the subsequent years, this technology has further been evaluated in larger screening cohorts, including a transition from academic centers to community practices [1, 2]. The two key features of this ongoing transition from academic to community practice are evidence-based medicine and clearly defined standards for the performance of CTC [3, 4].

This transition closely parallels the core ideas of quality management, namely scientific method and standardization [5]. In quality management, standardization minimizes variability and subsequently allows the performance of a test or procedure to be more easily monitored by applying uniform performance metrics. Once the baseline data are collected, areas for potential improvement can be identified and subsequent interventions can be implemented and monitored for efficacy.

In the USA, quality management is often performed utilizing the principles of continuous quality improvement. This concept was originally developed in the 1950s by an operations researcher named W. Edwards Demming [6]. The core

E. G. McFarland (✉)
Department of Radiology, SSM St. Joseph West Medical Center,
100 Medical Plaza; Lake St. Louis,MO 63367
e-mail: mcfarlandb123@gmail.com

J. Yee
Department of Radiology and Biomedical Imaging,
University of California, San Francisco, CA, USA

A. H. Dachman
Department of Radiology, The University of Chicago Medical Center, Chicago, IL, USA

P. M. Knechtges
Department of Radiology, Medical College of Wisconsin, Milwaukee, WI, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_5

concept of continuous quality improvement is a repeated cycle of improvements also known as the plan, do, study, and act (PDSA) cycle (Table 5.1). This methodology has also been adopted by the American Board of Radiology (ABR). The ABR currently requires diplomats to perform practice quality improvement (PQI) projects for maintenance of certification (MOC) and these projects are required to follow the PDSA cycle [7].

This chapter discusses the recommended, standardized techniques for performing and reporting CTC that have been derived from peer-reviewed, evidence-based research. In addition, this chapter introduces the development of CTC quality metrics and a data registry for instituting a cyclical quality improvement program into clinical practice.

Brief History of CTC

Early validation trials of CTC in enriched patient cohorts demonstrated sensitivity of 90 % detection of 1 cm and greater polyps and 98 % detection of colorectal cancer [8, 9]. Initial clinical uses of CTC began as an adjunct diagnostic examination following incomplete optical colonoscopy, largely in patients with redundant colons or obstructive cancers. Since 2007, CTC has had Medicare coverage in 47 states for diagnostic indications, predominantly in patients following incomplete colonoscopy or in patients at risk for colonoscopy [10]. This coverage decision, also supported by private insurance, was largely based on the diagnostic accuracy of the exam to detect colorectal polyps and cancer, along with its low-risk profile.

By early 2000, validation trials in asymptomatic cohorts began to show evidence that CTC could be used for colorectal screening. In 2003, the multicenter Navy trial of 1233 asymptomatic patients reported results of per-polyp sensitivities for detection of ≥6 and ≥10 mm polyps of 89 and 94 %, respectively [11]. In 2008, the multicenter trial of American College of Radiology Imaging Network (ACRIN) published similar results in a more diverse trial of 15 centers, including academic and private sectors [1]. In this trial, the per-polyp sensitivities for detection of ≥6 and ≥10 mm polyps were 78 and 90 %, respectively. In 2008, the American Cancer

Table 5.1 Continuous quality improvement elements of PDSA cycle

Start small but start immediately	Identify a process to improve
Plan	Define performance metrics and collect baseline data
Do	Develop and implement an action plan
Study	Review the results of the intervention
Act	If the intervention is ineffective, repeat the cycle with another intervention If the intervention proves effective, go to the next step
Repeat the cycle	Use this process to address the next problem

PDSA plan, do, study, and act

Society jointly with the US Multisociety Task Force on Colorectal Cancer and the American College of Radiology (ACR) endorsed CTC to be used for colorectal screening [12]. In that same time period, the US Preventative Task Force gave CTC an "I" rating (indeterminate), not able to include the ACRIN trial in their meta-analysis, largely due to stated risks of radiation dose, burden of extra-colonic findings, and small polyps left behind in the Medicare population [13].

ACR Practice Parameters for Use of CTC in Adults

After the initial publication of ACR practice guidelines for use of CTC in 2005, the document was revised in 2009, with the most recent update completed in 2014 [3]. These standards define aspects of indications and contraindications of CTC, qualifications of interpreting physicians, specifications of exam techniques, and documentation and reporting of findings.

Indications and Contraindications

The indications for CTC examination in screening individuals include patients who are at average for developing colorectal neoplasia. Considering age-related risk, patients at average risk include patients who are 50 years or older with no symptoms and with no other risk factors. Also managed as low risk are those who have a first-degree relative with colorectal cancer after the age of 60 or multiple second-degree relatives at any age with colorectal neoplasia [12]. Patients with moderate risk include patients who have a first-degree relative with colorectal neoplasia before age 60 or multiple first-degree relatives with colorectal cancer. Moderate-risk patients can be considered for CTC screening in patients who are asymptomatic, in the appropriate clinical context. CTC is not indicated for screening in patients at high risk, which includes patients with inflammatory bowel disease or patients with defined genetic syndromes. It is encouraged that well-defined algorithms for CTC screening indications are defined with community standards among radiologists, gastroenterologists, and referring physicians. As implemented by the large screening program of the Colon Health Initiative at Bethesda, study coordinators or trained radiology or gastroenterology scheduling staff are instrumental in screening patients for current symptoms and family history to ensure that each patient gets triaged into the appropriate screening modality.

The indications for CTC examination for diagnostic indications in symptomatic patients include those who have undergone an incomplete optical colonoscopy in multiple clinical settings, such as abdominal pain, weight loss, gastrointestinal bleeding, anemia, or weight loss. Also for patients who have undergone an incomplete optical colonoscopy, CTC can be done for surveillance of lesions or for further characterization of lesions found to be indeterminate at optical colonoscopy. In addition, diagnostic indications include patients who are at increased risk to undergo

optical colonoscopy, such as advanced age, anticoagulant therapy, sedation risk, or prior history of incomplete colonoscopy.

Relative contraindications for CTC and those patients not indicated for CTC are shown in Table 5.2. It is important to perform proper screening of patients for these contraindications before the exam. For same-day incomplete colonoscopy, clear communication between the gastroenterologist and the radiologist is important to convey if deep biopsies or polypectomies are done. If therapeutic interventions have been performed, patients should wait several weeks before undergoing the completion of CTC examination.

Qualifications of Interpreting Physicians

Proper training of physicians for the performance of CTC is essential for ensuring both the quality and safety of the examination. In 2005, the ACR first issued practice guidelines for the performance of CTC in adults [3]. These practice guidelines provided for the first time a framework of suggested training needed by physicians in order to be able to perform and interpret CTC. Suggested general qualifications for the radiologic technologist to perform CTC are also included.

Fundamental to the ACR standards is that the physician performing CTC assumes responsibility for all parts of the examination. This includes initially ensuring that the study is being performed for an appropriate indication and then making certain that the correct low-dose multidetector CT protocol is employed in a safe manner. The use and volume of oral contrast for tagging of residual material or of intravenous contrast for a diagnostic CTC examination must be monitored. Image reconstructions including multiplanar reformations and three-dimensional (3D) images must be of diagnostic quality for optimal detection of lesions. Finally, accurate interpretation of all images should be recorded in an official report.

Suggested physician training is divided into two broad categories based on previous formal training and ability. The first category is meant for physicians

Table 5.2 Contraindications for CTC

Relative contraindications for CTC
Suspected bowel perforation or high-grade bowel obstruction
Recent or current colitis or diverticulitis
Recent colorectal surgery
Recent deep endoscopic biopsy or polypectomy
Known colon-containing abdominal wall hernia
Not indicated for CTC
Patients at high risk (known genetic syndromes)
Patients with inflammatory bowel disease
Evaluation of anal canal disease

who have prior qualifications in general and/or abdominal–pelvic CT interpretation, such as that attained in an accredited residency and/or fellowship program. This category encompasses standards for those physicians who already meet the qualifications set forth in the ACR practice parameters for performing and interpreting diagnostic CT which helps ensure consistency of qualifications across a broader category within the organization [14]. As a baseline, physicians in this category should have training in radiation biology, the physics of CT scanning, CT image acquisition, and post processing. Prior to specific CTC training, these physicians should already have significant experience in interpretation of CT studies, including the ability to detect extra-colonic findings on CTC studies. If these preliminary qualifications are met, then additional CTC-specific training is recommended, including education in bowel cleansing and insufflation techniques as well as CT image acquisition. Formal interactive training using a computer workstation with dedicated CTC software is required with interpretation, reporting, and/or supervised review of at least 50 colonoscopy proven cases. Hands-on interactive training is critical for developing problem-solving skills using both 2D and 3D images for review of a variety of cases.

The second category is designated for physicians who do not have prior qualifications in general and/or abdominal–pelvic CT interpretation. Physicians in this category need to undergo more intensive educational efforts for learning both about current CT scanning and then specifically about CTC in order to be qualified to safely perform this test within quality standards. This is particularly important since CT scanning uses ionizing radiation and physicians must follow the as low as reasonably achievable (ALARA) principle. In addition to completing an accredited specialty training program, physicians in this category must also document 200 h of continuing medical education in the performance and interpretation of abdominal–pelvic CT and review of 500 CT cases. Similar to physicians in the first category, additional training is needed for CTC including instruction in colonic cleansing, distention, and CTC data acquisition. Formal interactive training of at least 75 colonoscopy proven cases is suggested to include a variety of polyps and cancers.

The maintenance of skills following the initial training period is recommended with review of 50 CTC cases every 2 years. Various methods to accomplish this include actual on-site performance of cases and correlation with follow-up colonoscopy or surgery as well as through attendance at review courses or using electronic media. Maintaining and improving CTC skills may also occur through mentored supervision, double reads, and individual study.

Radiologic technologists are an important part of the CTC team and should be familiar with the correct technical parameters for performing CTC. They should be able to select appropriate CT scanning parameters and help position the patient properly in opposing positions. Technologists should also be able to assist with safe placement and removal of the rectal tube and insufflation of the colon using manual or automated techniques. An important function of the technologist is ensuring a diagnostic study before the patient is released or to alert the physician that additional maneuvers may be needed in order to clear a particular colonic segment.

Specifications of the Exam Techniques

Optimization of CTC technique includes employment of state-of-the-art strategies for each component of the examination. A diagnostic quality of CTC examination includes a properly cleansed and distended colon, allowing the reader to maximize lesion detection ability and to decrease false positives and unnecessary follow-up colonoscopies. Concurrently, multidetector CT parameters should be employed that allow data acquisition, providing excellent image quality balanced with an appropriately low radiation dose. The ACR practice guideline for the performance of CTC in adults includes recommendations for colon preparation and specifics of the examination technique. In particular, suggestions are provided for a quality control program.

Colonic cleansing is required for CTC and consists of ingestion of a saline cathartic and/or polyethylene glycol in combination with dietary limitation on the day before the procedure. Tagging of residual material is suggested using ingested water-soluble contrast alone or in combination with low volume barium. The ingested contrast will increase the density of residual colonic contents allowing easier differentiation from the soft tissue density of polyps and carcinoma. Although a fully cleansed colon is preferred, there is adequate data to support the use of limited cathartic CTC in combination with tagging in the minority of patients who may not be able to comply with or tolerate full catharsis [15–17].

Colonic distention is achieved by the insufflation of room air or carbon dioxide. The preferred method of colonic insufflation is with electronic administration of carbon dioxide which provides reliable and more comfortable colonic distention [18]. If a distended rectal balloon is employed to aid in gaseous retention, careful balloon insufflation is needed. Persistent and severe pain experienced by the patient during rectal balloon insufflation may indicate increased possibility of perforation. Using the scout image of the gas-filled colon in each of two opposing position, it should be ensured that there is complete anatomic scanning of the entire colon. If there is suboptimal distention or collapse of the same colonic segment on supine and prone views, then a limited rescan of the particular segment only may be performed in a decubitus position to assure diagnostic ability of the CTC examination.

Screening CTC consists of a low radiation dose CT of the abdomen and pelvis without the administration of intravenous contrast [19, 20]. A multidetector CT (MDCT) scanner is required to rapidly image patients using a slice thickness of 1–1.25 mm with a breathhold less than 25 s. Heightened awareness of radiation dose from imaging tests over the past several years has helped to ensure that CT scans are performed using the ALARA principle. All CT scanners are required to be able to provide a volumetric CT dose index (CTDIvol) in milligray representing the average radiation dose imparted in the scanned volume. For CTC, this includes dose information from at least two scans, typically the supine scan and the prone scan. The suggested CTDIvol for screening CTC is up to 6.25 mGy per position or up to 12.5 mGy for dual position CTC. This represents one half of the suggested dose limits for routine CT abdomen and pelvis in adults, which is 25 mGy.

Dose reduction strategies are widely available that may be easily applied to CTC examinations. These strategies are particularly important to recognize and

implement for screening CTC which is suggested to be repeated at 5-year intervals. Reduction of tube current (milliampere), exposure time (second), tube current–time product (milliampere-second), or tube potential (kilovolt) will result in a decrease in effective radiation dose [21–23]. Other techniques that can significantly reduce radiation dose include automatic dose modulation, image-based noise reduction algorithms and iterative reconstruction techniques [24, 25]. The use of these techniques allows for reduction of CTC effective dose to 3 mSv or less which is equivalent to the average annual background radiation dose and more than 60% lower than prior screening CTC doses [26].

A quality control program for review of CTC examinations is necessary to identify site-specific areas requiring adjustment or improvement. A minimum colonic cleansing and distention should be adequate for the identification of 10 mm or larger polyps. The radiologic technologist and physician should make certain that the CTC examination is of sufficient quality for diagnosis before the patient leaves so that if an additional limited series is required, it can be performed during the same visit. After starting a CTC program, it is recommended that correlation of radiologic, colonoscopic, and pathologic findings be performed whenever possible. Periodic monitoring of the detection rates of polyps and colorectal cancers should be performed and there should be an evaluation of false-positive rates for reported polyps in patients undergoing follow-up colonoscopy. In conjunction with establishing a quality control program, sites performing CTC are suggested to participate in the ACR National Radiology Data Registry (NRDR) for CTC.

Documentation and Communication of Results

Documentation of CTC results should clearly communicate the presence of clinically significant polyps or cancers found. The size threshold for reporting polyps at CTC is 6 mm, with the surveillance interval for follow-up of a negative or benign CTC examination of 5 years. This is in accordance with the American Cancer Society's joint colorectal screening guidelines in 2008, which states that polyps 6 mm and greater should be reported at CTC, with the recommendation for optical colonoscopy in appropriate patients [12]. Those patients with other comorbidities or risks may be better suited to undergo surveillance, as clinically indicated. Recent large trials in screening cohorts have reported lower rates of high-grade dysplasia and cancer in diminutive and small polyps, compared to earlier studies of mixed cohorts at greater risk for neoplasia. Specifically, in the Clinical Outcomes Research Initiative (CORI) database of 13,992 asymptomatic patients, the percentages of cancer, high-grade dysplasia, and tubulovillous histologies were 0, 0, and 1.2%, respectively, in 1–5 mm polyps and 0.2, 0.8, and 4.4%, respectively, in 6–9 mm polyps [27]. This is significantly less than corresponding results in earlier studies [28]. This size threshold was designed to balance the low risk of neoplasia of these smaller lesions within an interval growth rate of 5 years of surveillance, with the costs and morbidity of polypectomy [29].

C-RADS, Structured Reporting of CTC

Consistency and standardization in reporting of findings at CTC have been aided by a reporting structure, called CTC reporting and data system (C-RADS), developed in 2005 [30]. This reporting structure was modeled after the successful development of breast imaging RADS (Bi-RADS) used in mammography. C-RADS describes how to report the individual colorectal findings based on lesion size, morphology, attenuation (density), and location. Namely, lesion size is defined as the linear long axis measurement of the polyp, with exclusion of the stalk if pedunculated, using a polyp window-level setting (e.g., image display that evaluates the polyp with surrounding air interface). For sessile or superficially elevated lesions, the long axis at the base of the lesion is measured (Fig. 5.1). Both 2D multiplanar (axial, sagittal, and coronal views) as well as 3D endoscopic (virtual endoscopic views) can be utilized to best portray maximal lesion size. Typically, 3D can give the best overall view of the polyp, but when the colon is tortuous, partially collapsed, or fluid filled with incomplete visualization of the lesion at 3D, the 2D views can play an important complimentary role and provide accurate measurement of lesion size. Morphological criteria include sessile (lesion base broader than lesion height by two times or more), pedunculated, flat (less than 3 mm of vertical height), and advanced mural lesion of cancer. Lesion attenuation or density describes whether the lesion is soft tissue or fatty. Polyps or masses have soft tissue attenuation, compared to the fat attenuation of lipomas or lipomatous ileocecal valves. With the use of high-density stool tagging agents, stool can be completely or predominantly tagged with barium or iodine agents. In contrast, the surface of polyps or cancers can have a linear or nodular high-density tagging in more than 40 % of lesions [31]. Lesion location uses the standardized six segments of rectum, sigmoid, descending colon, transverse colon, ascending colon, and cecum. Flexures are referred to generically, recognizing that correlation between flexures described at colonoscopy or based on anatomic definitions may defer from what is directly visualized at CTC. A key attribute of

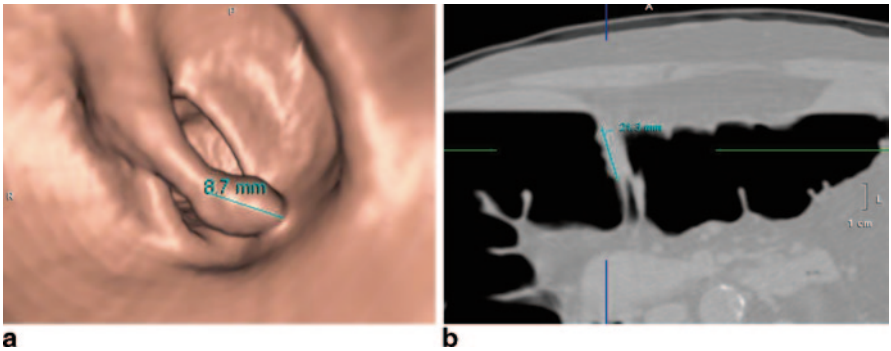

Fig. 5.1 Linear measurement of lesions as defined by C-RADS **a** Linear measurement of pedunculated polyp head, with exclusion of stalk, **b** Linear measurement along base of superficially elevated nonpolypoid polyp. *C-RADS* CTC reporting and data system

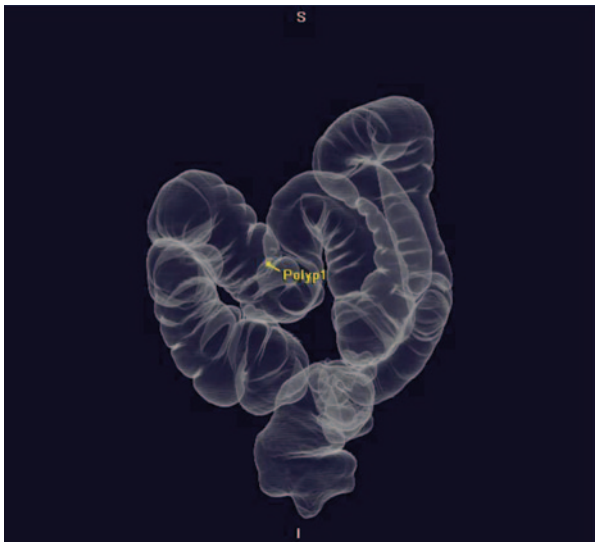

Fig. 5.2 CTC 3D edge-enhanced view to demonstrate location of lesion. *CTC* computed tomography colonography

CTC is the ability to provide very accurate localization of a polyp or cancer within the colon, using the 3D transparency view (i.e., barium enema like visualization) as an overview of the colon with the specific finding(s) marked within it (Fig. 5.2). This can be very helpful to orient the gastroenterologist or colorectal surgeon to understand the colonic anatomy and location of lesions found at CTC.

Importantly, C-RADS also developed a per-patient category score summarizing all individual colorectal findings, ranging from C0 (incomplete/limited study) to C4 (suspected or known cancer), which helps guide management decisions (Table 5.3). A C0 category includes an inadequate study that does not allow the detection of 10 mm and greater polyps. Specifically, this can be based on inadequate distension of the same segment that is not well insufflated on both views of supine and prone (or decubitus). Alternatively, inadequate visualization may be based on poor bowel preparation, with excessive retained stool or fluid that is not tagged in the same segment on both views. It is important to recognize that retained fluid that is tagged with high-density contrast can detect submerged soft tissue polyps, in contrast to retained fluid that is not tagged and is isodense to polyps, which decreases sensitivity of detection. The C0 category may also include patients with prior comparisons that are not available at the time of the dictation. This can be very important in the case of chronic diverticular changes of the sigmoid colon, with areas of colonic thickening which may have been stable for years when comparisons can be made. The C0 category is infrequently used, given the technique standards used in CTC. In a cohort of 1410 Medicare patients undergoing CTC for screening or surveillance of a polyp, a total of 3.3% (46 patients) had C0 scores [32]. Of these patients, a colonoscopy was recommended in 41.3% of patients (19 patients), excluding those who already had an incomplete colonoscopy.

Table 5.3 C-RADS reporting structure for CTC

Category	Definition	Description/examples
Colonic[a]		
C0	Inadequate study or awaiting comparison studies	Poor bowel prep or insufflation; need prior comparisons
C1	Normal or benign lesion	No polyps, or polyps ≤5 mm or benign lesion (lipoma)
C2	Few intermediate polyps or indeterminate lesion	<3 in number of 6–9 mm polyps or indeterminate lesion
C3	Multiple intermediate polyps or advanced adenoma	≥3 in number of 6–9 mm polyps or polyp(s) ≥10 mm
C4	Colonic mass, likely malignant	Advanced mural lesion
Extra-colonic[b]		
E0	Limited examination	Evaluation limited due to image artifact
E1	Normal study or benign anatomic variant	No findings, or horseshoe kidney, retro-aortic renal vein
E2	Clinically unimportant finding(s)	Simple renal or liver cysts, small lymph nodes
E3	Likely unimportant or incompletely characterized finding(s)	Hyperdense round renal lesion, enhancing liver lesion, aortic ectasia <4 cm
E4	Clinically important finding(s)	Lung base mass, large solid renal mass, adenopathy

CTC computed tomography colonography, *C-RADS* CTC reporting and data system

[a] Management recommendations for C1 is routine surveillance in 5 years, C2–C4 is recommendation for optical colonoscopy

[b] Additional imaging is recommended in E3 and E4 lesions which are not already known by history or by prior imaging

The remaining C-RADS categories include technically adequate examinations. A C1 category includes a normal colon with no polyps or polyps all 5 mm or less in size. Benign lesions such as lipomas are also included in C1. Routine surveillance with follow-up CTC or optical colonoscopy in 5 years is recommended. C2 category includes less than three in number of polyps 6–9 mm in size, with recommendation for optical colonoscopy in patients who are clinically suited. A C2 category also includes an indeterminate polyp finding in an adequately visualized segment. An indeterminate polyp finding may be a subtle flat lesion seen only in one view or a partially tagged lesion. Short-term surveillance is warranted for these lesions, with either repeat CTC or optical colonoscopy depending on lesion size, level of concern, and clinical factors. A C3 category is three or more polyps 6–9 mm in size or polyp(s) 10 mm and greater in size. A C4 category is a colonic mass, concerning for malignancy. Optical colonoscopy is recommended for C3 and C4 categories.

In addition to the colorectal scores, C-RADS also provides a similar scale for the extra-colonic findings (Table 5.3). This includes the categories of E0 (incomplete/limited exam), E1 (normal exam or anatomic variant), E2 (clinically unimportant, no work-up needed), E3 (unlikely to be clinically important but indeterminate, may need work up), and E4 (clinically significant, work up needed). Common E2 lesions

would include gallstones, renal stones, and simple liver and renal cysts. Range of E3 lesions includes larger hypodense renal or liver lesions which are not clearly cystic, complex cystic ovarian masses. E4 lesions include extra-colonic cancers, such as lung base or renal cancers, adenopathy, or large aortic aneurysms.

Currently, the incidence of significant extra-colonic findings at screening CTC ranges from approximately 4.5 to 16% [1, 11, 33–38]. This rate increases in diagnostic indications of CTC, including patients with detected colorectal cancer. Several studies have published results in the use of C-RADS E-scores for extra-colonic findings at screening CTC. In a Medicare cohort of 1410 patients 65 years and older who underwent CTC for either screening or polyp surveillance, 13.9% (196 patients) of patients had extra-colonic findings unlikely to be clinically significant (E3) and 2.9% (41 patients) had clinically significant (E4) findings [32].

It is important to discern difference in the incidence of reporting of findings versus additional imaging which results from these findings. For example, reporting of some common findings, such as gallstones or kidney stones, which may or may not be already known, typically do not require further imaging in asymptomatic patients. In a cohort of 2195 consecutive asymptomatic patients at screening CTC, a total of 9.3% (204 patients) had either E3 or E4 scores [38]. This dropped to 8.6% of patients when considering incidental findings not already known, with a total of 6.1% (133 patients) undergoing additional testing. In a retrospective study which evaluated 250 seniors (patients 65 years or older) and 204 nonseniors (mean age 52) who underwent CTC, a total of 74% of seniors versus 55.4% of nonseniors had at least one extra-colonic finding at CTC (low to high clinical significance); however, only 6% of seniors and 4.4% of nonseniors had recommendations for additional imaging [39].

In addition to C-RADS, the ACR incidental findings committee published a comprehensive white paper manuscript in 2010 regarding the management of incidental findings at abdominal CT [40]. This manuscript outlines important algorithms of how to follow or ignore common incidental findings based on size and morphology in both the general population and patients with limited life expectancy and/or comorbidity. This provides useful guidelines on how to manage common findings at CTC, such as hypodense liver and renal lesions, so as to decrease unnecessary follow-up. Since its publication, these algorithms have been further promoted with presentations at national meetings in radiology, such as the Society of Computed Body Tomography and Magnetic Resonance (SCBT/MR), Society of Abdominal Imaging (SAR), and Radiological Society of North America (RSNA). These algorithms are being considered for incorporation into clinical decision support in the future to expand their clinical use.

Development of CTC Quality Metrics and ACR NRDR Data Registry

The CTC registry was developed by the ACR in conjunction with consultants from the CTC community in 2008. It is one of the five registries in the NRDR offered by the ACR (nrdr.acr.org). These registries include the Dose Index Registry (DIR),

National Mammography Database (NMD), General Radiology Improvement Database (GRID), IV Contrast Extravasation Registry (ICE), and the CTC Registry (CTC). CTC and GRID were among the earliest registries, and DIR is the most recent. The registries have collectively tracked 765 facilities.

The guiding principle of all the registries is to empower facilities and physicians to create a cyclical quality improvement process. This process involves transmitting data to NRDR, receiving semiannual national benchmarking reports, comparing and analyzing your institution's results, and developing and implementing an improvement plan. Subsequent reports reveal which improvement activities had the desired effect. This comprises a PDSA cycle that can be easily implemented and conveniently monitored with each semiannual benchmark report. The ABR has endorsed participation in all five of these registries as an approved PQI project for the maintenance of certification of radiologists.

The CTC registry serves a similar purpose to the other registries, and is designed to support quality improvement. The metrics for the CTC registry comprise three process measures and three outcome measures (Table 5.4; [41]). It is assumed that in addition to the quantitative criteria listed in Table 5.4, the subjective application of these

Table 5.4 CTC image quality metrics in National Radiology Data Registry

Process measures	Data elements
Rate of adequate bowel cleansing and distention	Image quality that decreases ability to detect ≥1 cm polyps in both positions based on: Excess untagged fluid/fecal matter or Segmental collapse
Rate of adequacy of screening CTC exams	Slice thickness ≤3 mm Interval ≤2 mm CTDIvol within prescribed level and two patient position acquisitions of supine and prone or substitution of a decubitus position Visualization of the entire colon
Rate of adequacy of diagnostic CTC exams	Slice thickness ≤3 mm Interval ≤2 mm CTDIvol within prescribed level and two patient position acquisitions of supine and prone or substitution of a decubitus position Visualization of the entire colon
Outcome measures	
Rate of colonic perforation	Etiology if known (rectal tube trauma, recent polypectomy, diverticulitis, IBD) Type of perforation (extraperitoneal, intraperitoneal) Symptomatic from perforation (yes or no)
True positive rate (PPV)	For polyps 10 mm and greater Use optical colonoscopy as reference standard
Extra-colonic findings	E3 or E4 findings using C-RADS, which may require additional imaging Not otherwise known from history or prior imaging

C-RADS CTC reporting and data system, *CTC* computed tomography colonography, *CTDIvol* computed tomography dose index volume, *IBD* inflammatory bowel disease

metrics is guided by the detailed information described in the ACR white paper on CTC and the C-RADS guidelines. Thus, while some of the quality metrics have some subjectivity, the guiding principle is that the exam must be adequate for at least the detection of ≥10 mm lesions and preferably ≥6 mm lesions in all colonic segments.

Participants who choose to use the registry as a PQI project can choose to improve any of these measures. As CTC becomes accepted by insurers and as CTC is reevaluated for screening reimbursement by CMS, this quality metric could be used by hospital credentialing agencies such as the National Committee for Quality Assurance (NCQA) and the Joint Commission (TJC; previously known as the Joint Commission on Accreditation of Healthcare Organizations, JCAHO). It could also potentially be used as a quality assurance metric to avoid Medicare reimbursement penalties in 2016. The number of facilities participating in CTC increased from 5 in 2008 to 13 in 2013. A total of more than 6000 cases have been entered in the registry to date. The total registry accumulation by number of facilities, cases, and stratification by age cutoff of 65 years is shown in Fig. 5.3. The two highest-volume CTC sites which have collectively done over 25,000 patients to date are, namely the University of Wisconsin and Colon Health Initiative in Bethesda. These two sites currently have not entered patient data in the registry, but hopefully this will be accomplished in the future. Further advances in electronic medical record software and standards will make data entry to NRDR semiautomated. It is also anticipated that with wider acceptance and reimbursement of screening CTC, participation in the database will substantially increase.

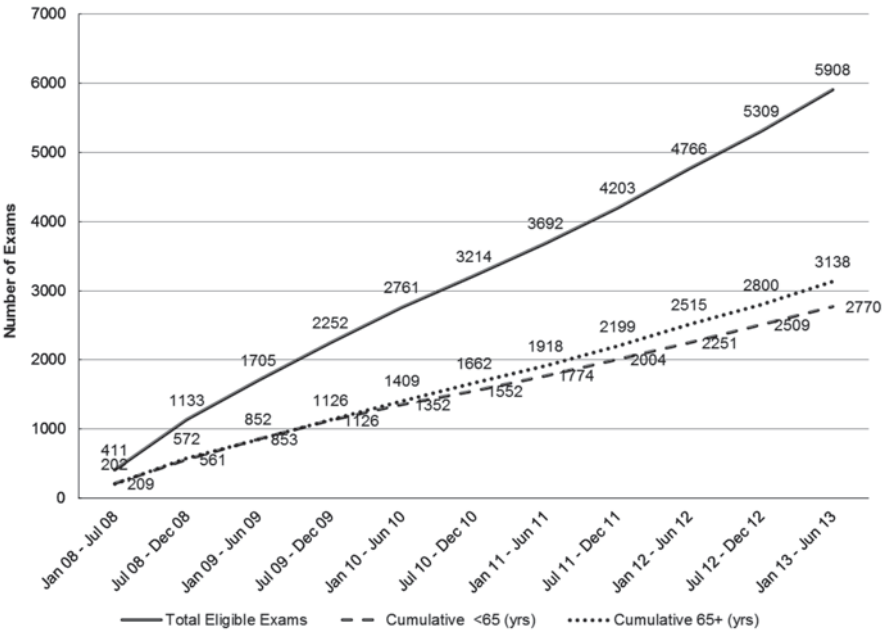

Fig. 5.3 Cumulative recruitment of CTC exams into CTC data registry. CTC computed tomography colonography

Conclusion

In summary, in the decade following the initial large validation trial of CTC as a screening modality in 2003, standards, guidelines, and a data registry have been developed and put into practice by the ACR. The current limits on global reimbursement for CTC screening have decreased the more general use of this technique in the community. Hopefully, as reimbursement improves, there will be a larger penetration of this examination in the appropriate screening and diagnostic patient cohorts, guided by these quality assurance efforts. Ongoing collaboration and communication with the referring physicians and the gastroenterology community will help to expand and improve the safe and effective use of CTC in clinical practice.

Acknowledgments We would like to acknowledge the efforts of the American College of Radiology NRDR Data Registry staff, including Mythreyi Chatfield and Debapriya Sengupta. We also thank Michael Vannier for his editorial assistance.

References

1. Johnson CD, Chen MH, Toledano AY, Heiken JP, et al. The national CT colonography trial: multicenter assessment of accuracy for detection of large adenomas and cancers. N Engl J Med. 2008;359:1207–17.
2. Edwards JT, Mendelson RM, Fritschi L et al. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community based study. Radiology. 2004;230:459–64.
3. American College of Radiology. ACR-SAR-SCBT-MR practice parameters for the performance of computed tomography (CT) colonography in adults. Chicago, IL: American College of Radiology; 2005, 2009, revised 2014. http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/CT_Colonography.pdf. Accessed 11 Sept 2014.
4. McFarland EG, et al. ACR Colon Cancer Committee white paper: status of CT colonography 2009. J Am Coll Radiol. 2009;6(11):756–72, e4.
5. Kemp S. Quality management demystified. New York: McGraw-Hill; 2006.
6. Applegate K. Continuous quality improvement for radiologists. Acad Radiol. 2004;11:155–61.
7. Maintenance of Certification. American Board of Radiology. 2014. http://www.theabr.org/pdsa-overview. Accessed 11 Sept 2014.
8. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. Ann Intern Med. 2005;142:635–50.
9. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology. 2005;237:893–904.
10. Knechtges PM, McFarland BG, Keysor KJ, Duszak R Jr, Barish MA, Carlos RC. National and local trends in CT colonography reimbursement: past, present, and future. J Am Coll Radiol. 2007;4:776–99.
11. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med. 2003;349:2191–200.
12. Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps 2008: a joint guideline from the American Cancer Society, the US Multi-society task force on colorectal cancer, and the American College of Radiology. Ca Cancer J Clin. 2008;58:130–60.

13. Whitlock EP, Lin JS, Liles E. Screening for colorectal cancer: a targeted, updated systematic review for the US Preventative Task Force. Ann Int Med. 2008;149:638–58.
14. American College of Radiology. ACR practice guideline for performing and interpreting diagnostic computed tomography. Chicago, IL: American College of Radiology; 2001. Revised 2011. http://www.acr.org/~/media/ADECC9E11A904B4D8F7E0F0BCF800124.pdf. Accessed 11 Sept 2014.
15. Florie J, van Gelder RE, Schutter MP, et al. Feasibility study of computed tomography colonography using limited bowel preparation at normal and low-dose levels study. Eur Radiol. 2007;17:3112–22.
16. Jensch S, Bipat S, Peringa J, et al. CT colonography with limited bowel preparation: prospective assessment of patient experience and preference in comparison to optical colonoscopy with cathartic bowel preparation. Eur Radiol. 2010;20:146–56.
17. Keedy AW, Yee J, Aslam R, et al. Reduced cathartic bowel preparation for CT colonography: prospective comparison of 2-L polyethylene glycol and magnesium citrate. Radiology. 2011;261:156–64.
18. Burling D, Taylor SA, Halligan S, et al. Automated insufflation of carbon dioxide for MDCT colonography: distension and patient experience compared with manual insufflation. AJR Am J Roentgenol. 2006;186:96–103.
19. Iannaccone R, Laghi A, Catalano C, et al. Detection of colorectal lesions: lower-dose multidetector row helical CT colonography compared with conventional colonoscopy. Radiology. 2003;229:775–81.
20. van Gelder RE, Venema HW, Florie J, et al. CT colonography: feasibility of substantial dose reduction–comparison of medium to very low doses in identical patients. Radiology. 2004;232:611–20.
21. van Gelder RE, Venema HW, Serlie IW, et al. CT colonography at different radiation dose levels: feasibility of dose reduction. Radiology. 2002;224:25–33.
22. Ginsburg M, Obara P, Wise L, Wroblewski K, Vannier MW, Dachman AH. BMI-based radiation dose reduction in CT colonography. Acad Radiol. 2013;20:486–92.
23. Chang KJ, Yee J. Dose reduction methods for CT colonography. Abdom Imaging. 2013;38:224–32.
24. Flicek KT, Hara AK, Silva AC, Wu Q, Peter MB, Johnson CD. Reducing the radiation dose for CT colonography using adaptive statistical iterative reconstruction: a pilot study. AJR Am J Roentgenol. 2010;195:126–31.
25. Yoon MA, Kim SH, Lee JM, et al. Adaptive statistical iterative reconstruction and Veo: assessment of image quality and diagnostic performance in CT colonography at various radiation doses. J Comput Assist Tomogr. 2012;36:596–601.
26. Boellaard TN, Venema HW, Streekstra GJ, Stoker J. Effective radiation dose in CT colonography: is there a downward trend? Acad Radiol. 2012;19:1127–33.
27. Lieberman D, Moravec M, Holub J, et al. Polyp size and advanced histology in patients undergoing colonoscopy screening: implications for CT colonography. Gastroenterology. 2008;135:1100–5.
28. Butterly LF, Chase MP, Pohl H, Fiarman GS. Prevalance of clinically important histology in small adenomas. Clin Gastroenterol Hepatol. 2006;4:343–8.
29. Levin TR, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med. 2006;145:880–6.
30. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. Radiology. 2005;236:3–9.
31. O'Connor SD, Summer RM, Choi JR, Pickhardt PJ. Oral contrast adherence to polyps on CT colonography. J Comput Assit Tomogr. 2006;30:51–7.
32. Brooks C, Riddle MS, Bhattacharya I, et al. CT colonography of a Medicare-aged population: outcomes observed in an analysis of more than 1400 patients. AJR. 2008;199:27–34.
33. Edwards JT, Wood CJ, Mendelson RM, Forbes GM. Extracolonic findings at virtual colonoscopy: implications for screening programs. Am J Gastroenterol. 2001;96:3009–12.

34. Gluecker TM, Johnson CD, Wilson LA, et al. Extracolonic findings at CT colonography: evaluation of prevalence and cost in a screening population. Gastroenterology. 2003;124:911–6.
35. Rajapaksa RC, Macari M, Bini EJ. Prevalence and impact of extracolonic findings in patients undergoing CT colonography. J Clin Gastroenterol. 2004;38:767–71.
36. Yee J, Kumar NN, Godara S, et al. Extracolonic abnormalities discovered incidentally at CT colonography in a male population. Radiology. 2005;236:519–26.
37. Chin M, Mendelson R, Edwards J, Foster N, Forbes G. Computed tomographic colonography: prevalence, nature, and clinical significance of extracolonic findings in a community screening program. Am J Gastroenterol. 2005;100:2771–6.
38. Pickhardt PJ, Hanson ME, Vanness DJ, et al. Unsuspected extracolonic findings at screening CT colonography: clinical and economic impact. Radiology. 2008;249:151–9.
39. Macari M, Nevsky G, Bonavita J, Kim DC, Megiblow AJ, Babb JS. CT colonography in seniors versus nonsenior patients: extracolonic findings, recommendations for additional imaging and polyp prevalence. Radiology. 2011;259:767–74.
40. Berland LL, Silverman SG, Gore RM. Managing incidental findings on abdominal CT: white paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2010;7:754–73.
41. Computed Tomography Colonography Measures. American College of Radiology. Revised April 28, 2011. http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/NRDR/CTC/MeasuresCTC.pdf. Accessed 11 Sept 2014.

Chapter 6
Stool DNA for Colorectal Cancer Screening: From Concepts to Quality Care

David A. Ahlquist and John B. Kisiel

Abbreviations

ACO	Accountable care organization
CLIA	Clinical Laboratory Improvement and Amendment
cm	Centimeter
CMS	Centers for Medicare and Medicaid Services
CRC	Colorectal cancer
DeeP-C	Multi-target colorectal cancer screening test for the detection of colorectal advanced adenomatous polyps and cancer
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
FIT	Fecal immunochemical test for hemoglobin
IDE	Investigational device exemption
MT-sDNA	Multi-target stool DNA test
NCD	National coverage decision
NCQA	National Committee for Quality Assurance
PMA	Premarket approval
QuARTS	Quantitative allele-specific real-time target and signal amplification
sDNA	Stool DNA

D. A. Ahlquist (✉)
Division of Gastroenterology and Hepatology, Mayo Clinic,
200 First Street SW, Rochester, MN 55905, USA
e-mail: ahlquist.david@mayo.edu

J. B. Kisiel
Department of Internal Medicine, Division of Gastroenterology
and Hepatology, Mayo Clinic, Rochester, MN, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_6

Introduction

Encouragingly, widespread screening appears to have contributed to the observed downward trends in colorectal cancer (CRC) incidence and mortality [1]. Yet, CRC remains one of the most common cancer killers in the USA [1] and worldwide [2]. The distinctly lower impact of current screening tools on proximal CRC is of particular concern; [3–5] this may be due to both the difficulty in detecting the flat precursor lesions, sessile serrated polyps, in the proximal colon [5] and to a more aggressive biology [6]. Accordingly, there is justification, and indeed an imperative, to improve screening outcomes through the responsible introduction of more effective screening tools with higher detection accuracy, better patient compliance, and fewer barriers to access. A critical appraisal of existing gaps with current approaches is required to inform the design of meaningfully innovative screening approaches. Such new tools should meet rigorous technical quality standards, robust validation of clinical performance thresholds, and desired measures of value before their implementation.

Gaps with current screening tools can best be understood by considering each against an ideal approach. An ideal CRC screening tool would accurately detect early-stage cancers and the critical precursor lesions throughout the colorectum; would be safe, noninvasive, and require no bowel preparation; could be done at home without diet or medication restrictions, and not interfere with work or daily routines; and would be readily accessible without financial, capacity, or geographic impediments. To varying degrees, all current tools fall short of such an ideal. Fecal blood tests, whether guaiac [7] or immunochemical (FIT), [8], have limited sensitivity for colorectal neoplasia, especially for precursor lesions [9] which may explain their minimal historical effect on CRC incidence [10]. Sigmoidoscopy is ineffective for proximal colon disease [11,12] Colonoscopy, as currently practiced, is proportionately less effective on incidence and mortality reduction from proximal than from distal CRC, [4,5,13] associated with low but real morbidity and mortality rates, [14] operator dependent with varying performance quality, [15] and resource intensive.

Against this context, stool DNA (sDNA) testing has emerged as a user-friendly, noninvasive screening tool which may achieve each of the ideal characteristics described above. Advances in assay technology now appear to be delivering the biological promise of this approach. Next-generation stool assay of signature DNA changes exfoliated from colorectal neoplasms allows detection of early-stage CRC and the most advanced precursor lesions at high sensitivity regardless of site within the colorectum. However, sDNA testing cannot be viewed as a single entity. Rather, there is enormous potential variation in the nature and combination of markers targeted, sample preparation methods, type of assay platforms, degree of automation, use of analytical software, and other elements between potential test approaches. As such, it is important that each individual future sDNA test be evaluated through a discriminating lens that ensures technical quality and rigorous validation of performance accuracy before it is widely applied to population screening.

In this chapter, we provide an update on Cologuard, a multi-target sDNA test (MT-sDNA) for CRC screening that is now commercially available. We describe the rigorous validation process this test has undergone. Informed by this experience, we suggest technical quality requisites, clinical performance standards, and value assessments for sDNA testing in general. We also address clinical questions for evaluation in post-market studies and future directions for expanded application of this technology.

sDNA Comes of Age

sDNA screening is based on the rational biology of tumor exfoliation [16]. Early sDNA assays of point mutations detected significantly more CRC and advanced adenomas than did guaiac-based fecal occult blood testing [7,17]. However, overall sensitivity for screen-relevant neoplasms was limited by several key technical factors, including analytical insensitivity, lack of a stabilizing buffer, and suboptimal marker coverage. As a reflection of the biologic heterogeneity of CRC, only 66% of neoplastic tissues contained a target marker within the test panel [7]. Next-generation sDNA tests have overcome these limitations with dramatic improvements in analytical sensitivity [18,19], addition of effective stabilizing buffers to prevent DNA degradation during stool transport [20], and high-coverage marker panels. Selected markers of aberrant DNA methylation are significantly more informative, requiring as few as two candidate markers to achieve 100% sensitivity and specificity in tissues [21–23].

Case-Control Studies

Rigorous clinical studies in the referral setting have established that a next-generation MT-sDNA test is capable of high detection rates for CRC and the most advanced precancers (Table 6.1). In a large case-control study, the MT-sDNA test accurately detected colorectal neoplasms irrespective of lesion site, and adenoma detection increased progressively with polyp size and associated risk of CRC progression (Fig. 6.1b) [28]. In a paired sample study [25]. the MT-sDNA prototype was shown to be significantly more sensitive than a commercial DNA-based plasma test, particularly for early-stage CRC and precancers. With a technically optimized MT-sDNA test performed manually [22] or in automated fashion [28], CRC detection rates of 98% have been achieved at 90% specificity cutoffs, irrespective of cancer stage (Fig. 6.1a). The optimized MT-sDNA test detected approximately 60% of adenomas> 1 cm and> 80% of those with high-grade dysplasia, most of which were> 2 cm in size [22]. Furthermore, the MT-sDNA test detected sessile serrated polyps ≥ 1 cm at sensitivities of 55–60% compared to 0–10% by FIT at matched specificities [22,29].

Table 6.1 Next-generation stool DNA test performance in case-control studies. (Reprinted from Ref. [56]. With permission from Sage Publications)

	Sensitivity (%)		Specificity (%)
	CRC	Adenoma> 1 cm	
Prototypes			
Ahlquist et al. [24]	85	64	90
Ahlquist et al. [25]	91	(82[a])	91
Optimized assay			
Lidgard et al. [26]	98	64	91
Lidgard et al. [27]	98	60	90

CRC Colorectal cancer
[a] From referred patients with large adenomas

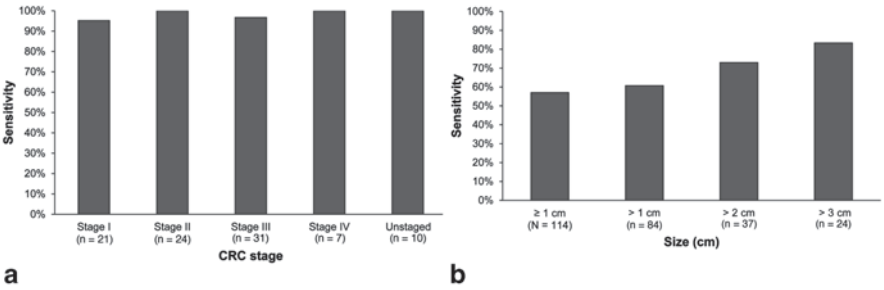

Fig. 6.1 **a** Multi-target sDNA sensitivity by colorectal cancer (CRC) stage. Sensitivity for screen-relevant CRC (stages I—III) was 97% overall (74 of 76), 100% for lesions at or proximal to the splenic flexure (proximal), and 94% for lesions distal to the splenic flexure.**b** Multi-target sDNA sensitivity for advanced precursor lesions (advanced adenoma + sessile serrated adenoma) increases with increasing lesion size. This parallels the occurrence of high-grade dysplasia (HGD); 94% of HGD (16 of 17) occurred in adenomas> 2 cm, and sDNA sensitivity for HGD was 83% (15 of 18).*sDNA* stool DNA. (Adapted from Ref. [28]. With permission from Elsevier)

Validation in the Screen Setting: Pivotal Multicenter Cross-Sectional Study

A pre-commercial version of the optimized and automated MT-sDNA test (Cologuard; Exact Sciences, Madison, WI) has now been validated in a multicenter study on> 10,000 patients from the screen setting [30]. The study was based on a cross-sectional design in which the MT-sDNA test was compared to a commercial FIT using colonoscopy as the criterion standard (ClinicalTrials.gov Identifier: NCT01397747). The Cologuard MT-sDNA utilizes a quantitative allele-specific real-time target and signal amplification (QuARTS) assay of mutant *KRAS,* methylated *BMP3*, methylated *NDRG4*, and unmethylated *β-actin* as well as an immunochemical test for hemoglobin (Fig. 6.2). Cutoff values were preestablished using an analytic regression algorithm to determine an overall test score [22].

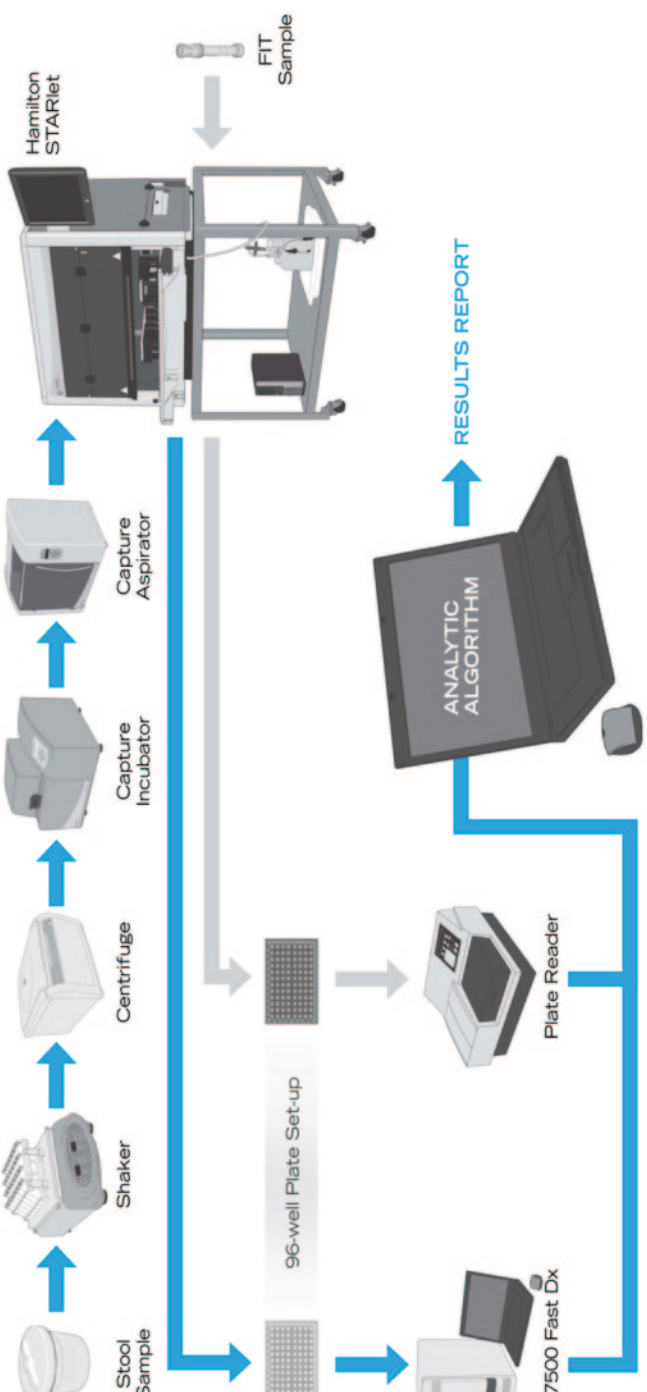

Fig. 6.2 The exact sciences automated analytic platform. Multi-target sDNA analytic process. Patient samples are homogenized in the collection container, aliquoted, and centrifuged. DNA markers are captured with target-specific magnetic beads (capture incubator), washed (capture aspirator), and magnetically separated. Bead-bound sDNA biomarkers are transferred to a Hamilton Microlab STARlet (Reno, NV). The portion of sDNA for methylation assay is bisulfite treated, and the portion for KRAS mutation assay is pH neutralized. Treated DNA is then combined with reagents for quantitative allele-specific realtime target and signal amplification (QuARTS) on an ABI 7500 FastDx (Carlsbad, CA) that generates results in log strands of DNA. Fecal hemoglobin samples are transferred to enzyme-linked immunosorbent assay plates with Hamilton Microlab STARlet liquid handler and then read (BioTek ELx808 plate reader, Winooski, VT). Software algorithmically integrates results of assays to calculate a dichotomous "positive" or "negative" result. (Adapted from Ref. [28]. With permission from Elsevier)

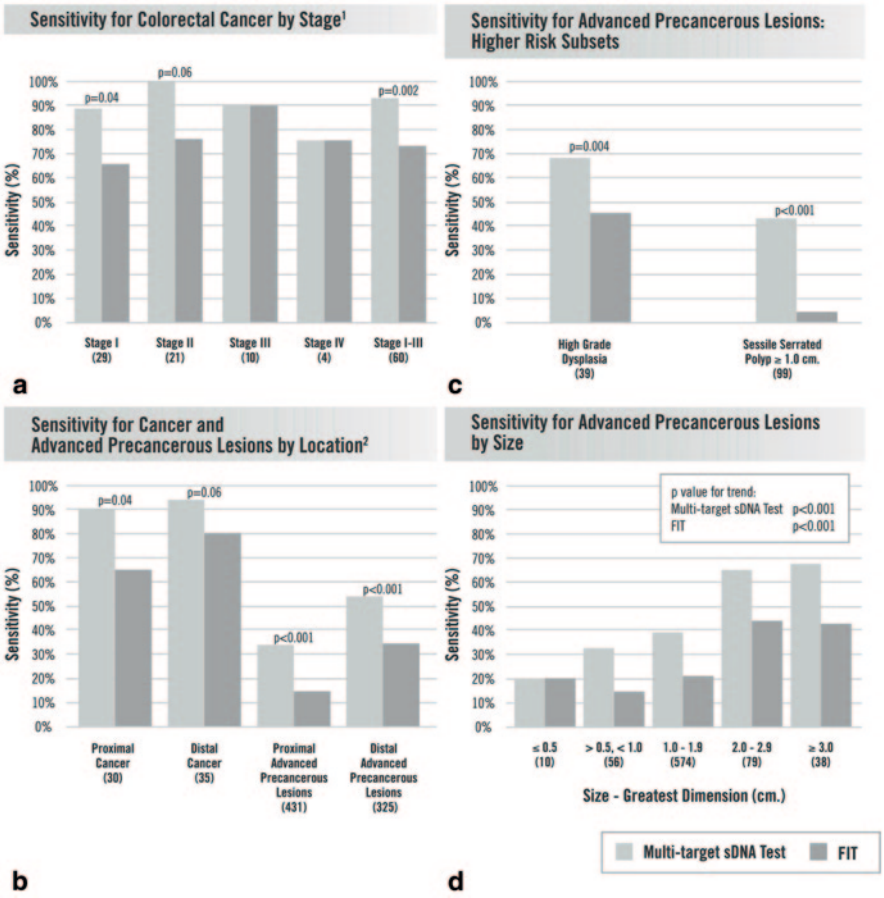

Fig. 6.3 Results of the multi-target sDNA test and commercial fecal immunochemical test in analyzed subgroups. Numbers in parentheses ( ) are sample sizes.**a** sensitivity for colorectal cancer by stage (*1* The stage of one colorectal cancer was not available),**b** sensitivity for cancer and advanced precancerous lesions by location (*2* The location of one advanced precancerous lesion was not available),**c** sensitivity for advanced precancerous lesions: higher risk subsets,**d** sensitivity for advanced precancerous lesions by size. (Adapted from Ref.30. With permission from Massachusetts Medical Society)

At predetermined cutoffs, Cologuard detected significantly more lesions than did FIT for all categories: 93% versus 73% for curable-stage CRC (Fig. 6.3a); 68% versus 45% for adenomas with high-grade dysplasia (Fig. 6.3b); 66% versus 42% for adenomas ≥2 cm, 42% versus 24% for all advanced adenomas, 17% versus 8% for non-advanced polyps (Fig. 6.3d); and, 43% versus 5% for sessile serrated polyps ≥1 cm (Fig. 6.3b). As we have previously noted [21], CRC detection was not affected by stage or site (Fig. 6.3c), and polyp detection increased in proportion to lesion size (Fig. 6.3d). Based on patients with normal colonoscopy, specificity was

lower with Cologuard at 90% compared to FIT at 95%. Age influenced Cologuard specificity which was 94% in those < 65 years of age and 87% in those ≥ 65 years of age. Given the known variability in colonoscopy detection rates, it is possible that some of the "false-positive" stool test results represent lesions missed by the criterion standard. In addition to these pivotal trial data, rigorous technical studies demonstrate reliability of Cologuard performance in compliance with the highest regulatory standards for diagnostic testing.

Technical Quality and Regulatory Pathways

To better understand the quality benchmarks required for CRC screening by sDNA, the regulatory mechanisms of new in vitro diagnostic tests deserve further review. Broadly speaking, there are two major pathways for new tools to enter the laboratory medicine marketplace in the USA; these are Clinical Laboratory Improvement and Amendment (CLIA) certification and/or premarket approval (PMA) by the Food and Drug Administration (FDA) [31]. Tests developed by a single laboratory for use at a single site are historically regulated by the Centers for Medicare and Medicaid Services (CMS) under the CLIA Act of 1988 [31]. The focus of CLIA certification is analytical test accuracy. While quality control metrics are reviewed, the requirements for demonstration of clinical effectiveness and clinical validation are less strictly defined by this approval mechanism. In contrast, tests intended for broader licensure or distribution are subjected to a more rigorous premarket demonstration of safety and efficacy by the FDA. Within the FDA, a diagnostic device that bears substantial equivalence to another cleared *predicate* product may qualify for premarket notification (e.g., 510 (k) review). In other cases, where no predicate exists or the test is a new device, the US Code of Federal Regulation (CFR) requires PMA. The extensive and detailed evidence needed to support a PMA is defined in Code of Federal Regulations 21 CFR, part 814.

The FDA encourages early engagement and collaboration in the PMA process [32]. For example, clinical trials are usually needed to generate the evidence required to establish safety and efficacy. Prior to clinical studies of unapproved diagnostics or other medical devices, manufacturers may interact with the FDA to establish trial objectives and endpoints required to substantiate approvability. This interaction is referred to as the pre-Investigation Device Exemption (IDE) process [31]. In the pre-IDE, the FDA may help prioritize scientific issues required for the PMA and perform preliminary review of the device technology. In the pre-IDE process for Cologuard, the FDA determined that FIT was not a clear predicate test because DNA is a fundamentally different analyte than hemoglobin, and the overall MT-sDNA assay process is substantially more complex. In addition, Cologuard required demonstration of safety and effectiveness in the average-risk screen setting, subject to accepted standards for reporting diagnostic accuracy [33]. Therefore, a PMA was required.

In addition to demonstration of safety and efficacy, a PMA requires submission of extensive technical or "nonclinical" data according to FDA guidelines, including careful description of the diagnostic test device, quality controls on all analytical reagents and assay equipment, laboratory analytical performance, prespecified cut-offs, and the technical limits of assay detection. The automated assay equipment for high-throughput testing (Fig. 6.2) [28] was subjected to similar rigorous verification and validation.

The optimized Cologuard MT-sDNA assay [22] was designed, defined, and reviewed a priori to any final screen setting clinical validation. The test then was subjected to tests of reproducibility in three independent clinical labs, each using the final, fully automated assay platform. At each lab, two independently operating teams performed the assay over 20 work shifts.

Nonclinical testing also studied the potential for artifactual assay interference or inhibition. Samples were pooled to achieve specific Cologuard cutoff scores and included both positive and negative cases as well as controls. Interference was tested separately for both the DNA and hemoglobin-based components of the assay. Prior to assay, samples were spiked with up to 56 items in nine classes from commonly ingested foods and medications including sources of animal hemoglobin and DNA, dietary fiber supplements, nonsteroidal anti-inflammatory drugs, and numerous other drugs.

Because methylation of *BMP3* and *NDRG4* has been reported in association with other disease processes, [34,35] studies were performed to rigorously measure assay specificity and cross-reactivity. Samples from patients with inflammatory bowel disease (IBD) and other gastrointestinal and genitourinary cancers were tested. While some cross-reactivity with liver and pancreatic cancers was anticipated [36], these would account for much fewer than 1 % of false positives.

Multivariate analysis of demographic and anthropomorphic variables and patient exposure characteristics demonstrated that there was measurable influence from age on methylated DNA marker levels [37]. However, sex, race, body mass index, alcohol use, and smoking history did not impact test results. Importantly, family history of CRC and personal history of colorectal neoplasia had no significant influence [37].

The FDA also had input on methods to provide the appropriate clinical evidence for Cologuard, and suggested design elements for a prospective clinical study of average-risk patients in the screen setting was required (see DeeP-C study results, above). The PMA submission to the FDA, including results of DeeP-C, was subsequently completed in the summer of 2013. On the basis of the clinical performance and safety demonstrated in the DeeP-C study, the FDA advisory panel unanimously endorsed Cologuard on March 27, 2014. On August 11, 2014, Cologuard became the first device to obtain full FDA approval and a simultaneous proposed national coverage determination from CMS.

Program Performance and Effectiveness

Based on what is known about the natural history of colorectal neoplasm progression and the point-in-time performance of the Cologuard test, models can be developed to derive an optimal testing frequency. While not finalized yet, our early modeling suggests that an interval of every 3 years could reduce CRC mortality and incidence at rates comparable to those by colonoscopy done at an interval of every 10 years. Based on early-generation sDNA data, the American College of Gastroenterology has also agreed that sDNA testing be implemented at 3-year testing intervals [38]. Furthermore, CMS coverage was also approved for this interval.

Program Sensitivity

CRC prevention (i.e., incidence reduction) depends on how effectively over time a screening program identifies and removes those premalignant lesions at greatest risk for cancer progression. Observational studies suggest that the majority of 1 cm polyps do not progress and polyps that do progress grow slowly with average doubling times of every 4–6 years [39–41]. Further, we noted in a recent study that >90% of all high-grade dysplasia was found in adenomas ≥2 cm, a size range where MT-sDNA sensitivity is high [28]. As such, longitudinal screening by Cologuard may yield excellent cumulative sensitivity for a cohort of advanced adenomas as they slowly grow and progress through high-grade dysplasia (Table 6.2). In contrast, CRC mortality reduction mandates very high point sensitivities for early-stage CRC; one cannot rely on repeated screening for effective detection as the window of cancer progression from early-to-late stages may be narrow [42]. With validated sensitivity for curable-stage CRC of 93% in the screen setting, Cologuard noninvasively achieves detection rates similar to those of colonoscopy and meets this requisite of high curable-stage CRC detection (Table 6.2).

Table 6.2 Hypothetical programmatic sensitivity of MT-sDNA testing at a 3-year screening frequency

	Cumulative sensitivity (%)	
	Adenoma> 1 cm[a]	Curable-stage CRC
Screen 1	42–66	93
Screen 2	71–91	99
Screen 3	90–98	–

CRC colorectal cancer, *cm* centimeter

[a] Estimated starting sensitivities shown for 1 and 2 cm size cutoffs; model assumes polyp volume doubling time of every 6 years [39]

Program Specificity

Nonspecificity in CRC screening tests leads to false-positive results and, consequently, to unnecessary and costly colonoscopies. From a program standpoint, it is cumulative false positives over time (or the rate of false positives) that is most relevant. The false-positive rate is a function of both specificity and testing frequency. Cologuard, with a point specificity of 87–90 % (10–13 % false-positives), applied at a frequency of every 3 years would yield an average rate of 3.3–4.3 false positives per year. FIT with a point specificity of 95 % performed at an annual frequency would yield 5 % false positives per year. Thus, the program specificity of an MT-sDNA test could prove to be comparable to or even higher than that of FIT.

Perceived Value in an Accountable Care Era

Perception of value is an important driver of test choice. Yet, a screening test's value may be differently perceived across the various stakeholders, including patients, health-care providers, third-party payers, employers, industry, or society as a whole. For example, a reimbursement perspective of a CRC-screening approach may not account for patient inconvenience and costs (such as disrupted daily routines, missed work, and time and expense of travel) or for societal costs (such as lost work productivity required for screening). A reimbursement perspective may differ dramatically between cradle-to-grave lifetime coverage programs and those that cover only specific patients, such as Medicare beneficiaries. As such, cost-effectiveness and other value models may reach substantially different and competing conclusions based on the same available data [43].

Let us first consider the perspective of reimbursement for Medicare beneficiaries. The goal of the CMS review was to determine whether or not a new innovation is reasonable and necessary for the Medicare population to justify a national coverage decision (NCD) [44]. While the CMS review process utilized FDA assessments of safety and efficacy, FDA approval alone was not sufficient for the NCD. In this process, CMS requires an explanation of the relevance of the evidence presented for the NCD and the rationale for how this evidence demonstrates medical benefit specific to the Medicare population. The DeeP-C trial was designed to address these questions; of the patients enrolled in DeeP-C, 61 % were over the age of 65, and therefore MT-sDNA performance can be specifically assessed in those potentially eligible for Medicare coverage.

The effectiveness of neoplasm detection at the population level is a product of test accuracy, patient compliance to testing, and test access. In addition to high test sensitivity, sDNA testing has potential to improve both compliance because of its patient-friendly features and test access because of its convenient delivery and return by mail. In cost-effectiveness models, which vary the programmatic adherence, CRC screening effectiveness increases significantly as utilization increases [45–47].

Results from cost-effectiveness models that include updated sDNA performance assumptions, and ranges of compliance and access have not yet been published.

In an increasingly resource-constrained environment, the most successful screening approaches will incorporate value metrics of multiple stakeholders. The accountable care organization (ACO) movement is a step in this direction as it seeks alliance and shared values between three key stakeholders—patients, a network or group of collaborating providers, and a primary payer, like CMS [48]. As the ACO movement establishes performance measurement pathways for specific conditions, new cost and health outcome measures may become available to better assess value of individual CRC screening options, the combined effectiveness of multiple screening test choices, and the potentially unmeasured costs of screening delivery. One organization, well positioned to make such assessments, is the National Committee on Quality Assurance (NCQA), whose Healthcare Effectiveness Data and Information Set (HEDIS) measures have been broadly adopted to track CRC screening compliance of patients at participating facilities. Indeed, NCQA has begun review of Cologuard performance data with this goal in mind.

Performance Standards for sDNA CRC Screening: Setting a High Bar

Based on data from early-generation sDNA tests, several professional organizations elected to include this approach in their CRC screening guidelines, including the American Cancer Society, American College of Radiology, and US Multi-Society Task Force [49], and the American College of Gastroenterology [38]. The US Preventive Services Task Force took a neutral position on sDNA testing based on the early data [50]. However, the robustly validated accuracy of the Cologuard next-generation MT-sDNA test and the rigorous FDA review it has undergone, set a new high bar for CRC screening standards by noninvasive approaches.

Based on peer-reviewed data from studies examining the next-generation MT-sDNA test performance and on regulatory reviews, we propose that the following criteria be considered in developing standards for noninvasive tests intended for general population CRC screening:

1. Pass technical quality and safety requirements via stringent regulatory review, such as by the US FDA.
2. Achieve high point sensitivity (>90%) for CRC. This should be demonstrated for curable-stage disease (stages I–III) and for both distal and proximal locations in a sufficiently powered cross-sectional study of average-risk persons from the screen setting.
3. Achieve moderate-point sensitivity (>50%) for those precursor lesions at highest risk of progressing to CRC (i.e., the aggregate of high-grade dysplasia, adenomas >2 cm, and sessile serrated polyps> 1 cm) located throughout the colorectum. Such a point-sensitivity threshold should translate into high cumulative

detection (program sensitivity) of these high-risk lesions and, thereby, into effective reduction of CRC incidence (secondary prevention). Demonstration should be based on a sufficiently powered cross-sectional study of average-risk persons from the screen setting.
4. Produce program false positives at an average rate of ≤5% per year of screening. This rate would be a factor of point specificity and testing frequency. For example, a test with a point specificity of 85% (15%) performed every 3 years and a test with a point specificity of 95% performed annually would have equivalent average false-positive rates of 5% per year.
5. Meet cost-effectiveness thresholds deemed acceptable and reimbursable by CMS (Medicare) and other third-party payers.

CRC Surveillance and Other Future Applications

Inflammatory Bowel Disease (IBD)

In addition to screening for average-risk CRC, sDNA is under study for surveillance of high-risk populations, including those with IBD. Recent pilot data demonstrate that sDNA is feasible for the detection of CRC and precancers in patients with either Crohn's disease of the colon or chronic ulcerative colitis [51]. Methylated *BMP3* and *NDRG4* were 100% sensitive for CRC and high-grade dysplasia and 67% sensitive for low-grade dysplasia, both at 89% specificity. A multicenter clinical trial, Detection of Advanced Colorectal Neoplasia by sDNA in IBD ((OCEANIA), ClinicalTrials.gov Identifier: NCT1819766) is in progress to confirm these findings. Patient subsets with a history of colorectal polyps or CRC may also benefit from the use of sDNA testing as an adjunct to colonoscopy, and appropriately designed studies would be needed to examine the value of such.

Upper Gastrointestinal Neoplasia

There is great potential for the use of sDNA technology in the diagnosis and screening of neoplasms throughout the gastrointestinal tract. Early proof-of-concept observations support the feasibility of sDNA to detect mutations from upper gut cancers [52,53]. As subsequent case-control studies confirm findings with methylation markers assayed from stool [36] and other biological media, such as pancreatic juice [54], work is also in progress to identify markers which might be specific to neoplasms from a specific anatomic site in order to inform diagnostic workup following a positive DNA-based screening test [55].

Conclusions

sDNA testing for CRC and precancers has strong biological rationale and demonstrated excellent sensitivity and specificity in several large case-control studies. Now, in the screen setting of average-risk patients, Cologuard achieved sensitivity for curable-stage CRC similar to that of colonoscopy and detection rates for both CRC and advanced precancers superior to those of FIT. Because sDNA test performance is dependent on marker selection, assay technology, and sample processing, there is considerable potential for heterogeneity in performance and value among competing novel sDNA test products. The Cologuard MT-sDNA sets an important and high threshold for subsequent regulation and quality assessment.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30.
2. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. CA Cancer J Clin. [Review]. 2009;59(6):366–78.
3. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer: a population-based, case-control study. Ann Intern Med. 2009;150(1):1–8.
4. Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst. 2010;102(2):89–95.
5. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12):1095–105. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't).
6. Lu FI, van Niekerk de W, Owen D, Tha SP, Turbin DA, Webber DL. Longitudinal outcome study of sessile serrated adenomas of the colorectum: an increased risk for subsequent right-sided colorectal carcinoma. Am J Surg Pathol. 2010;34(7):927–34.
7. Ahlquist DA, Sargent DJ, Loprinzi CL, Levin TR, Rex DK, Ahnen DJ, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med. 2008;149(7):441–50, W81.
8. van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135(1):82–90. (Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't).
9. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology. 2005;129(2):422–8.
10. Heresbach D, Manfredi S, D'Halluin P N, Bretagne JF, Branger B. Review in depth and meta-analysis of controlled trials on colorectal cancer screening by faecal occult blood test. Eur J Gastroenterol Hepatol. [Meta-Analysis Review]. 2006;18(4):427–33.
11. Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624–33. [Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't].
12. Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366(25):2345–57. (Comparative Study Multicenter Study Randomized Controlled Trial Research Support, N.I.H., Extramural).

13. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009;150(1):1–8.
14. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst. 2003;95(3):230–6.
15. Kahi CJ, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol. 2011;9(1):42–6.(The Official Clinical Practice Journal of the American Gastroenterological Association. [Evaluation Studies].)
16. Ahlquist DA, Harrington JJ, Burgart LJ, Roche PC. Morphometric analysis of the "mucocellular layer" overlying colorectal cancer and normal mucosa: relevance to exfoliation and stool screening. Hum Pathol. 2000;31(1):51–7.
17. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med. 2004;351(26):2704–14.
18. Zou H, Taylor WR, Harrington JJ, Hussain FT, Cao X, Loprinzi CL, et al. High detection rates of colorectal neoplasia by stool DNA testing with a novel digital melt curve assay. Gastroenterology. 2009;136(2):459–70.
19. Zou H CX, Domenico M, Harrington J, Taylor W, Yab T, Ahlquist D, Lidgard G. Sensitive quantitation of methylated markers with a novel methylation-specific technology. Clin Chem. 2010;56:A199.
20. Zou H, Harrington JJ, Klatt KK, Ahlquist DA. A sensitive method to quantify human long DNA in stool: relevance to colorectal cancer screening. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1115–9.
21. Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology. 2012;142(2):248–56.
22. Lidgard GP, Domanico M, Bruinsma JJ, Gagrat ZD, Oldham-Haltom R, Fourrier KD, et al. An optimized multi-marker stool test for colorectal cancer screening: initial clinical appraisal. Gastroenterology. 2012;142(5, Suppl 1):S–770.
23. Zou H, Allawi H, Cao X, Domanico M, Harrington J, Taylor WR, et al. Quantification of methylated markers with a multiplex methylation-specific technology. Clin Chem. 2012;58(2):375–83.
24. Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology. 2012;142(2):248–56.
25. Ahlquist DA, Taylor WR, Mahoney DW, Zou H, Domanico M, Thibodeau SN, et al. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Clin Gastroenterol Hepatol. 2012;10(3):272–7e1.(The Official Clinical Practice Journal of the American Gastroenterological Association. [Comparative Study Evaluation Studies Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]).
26. Lidgard GP, Domanico M, Bruinsma JJ, Gagrat ZD, Oldham-Haltom R, Fourrier KD, et al. Tu1189 an optimized multi-marker stool test for colorectal cancer screening: initial clinical appraisal. Gastroenterology. 2012;142(5, Supplement 1):S–770.
27. Lidgard GP, Domanico MJ, Bruinsma JJ, Light J, Gagrat ZD, Oldham-Haltom RL, et al., editors. An optimized molecular stool test for colorectal cancer screening: evaluation of an automated analytic platform and logistic algorithm. AACR International Conference on Frontiers in Cancer Prevention Research; 2012; Anaheim, California.
28. Lidgard GP, Domanico MJ, Bruinsma JJ, Light J, Gagrat ZD, Oldham-Haltom RL, et al. Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia. Clin Gastroenterol Hepatol. 2013;11(10):1313–18.
29. Heigh RI, Yab TC, Taylor WR, Hussain FNT, Smyrk TC. Detectionof colorectal serrated polyps by stool DNA testing: comparison with fecal immunochemical testing for occult blood (FIT). PL. S One. 2014;9(1):e85659.

30. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, et al. Multitarget stool DNA test for colorectal cancer screening: prospective, multicenter assessment and comparison with fecal immunochemical testing in an average-risk population. N Engl J Med. 2014;370(14):1287–97.
31. Hackett JL, Gutman SI. Introduction to the food and drug administration (FDA) regulatory process. J Proteome Res. [Review]. 2005;4(4):1110–3.
32. Administration USFaD. Premarket Approval (PMA). 2012.http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketapprovalpma/. Accessed: 20 Sept 2013.
33. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for reporting of diagnostic accuracy. Clin Chem. 2003;49(1):1–6. (Comment Consensus Development Conference Research Support, Non-U.S. Gov't Review).
34. Schilling SH, Hjelmeland AB, Radiloff DR, Liu IM, Wakeman TP, Fielhauer JR, et al. NDRG4 is required for cell cycle progression and survival in glioblastoma cells. J Biol Chem. 2009;284(37):25160–9.
35. Dai Z, Popkie AP, Zhu WG, Timmers CD, Raval A, Tannehill-Gregg S, et al. Bone morphogenetic protein 3B silencing in non-small-cell lung cancer. Oncogene. 2004;23(20):3521–9.
36. Kisiel JB, Yab TC, Taylor WR, Chari ST, Petersen GM, Mahoney DW, et al. Stool DNA testing for the detection of pancreatic cancer: assessment of methylation marker candidates. Cancer. 2012;118(10):2623–31. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't).
37. Ahlquist DA, Taylor WR, Yab TC, Devens ME, Mahoney DW, Boardman LA, et al. Aberrantlymethylated gene marker levels in stool: effect of demographic exposure, body mass, and other patient characteristics. J Mol Biomark Diagn. 2012;3(5):133.
38. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American college of gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104(3):739–50.
39. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. Gastroenterology. 1987;93(5):1009–13.
40. Hofstad B, Vatn MH, Andersen SN, Huitfeldt HS, Rognum T, Larsen S, et al. Growth of colorectal polyps: redetection and evaluation of unresected polyps for a period of three years. Gut. 1996;39(3):449–56. (Research Support, Non-U.S. Gov't).
41. Pickhardt PJ, Kim DH, Pooler BD, Hinshaw JL, Barlow D, Jensen D, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. Lancet Oncol. 2013;14(8):711–20. (Multicenter Study Research Support, N.I.H., Extramural Video-Audio Media).
42. Edge SBB DR, Compton CC, Fritz AG, Greene FL, Trotti A. editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
43. Kisiel JB, Ahlquist DA. Stool DNA screening for colorectal cancer: opportunities to improve value with next generation tests. J Clin Gastroenterol. 2011;45(4):301–8. (Research Support, Non-U.S. Gov't Review).
44. Scully TA, Thompson TG. Medicare program; revised process for making medicare national coverage determinations. Federal Register. 2003;68(187):55634–41.
45. Zauber AG L-VI, Wilschut J, Knudsen AB, van Ballegooijen M, Kuntz KM. Cost-effectiveness of DNA stool testing to screen for colorectal cancer: report to AHRQ and CMS from the Cancer Intervention and Surveillance Modeling Network (CISNET) for MISCAN and SimCRC Models. 2007.https://www.cms.hhs.gov/mcd/viewtechassess.asp?where=index&tid=52. Accessed: 30 Oct 2009.
46. Parekh M, Fendrick AM, Ladabaum U. As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. Aliment Pharmacol Ther. 2008;27(8):697–12.
47. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. Am J Gastroenterol. 2013;108(1):120–32. (Comparative Study Evaluation Studies).

48. Fisher ES, McClellan MB, Bertko J, Lieberman SM, Lee JJ, Lewis JL, et al. Fostering accountable health care: moving forward in medicare. Health Aff (Millwood). 2009;28(2):w219–31. (Research Support, N.I.H., ExtramuralResearch Support, Non-U.S. Gov't).
49. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008 May;134(5):1570–95.
50. U.S. Preventive Services Task Force. Screening for colorectal cancer: recommendation and rationale. Ann Intern Med. 2002;137(2):129–31.
51. Kisiel JB, Yab TC, Nazer Hussain FT, Taylor WR, Garrity-Park MM, Sandborn WJ, et al. Stool DNA testing for the detection of colorectal neoplasia in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2013;37(5):546–54. (Research Support, Non-U.S. Gov't).
52. Berndt C, Haubold K, Wenger F, Brux B, Muller J, Bendzko P, et al. K-ras mutations in stools and tissue samples from patients with malignant and nonmalignant pancreatic diseases. Clin Chem. 1998;44(10):2103–7.
53. Zou H, Harrington JJ, Taylor WR, Devens ME, Cao X, Heigh RI, et al. T2036 pan-detection of gastrointestinal neoplasms by stool DNA testing: establishment of feasibility. Gastroenterology. 2009;136(5, Supplement 1):A–625.
54. Raimondo M, Yab TC, Mahoney DW, Taylor WR, Anderson KS, Ahlquist DA. Methylated DNA markers in pancreatic juice discriminate pancreatic cancer from chronic pancreatitis and normal controls. Gastroenterology. 2013;144(5, Supplement 1):S–90.
55. Kisiel JB, Taylor WR, Yab TC, Mahoney DW, Sun Z, Middha S, et al. 769 novel methylated DNA markers predict site of gastrointestinal cancer. Gastroenterology. 2013;144(5, Supplement 1):S–84.
56. Kisiel JB, Ahlquist DA. Stool DNA testing for cancer surveillance in inflammatory bowel disease: an early view. Therap Adv Gastroenterol. 2013;6(5):371–80.

Chapter 7
Quality Indicators for Colonoscopy

Victoria Gómez and Michael Bradley Wallace

Excerpt reprinted from Quality improvement of gastrointestinal endoscopy: guidelines for clinical application. From the ASGE. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc. 1999;49(6):842–4. With permission from Elsevier

Introduction: A Revolution in Quality

The invention of the colonoscope has revolutionized the way we evaluate luminal diseases of the colon. With colorectal cancer being the third most commonly diagnosed cancer as well as the third most frequent cause of cancer-related mortality in both men and women, colonoscopy offers an advantage of detecting cancer and the ability to remove precancerous lesions [1]. As a result of its effectiveness in the detection and prevention of colorectal neoplasms, colonoscopy has become the screening test of choice for many gastroenterologists and patients, and it is the preferred screening method endorsed by the American College of Gastroenterology (ACG) [2, 3]. More than 14 million colonoscopies are performed annually in the USA [4]. However, the practice of gastrointestinal (GI) endoscopy has been facing challenges over the past 5–10 years. With decreased reimbursement for endoscopic procedures in the setting of increasing demand for endoscopy, performing endoscopists have been faced with trying to balance high-volume demand while maintaining or improving the quality of the services being provided to patients [5]. Recently, the question of what constitutes a high-quality colonoscopy has been discussed. Until recently, issues in quality assurance in colonoscopy were brought by different medical societies without a common backbone or structure. A study by Robertson

M. Bradley Wallace (✉)
Department of Gastroenterology and Hepatology, Mayo Clinic Florida,
4500 San Pablo Rd., Jacksonville, FL 32224, USA
e-mail: Wallace.michael@mayo.edu

V. Gómez
Department of Gastroenterology, Mayo Clinic, Jacksonville, FL, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_7

et al., using the 1997 American Society for GI Endoscopy guidelines for endoscopy reporting in 2002, demonstrated that clinicians' colonoscopy reporting practices were highly variable and frequently suboptimal [6].

In 2000, the US Multi-Society Task Force on Colorectal Cancer consisted of representatives of the American College of Physicians-American Society of Internal Medicine (ACP-ASIM), The American Gastroenterological Association (AGA), and the American Society for GI Endoscopy (ASGE) created a task force to address issues in quality in colonoscopy and its impact on the detection and prevention of colorectal neoplasia [7]. Later, the ASGE with the support of the ACG created a Task Force on Quality in Endoscopy, which further refined these quality indicators with an emphasis on improving aptitude in performing colonoscopy [8]. A summary of the proposed quality indicators is provided in Table 7.1. We discuss a few of these notable quality indicators and review the evidence-based studies that support these measures.

Interval Cancers and Deaths and Surrogate Measures

The primary goal of colonoscopy in most instances is the prevention of colorectal cancer-related death [8]. Results of the National Polyp Study in 1993 showed that colonoscopy reduced the incidence of colorectal cancers by 76–90% [9]. In a case–control study using Surveillance, Epidemiology and End Results (SEER) datasets, Baxter et al. demonstrated a 60% reduction in death from colorectal cancer. This protective association was strongest when colonoscopies were performed by gastroenterologists for distal lesions [10]. Despite the advances in colonoscope technology, the gastroenterologic societies realized that the protective benefits of colonoscopy were not as high as previously thought and that several explanations may account for these findings.

"Interval cancers," colorectal cancers found at or before the next recommended screening/surveillance colonoscopy, are thought to be partly explained by missed lesions during the index colonoscopy [8, 11–13]. Large, retrospective, population studies from the USA and Canada have been performed to estimate the prevalence of interval cancers [11]. Findings were impressive, with 7.2–9% of colorectal cancers meeting definition of interval cancers [13–15] (Table 7.2). There was a consistently higher probability of interval cancer occurring in the proximal compared to the distal colon.

While it is proposed that some interval cancers may arise from neoplastic lesions that harbor genetic features that are associated with a more rapid progression to cancer, as well as lesions that may have been incompletely resected, there is strong evidence to demonstrate that the quality of the colonoscopy is related to the rate of interval cancers [11, 12, 17–19].

The adenoma detection rate (ADR), which is the proportion of average-risk patients undergoing screening colonoscopy in whom an adenoma or colorectal cancer is found, is regarded as a robust measure of colonoscopy performance quality that

Table 7.1 Summary of proposed quality indicators for colonoscopy[a]. (Adapted from Ref. 8. With permission from Elsevier)

Quality indicator	Grade of recommendation
Appropriate indication	1C+
Informed consent is obtained, including specific discussion of risks associated with colonoscopy	3
Use of recommended postpolypectomy and post-cancer resection surveillance intervals	1A
Use of recommended ulcerative colitis/Crohn's disease surveillance intervals	2C
Documentation in the procedure note of the quality of the preparation	2C
Cecal intubation rates (visualization of the cecum by notation of landmarks and photo documentation of landmarks should be present in every procedure)	1C
Detection of adenomas in asymptomatic individuals (screening)	1C
Withdrawal time: mean withdrawal time should be ≥6 min in colonoscopies with normal results performed in patients with intact anatomy	2C
Biopsy specimens obtained in patients with chronic diarrhea	2C
Number and distribution of biopsy samples in ulcerative colitis and Crohn's colitis surveillance. Goal: 4 per 10-cm section of involved colon or approximately 32 specimens per case of pancolitis	1C
Mucosally based pedunculated polyps and sessile polyps <2 cm in size should be endoscopically resected or documentation of unresectability obtained	3
Incidence of perforation by procedure type (all indications vs. screening) is measured	2C
Incidence of postpolypectomy bleeding is measured	2C
Postpolypectomy bleeding managed nonoperatively	1C

[a] This list of potential quality indicators was meant to be a comprehensive listing of measureable endpoints. It is not the intention of the ASGE/ACG Task Force that all endpoints be measured in every practice setting. In most cases, validation may be required before a given endpoint may be universally adopted

correlates with subsequent cancer risk [20–22]. It has been suggested that adenomas should be detected in 25% or more of men and 15% or more of women 50 years of age and older [23]. However, numerous studies have been published showing significant heterogeneity in endoscopist ADR. In a provocative landmark study by Kaminski et al., in which 45,026 patients involved in a Polish nationwide colorectal cancer screening program were followed over time, and interval cancers were determined at the scheduled time of surveillance colonoscopy, endoscopists with ADRs less than 20% (categorized as less than 11.0%, 11.0–14.9%, 15.0–19.9%, and 20.0% or more) had a more than tenfold higher rate of interval colorectal cancers than those with higher ADRs [22]. Another more recent study that also supports the relationship between ADR and interval cancer comes from Corley and colleagues.

Table 7.2 Frequency and location of interval CRCs. (Adapted from Ref. 51. With permission from Elsevier)

Study	Data source	Total detected cancers, *n*	Interval cancers		
			Overall, *n* (%)	Proximal, *n* (%)	Distal, *n* (%)
Baxter et al. 2011 [13]	Ontario cancer registry (2000–2005)	24,213	1260 (9%)	676 (12.4%)	584 (6.8%)
Singh et al. 2010 [14,16]	Manitoba cancer registry (1992–2008)	4883	388 (7.9%)	225 (11.3%)	147 (5.3%)
Cooper et al. 2012 [15]	SEER-medicare database (1994–2005)	57,839	4192 (7.2%)	2851 (9.9%)	1253 (4.5%)

SEER Surveillance, Epidemiology and End Results, *CRC* colorectal cancer

Physician ADR (range: $<20.3\%$–$\geq 32.0\%$) was found to be an independent predictor of subsequent colorectal cancer risk following a negative colonoscopy, findings that were consistent for proximal and distal cancers, and irrespective of patient sex [24]. What remains to be determined is at what threshold we start to observe no further protective benefit of a very high ADR.

Some interval cancers may arise from rapidly growing lesions that develop de novo between scheduled colonoscopies. It is now well recognized that some colorectal cancers arise from a different carcinogenesis pathway, arising from the sessile serrated adenoma pathway. This pathway is characterized by mutations in the BRAF oncogene, gene promoter hypermethylation (i.e., CpG island methylator phenotype; CIMP) and a more rapid progression to colorectal cancer; these lesions are also more prevalent in the proximal colon, a location where we recognize colonoscopy to be less protective for colorectal cancer compared to the distal colon [25–27]. Recent studies suggest that these sessile serrated adenomas may partially account for some of the interval cancers. However, in a retrospective study by Kahi and colleagues, the proportion of screening colonoscopies with at least one proximal serrated polyp was 13%, and, furthermore, endoscopist ADR correlated strongly with proximal serrated polyp detection rates [27]. To date, ADR remains the best surrogate for quality in colonoscopy and efforts are being undertaken to improve physician ADRs across many institutions.

Withdrawal time, the time measured from when the colonoscope reaches the cecum to the time the scope is withdrawn from the anus in the absence of polyp removal, has also been studied as a quality metric in colonoscopy. Studies have demonstrated that a withdrawal time of ≥ 6 min or more increased the detection of neoplastic lesions during colonoscopy in patients with intact colons [8]. However, due to heterogeneity in patient anatomy and lengths of colons, application of this standard is not feasible for every case [8].

Clinical studies have shown mixed results on improvements in adenoma detection with implementation of a longer withdrawal time [21]. Studies that have evaluated total withdrawal time alone as well as with feedback on performance failed to show statistically significant improvements in adenoma detection, while some showed improvement in nonadenomatous polyp detection [28–35]. When multiple interventions were implemented in studies by Imperiali et al. and Shaukat et al., including a 1% financial penalty for those endoscopists who did not achieve a ≥6-min withdrawal time for >95% of examinations in the latter study, no statistically significant changes in ADR were observed [36, 37]. However, in a study by Barclay and colleagues, in which an audible timer was used during withdrawal (implementing an 8-min withdrawal time) in addition to enhanced inspection techniques, ADR increased by 50% compared to baseline, a statistically significant finding ($P<0.0001$) [21, 38]. In summary, mandating longer withdrawal time alone is not likely to increase the rate of adenoma detection and ultimately reduce the incidence and mortality of colorectal cancer [8].

Cecal intubation, defined as the process where the colonoscope reaches a point proximal to the ileocecal valve with complete visualization of the entire cecum, should be achieved in ≥90% of all colonoscopies and in ≥95% of cases for screening colonoscopies. Documentation of reaching this landmark should be confirmed with photography of the cecal landmarks (i.e., appendiceal orifice and ileocecal valve) [8]. This quality indicator has been proposed due to the well-known findings that a large portion of colorectal neoplasms is located in the proximal colon, including the cecum [8].

The quality of colonoscopy is also assessed by process measures for health-care delivery [6]. Documentation of various measures has been proposed by the ASGE as well as the ASGE/ACG Task Force on Quality in Endoscopy [8, 39]. Moving forward with these proposed recommendations, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable (NCCRT) developed a standardized colonoscopy reporting and data system (CO-RADS) to improve the quality of colonoscopy [40]. Procedure reports should be created by programs to allow systematic documentation of the details of the colonoscopy that would include the indication(s), anatomic extent of the examination, findings, and complications, among others. The complete list of the recommended elements [39] is as follows:

1. Date of procedure
2. Patient identification data
3. Endoscopist(s)
4. Assistant(s)
5. Documentation of relevant patient history and physical examination
6. Indication of informed consent
7. Endoscopic procedure
8. Indication(s)
9. Type of endoscopic instrument
10. Medication (anesthesia, analgesia, sedation)
11. Anatomic extent of examination
12. Limitation(s) of examination

13. Tissue or fluid samples obtained
14. Findings
15. Diagnostic impression
16. Results of therapeutic intervention (if any)
17. Complications (if any)
18. Dispositions
19. Recommendations for subsequent care

An additional measure that has now been added is the quality of the bowel preparation [8]. A poor bowel preparation is associated with a prolonged cecal intubation time and withdrawal time, as well as a decrease in the detection of polyps overall [41, 42]. The ASGE/ACG Task Force recommends that a colonoscopy be considered adequate if it allows detection of polyps 5 mm or larger [7]. If inadequate, the colonoscopy should be repeated at a shorter interval, which is left to the discretion of the endoscopist. Recommendations for subsequent care, particularly surveillance interval for postpolypectomy and post cancer resection, should also be implemented for optimal outcomes in colonoscopy [8]. The recommended intervals have been outlined by the US Multi-Society Task Force on Colorectal Cancer, and they assume that cecal intubation was achieved, bowel preparation was adequate, and a careful examination was performed [43,44].

Emerging National Consensus Metrics

Accountability measures, in which a financial penalty or incentive is tied to a measure, have recently emerged with national endorsement by the National Quality Forum (NQF), the Centers for Medicare, and Medicaid [45]. The Physician Quality Reporting System (PQRS) uses a combination of incentive payments and payment adjustments to encourage reporting of quality information by professionals [46]. A pay for performance model and other forms of "value-based purchasing" (VBP) are strategies that encourage and reward high-quality health care and promote assessment of health-care structures and processes to ensure quality outcomes [47]. The ACG and ASGE have established the GI Quality Improvement Consortium (GIQuIC), a nonprofit organization implementing a national colonoscopy outcome registry, in which gastroenterologists are able to report multiple clinical data through an electronic interface [48, 49]. GIQuIC was created as a benchmark example of quality assessment and is discussed further in the following chapter. Using the ASGE/ACG quality indicators of colonoscopy, a set of candidate performance measures have recently been proposed for use as indicators of colonoscopy quality for the purpose of health-care payment reform: cecal intubation rate, ADR, and recommended post-polypectomy surveillance intervals [47]. Currently, the only colonoscopy performance-related measure listed in the PQRS is endoscopy and polyp surveillance (i.e., assigning correct interval recommendations for patients with a history of adenomatous polyps as well as after a normal colonoscopy exam) [50].

Conclusion

As health-care providers, we have an imperative responsibility not only to provide medical services to our patients but also to ensure that we do so in the safest and most effective fashion as possible. Quality indicators in colonoscopy have become available for practitioners and institutions to review and follow, to help ensure that our patients receive the best care possible, that they benefit from screening colonoscopies, with the ultimate goal to prevent or detect early colorectal cancer, and, finally, undergo appropriate treatment. Quality in colonoscopy means continuously improving the outcomes of our patients' health.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10–29.
2. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104(3):739–50.
3. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American cancer society, the US multi-society task force on colorectal cancer, and the American College of Radiology. Gastroenterology. 2008;134(5):1570–95.
4. Seeff LC, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS, et al. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. Gastroenterology. 2004;127(6):1670–7.
5. Bjorkman DJ, Popp JW Jr. Measuring the quality of endoscopy. Gastrointest Endosc. 2006;63(4 Suppl):S1–2.
6. Robertson DJ, Lawrence LB, Shaheen NJ, Baron JA, Paskett E, Petrelli NJ, et al. Quality of colonoscopy reporting: a process of care study. Am J Gastroenterol. 2002;97(10):2651–6.
7. Rex DK, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. multi-society task force on colorectal cancer. Am J Gastroenterol. 2002;97(6):1296–308.
8. Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, et al. Quality indicators for colonoscopy. Gastrointest Endosc. 2006;63(4 Suppl):S16–28.
9. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The national polyp study workgroup. N Engl J Med. 1993;329(27):1977–81.
10. Baxter NN, Warren JL, Barrett MJ, Stukel TA, Doria-Rose VP. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol. 2012;30(21):2664–9.
11. Patel SG, Ahnen DJ. Prevention of interval colorectal cancers: what every clinician needs to know. Clin Gastroenterol Hepatol. 2014;12(1):7–15.
12. Leung K, Pinsky P, Laiyemo AO, Lanza E, Schatzkin A, Schoen RE. Ongoing colorectal cancer risk despite surveillance colonoscopy: the polyp prevention trial continued follow-up study. Gastrointest Endosc. 2010;71(1):111–7.
13. Baxter NN, Sutradhar R, Forbes SS, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures associated with postcolonoscopy colorectal cancer. Gastroenterology. 2011;140(1):65–72.

14. Singh H, Nugent Z, Demers AA, Bernstein CN. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. Am J Gastroenterol. 2010;105(12):2588–96.
15. Cooper GS, Xu F, Barnholtz Sloan JS, Schluchter MD, Koroukian SM. Prevalence and predictors of interval colorectal cancers in medicare beneficiaries. Cancer. 2012;118(12):3044–52.
16. Singh H, Nugent Z, Mahmud SM, Demers AA, Bernstein CN. Predictors of colorectal cancer after negative colonoscopy: a population-based study. Am J Gastroenterol. 2010;105(3):663–73; quiz 74.
17. Sawhney MS, Farrar WD, Gudiseva S, Nelson DB, Lederle FA, Rector TS, et al. Microsatellite instability in interval colon cancers. Gastroenterology. 2006;131(6):1700–5.
18. Pohl H, Robertson DJ. Colorectal cancers detected after colonoscopy frequently result from missed lesions. Clin Gastroenterol Hepatol. 2010;8(10):858–64.
19. Farrar WD, Sawhney MS, Nelson DB, Lederle FA, Bond JH. Colorectal cancers found after a complete colonoscopy. Clin Gastroenterol Hepatol. 2006;4(10):1259–64.
20. Church J. Adenoma detection rate and the quality of colonoscopy: the sword has two edges. Dis Colon Rectum. 2008;51(5):520–3.
21. Corley DA, Jensen CD, Marks AR. Can we improve adenoma detection rates? A systematic review of intervention studies. Gastrointest Endosc. 2011;74(3):656–65.
22 Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med. 2010;362(19):1795–803.
23. Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, et al. Quality indicators for colonoscopy. Am J Gastroenterol. 2006;101(4):873–85.
24. Corley DAJ, Christopher D, Marks AR, Zhao W, Lee JK, Quesenberry C, Levin TR, Doubeni CA, van Ballegooijen M, Zauber AG, Schottinger JE, Quinn VP, Ghai NR. Physician adenoma detection rate variability and subsequent colorectal cancer risk following a negative colonoscopy. Gastroenterology. 2013;144(5):S2–S3.
25. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138(6):2088–100.
26. Kambara T, Simms LA, Whitehall VL, Spring KJ, Wynter CV, Walsh MD, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. Gut. 2004;53(8):1137–44.
27. Kahi CJ, Hewett DG, Norton DL, Eckert GJ, Rex DK. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol. 2011;9(1):42–6.
28. Taber A, Romagnuolo J. Effect of simply recording colonoscopy withdrawal time on polyp and adenoma detection rates. Gastrointest Endosc. 2010;71(4):782–6.
29. Velasquez J, Espinoza-Rios J, Huerta-Mercado J, Pinto J, De los Rios R, Piscoya A, et al. Impact assessment of increasing the time of withdrawal of colonoscopy in the detection rate of polyps in our midst. Rev Gastroenterol Peru. 2009;29(4):321–5.
30. Mellen JYJ, Cooper B, et al. Can feedback regarding adenoma dectection rates substantially enhance colonoscopy performance? [abstract]. Am J Gastroenterol. 2010;105(Suppl 1):S561.
31. Yuan JMJ, Cooper B, et al. How will the efficiency of colonoscopy change with an enhanced emphasis on adenoma detection? [abstract]. Am J Gastroenterol. 2010;105(Suppl 1):S561–S2.
32. Ramasamy DSR, Geenen DJ, et al. Analysis of colonoscopy withdrawal time and detection of adenomatous colon polyp in a high volume private practice endocenter [abstract]. Gastrointest Endosc. 2008;67:AB305.
33. Hall BS, Benson ME, Pfau P, et al. Improved adenoma detection rates at an academic gastroenterology unit following department colonoscopy assessment [abstract]. Gastrointest Endosc. 2010;71:AB107–8.
34. Sawhney MS, Cury MS, Neeman N, Ngo LH, Lewis JM, Chuttani R, et al. Effect of institution-wide policy of colonoscopy withdrawal time > or = 7 min on polyp detection. Gastroenterology. 2008;135(6):1892–8.

35. Lin OS, Kozarek RA, Arai A, Gluck M, Jiranek GC, Kowdley KV, et al. The effect of periodic monitoring and feedback on screening colonoscopy withdrawal times, polyp detection rates, and patient satisfaction scores. Gastrointest Endosc. 2010;71(7):1253–9.
36. Shaukat A, Oancea C, Bond JH, Church TR, Allen JI. Variation in detection of adenomas and polyps by colonoscopy and change over time with a performance improvement program. Clin Gastroenterol Hepatol. 2009;7(12):1335–40.
37. Imperiali G, Minoli G, Meucci GM, Spinzi G, Strocchi E, Terruzzi V, et al. Effectiveness of a continuous quality improvement program on colonoscopy practice. Endoscopy. 2007;39(4):314–8.
38. Barclay RL, Vicari JJ, Greenlaw RL. Effect of a time-dependent colonoscopic withdrawal protocol on adenoma detection during screening colonoscopy. Clin Gastroenterol Hepatol. 2008;6(10):1091–8.
39. American Society for Gastrointestinal Endoscopy. Quality improvement of gastrointestinal endoscopy: guidelines for clinical application. From the ASGE. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc. 1999;49(6):842–4.
40. Lieberman D, Nadel M, Smith RA, Atkin W, Duggirala SB, Fletcher R, et al. Standardized colonoscopy reporting and data system: report of the quality assurance task group of the national colorectal cancer roundtable. Gastrointest Endosc. 2007;65(6):757–66.
41. Froehlich F, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European panel of appropriateness of gastrointestinal endoscopy European multicenter study. Gastrointest Endosc. 2005;61(3):378–84.
42. Harewood GC, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. Gastrointest Endosc. 2003;58(1):76–9.
43. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US multi-society task force on colorectal cancer. Gastroenterology. 2012;143(3):844–57.
44. Rex DK, Kahi CJ, Levin B, Smith RA, Bond JH, Brooks D, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American cancer society and the US multi-society task force on colorectal cancer. Gastroenterology. 2006;130(6):1865–71.
45. Allen JI. Quality assurance for gastrointestinal endoscopy. Curr Opin Gastroenterol. 2012;28(5):442–50.
46. http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/index.html?redirect=/PQRS/. Accessed 11 June 2013.
47. Hewett DG, Rex DK. Improving colonoscopy quality through health-care payment reform. Am J Gastroenterol. 2010;105(9):1925–33.
48. Johnson DA. Quality benchmarking for colonoscopy: how do we pick products from the shelf? Gastrointest Endosc. 2012;75(1):107–9.
49. Pike IM, Vicari J. Incorporating quality measurement and improvement into a gastroenterology practice. Am J Gastroenterol. 2010;105(2):252–4.
50. http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/MeasuresCodes.html. Accessed 11 June 2013.
51. Patel SG, Ahnen DJ. Prevention of interval colorectal cancers: what every clinician needs to know. Clin Gastroenterol Hepatol. 2014;12(1):7–15. pii:S1542-3565(13)00587-9.

Chapter 8
Toward a Learning Health-Care System: Use of Colorectal Cancer Quality Measures for Physician Evaluation

Ziad F. Gellad and Joel V. Brill

Introduction

The development of evidence-based quality measures and benchmarks in colorectal cancer (CRC) screening is a critical step toward building a truly accountable health-care system [1]. Indeed, much of the gastroenterology research literature in quality has focused on the scientific merit and reliability of these measures. Less attention has been placed on understanding the use of these measures for physician evaluation, an equally important part of the performance measurement and improvement cycle [2].

In qualitative work performed in the past decade, Scanlon et al. acknowledged this limitation, noting that very few studies have focused on understanding the impact of performance measurement in practice [3]. Initially, measurement reports were used primarily to reduce cost and manage utilization at the system level [4]. More recently and with increasing frequency, organizations are using individual physician feedback reports for quality improvement. This change has been catalyzed by three main factors: the growth of financial incentive programs geared toward individual providers; the development of robust physician-level quality measures; the improvement in data systems to allow more efficient and timely access to individual physician-level data.

Scanlon et al. focused primarily on the use of the health plan employer data and information set (HEDIS) and consumer assessment of health plans survey

Z. F. Gellad (✉)
Division of Gastroenterology, Duke University Medical Center & Durham Veterans Affairs Medical Center, 2400 Pratt St., Rm. 0311, Terrace Level, Box 3850, Durham, NC 27705, USA
e-mail: ziad.gellad@duke.edu

J. V. Brill
Predictive Health LLC, Paradise Valley, AZ, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_8

(CAHPS), both of which are still widely in use today. In fact, in 2012, more than 1000 health plans, covering the lives of more than 125 million Americans, reported HEDIS measures [5, 6]. CRC screening rates were added to HEDIS measures in 2006. Since the development of the HEDIS performance measure on CRC screening rates, a number of more detailed quality measures have emerged for CRC screening and surveillance. There is very little existing literature on the use of these newer measures for physician evaluation or on their impact on improving quality care in gastroenterology. In fact, a recent evidence report by the Agency for Healthcare Research and Quality (AHRQ) on CRC screening found no published papers monitoring the quality of CRC screening at the population level; the bulk of effort in CRC screening has focused on increasing the use of screening, quality aside [7].

In this chapter, we will address this information gap by reviewing the use of CRC quality measurement for physician evaluation. Our focus will include the levers available for action in performance evaluation including evidence underlying these levers, examples of existing evaluation systems in government, commercial, regional, and integrated delivery systems, and the limitations of existing evaluation systems.

Levers for Action

In a recent perspective piece, authors from the Department of Health and Human Services, Centers for Medicare & Medicaid Services, Office of the National Coordinator for Health Information Technology, and AHRQ outlined a number of key goals for a modern quality measurement system (Table 8.1) [8]. The authors note that a quality measurement system has to be agile, broad-based, feasible, impactful, supportive of feedback, and vertically aligned. These goals build upon findings from earlier qualitative work by Scanlon et al. where managers of managed care organizations identified a number of shared characteristics of useful performance measures: relevant, actionable, timely, standardized, stable for trending, focused on the appropriate unit of analysis, and affordable [3].

Common to these frameworks is the importance of developing actionable measures for performance improvement. Action can take a number of forms, including performance feedback, pay for performance, public reporting, and physician designation. Each of these will be discussed separately below.

Performance Feedback

There are a number of theories as to how performance feedback can improve the quality of health-care practice. These include changing awareness about current practices, changing social norms, enabling self-efficacy, and facilitating goal setting [9]. The evidence suggests that “audit and feedback” approaches generally result in

Table 8.1 Key goals for a modern quality measurement system. (Based on data from [8])

Goal	Description
Agile	Cycle time for measurement development to implementation should be short to maximize adaptability to new evidence
Broad-based	Must address priority domains of the national quality strategy (e.g., clinical care, patient experience, population health, safety, care coordination, and cost/efficiency)
Feasible	Must minimize the burden for data collection and reporting
Impactful	Prioritize outcome measures over process measures
Support feedback	Should enable provider feedback through decision-support tools
Vertically aligned	Should capture quality information at the level of the clinician, provider group, and population

improvement in practice, and the degree of improvement depends on an individual's performance at baseline and the type of feedback provided [9]. For example, feedback has been shown to be more effective when it is provided by a supervisor or a colleague, when it is provided more than once, when it is provided in both verbal and written form, and when it provides unambiguous targets for action.

At the population level, the rate of CRC screening uptake is a key measure used in performance feedback systems. Studies have shown that assessment and feedback of provider performance in CRC screening leads to improved performance [10, 11]. As it relates to colonoscopy quality, a number of studies have examined the impact of performance feedback on quality measures, and the majority have shown no impact on polyp detection rates [12]. However, three studies deserve mention. The first described an intervention that combined audible withdrawal timer with improved inspection technique [13]. This feedback intervention resulted in a significant increase in the detection of polyps as well as an overall population-level increase in the detection of advanced adenomas. In a recent study in the Veterans Health Administration, a quarterly report card resulted in a significant increase in adenoma detection and cecal intubation rates [14]. In a third study, an educational intervention combined with monthly feedback of adenoma detection rates resulted in marked improvement in detection rates during the course of the intervention [15]. Of note, none of these studies found a significant increase in advanced adenoma detection among physicians. More importantly, none have been able to assess the impact on the truly meaningful outcome, namely CRC incidence.

Pay for Performance

Tying financial incentives to performance feedback is one potential mechanism to augment the impact of physician feedback programs. Pay-for-performance (P4P) programs are in place for traditional Medicare inpatient and Medicare advantage plans, where withholds for nonparticipation will be implemented for individual

physicians beginning in 2015. The individual physician program is based on the physician quality reporting system (PQRS) which has been in place since 2007 [16]. The physician value-based payment modifier (VBPM) will initially encourage participation but will quickly expand to incentivize performance on a defined set of measures [17].

Evidence on the impact of P4P programs is mixed [16]. Robust assessments of the impact of these interventions are lacking, and it is difficult to draw definitive conclusions from the existing literature [18]. The lack of impact of P4P programs may be related to inadequate incentive size, incentive structures, and even the choice of metrics themselves [19].

Dedicated studies evaluating the impact of P4P in CRC screening are not available although the American College of Gastroenterology (ACG) has identified a set of principles for the development and evaluation of these programs [20]. Furthermore, others have outlined recommendations for the use of payment reform to improve colonoscopy quality [21]. Several CRC screening quality measures are included in the government's P4P program and will be further described below.

Public Reporting

The belief that public reporting will result in improved quality is based on the notion that, in a competitive marketplace, information disclosure will cause self-regulation of the health-care system through actions on purchasers, consumers, policymakers, providers, and the public [22]. There are success stories in the general medical literature [23, 24], but the quality of the data is insufficient to make any broad conclusions on the impact of public reporting on consumer behavior, provider behavior, or clinical outcomes in health care [25, 26]. Furthermore, physicians are wary of public reporting programs because of concerns that these programs will distract the public from paying attention to the unmeasured components of health-care quality and will cause providers to avoid high-risk patients or perhaps even lower the quality of care through unintended consequences [27, 28].

In CRC screening, there are a few studies examining the impact of public reporting on the quality of care. Sarfaty and Myers found that the addition of a CRC screening rate to the HEDIS measures resulted in a number of changes by Pennsylvania health plans to increase screening rates in their populations [29]. This is notable because very few health plans had comprehensive management of CRC screening programs before that time [30]. The impact of public reporting of other quality measures in CRC screening is yet to be determined as many of these measures are still in their developmental stages.

Physician Designation

One particular method of public reporting is the use of "physician designation" programs. These are programs that rate, rank, or tier health-care providers based on

measures of quality and cost with the hopes of directing patients to the preferred providers. One of the earliest attempts at physician designation was the creation of preferred provider organizations (PPO), where physicians were either in or out of the network [31]. These networks surged in popularity in the late 1990s to early 2000s and remain as the predominant option for commercial payers, but have failed to deliver substantive cost or quality improvements [32].

More recent attempts at physician designation have relied on more sophisticated criteria of quality and cost, balancing performance feedback with elements of public reporting. Key to the success of these programs is the accuracy of information provided to the public, and accuracy has been one of the concerns prompting legal action around physician designation. One early example is action taken by the Attorney General of New York in 2007 [33]. In response to attempts by insurers to tier physicians on quality and cost-efficiency, the NY Attorney General initiated an investigation that lead to a wide-reaching agreement with a number of insurers to create a core set of principles for the accuracy and transparency of data used for physician tiering.

In 2008, Colorado enacted legislation-requiring standards and procedures for health insurers that are initiating physician-rating systems [31]. The *Physician Designation Disclosure Act* has a number of key requirements: first, the law requires that any public reporting or ranking of a physician's performance must include quality of care data; second, performance measures used in the ranking must be endorsed by the National Quality Forum, a national physician-specialty group or the Colorado Clinical Guidelines Collaborative and be measured in a statistically sound fashion; third, the rating must include a disclaimer advising patients not to rely solely on the ranking in choosing a physician; finally, the law gives physicians right to review the data on which his/her ranking is based and to take action should they feel the data misrepresent their practice. Similar legislation has been considered in a number of other states, including Oklahoma, Maryland, and Texas.

The impact of these programs on quality and cost of CRC screening remains unknown. In part, it is unclear to what extent differentiation of providers using existing performance metrics will impact the quality of care. Furthermore, physician cost profiling has been shown to be unreliable [34], and it remains to be seen how cost transparency will influence patient and physician behavior.

Existing Evaluation Systems

Using performance feedback, P4P, public reporting, and physician designation as the levers of action, a number of entities in the USA use CRC screening quality measures for physician evaluation. In this section, we will review a number of these programs with a specific focus on government, commercial, and regional programs as well as those of integrated delivery systems.

Table 8.2 Most commonly reported physician quality reporting system (PQRS) measures among gastroenterologists 2011

Rank #	Measure #	Description
1	124	Health information technology: adoption/use of electronic health records (EHR)
2	113	Preventive care and screening—colorectal cancer (CRC) screening
3	130	Documentation of current medications in the medical record
4	226	Tobacco use: screening and cessation intervention
5	185	Endoscopy and polyp surveillance: colonoscopy interval for patients with history of adenomatous polyps—avoidance of inappropriate use

Government

As discussed above, the PQRS is a P4P program that has been the primary government-level evaluation program geared toward physicians. In 2011, Centers for Medicare & Medicaid Services (CMS) paid more than US$ 261 million to 26,515 practices, which included 266,521 providers [35]. Included in this amount were 2370 gastroenterologists who participated in the program, representing 26.1% of the eligible professionals. This number is quite small when compared to the 41,998 internists and family practice physicians who participated in the program in 2011. However, it represents a significant increase since only 8.1% of the eligible gastroenterologists participated in 2008.

The tenth most commonly individual reported measure in the PQRS system among all providers was the CRC screening (Measure #113) measure. For gastroenterologists, the most commonly reported individual measures are listed in Table 8.2. PQRS measures around CRC screening for the 2013 reporting year are listed in Table 8.3. Screening colonoscopy adenoma detection rate (ADR) has been proposed by CMS for incorporation in the performance year 2014 and several new measures have been proposed by the gastrointestinal (GI) societies for 2015, including: repeat colonoscopy due to poor bowel preparation, and appropriate age for CRC screening [36].

To date, all current CRC quality measures (CRC screening rates, ADR detection rates, surveillance intervals after normal screening, and after adenomatous polyps) are process measures. Questions have arisen as to whether the existing CRC quality measures are satisfactory, or should be revised in view of updated recommendations from the special societies regarding surveillance intervals after polypectomy [37] as evidenced by the National Quality Forum's August 2013 decision to not endorse measure 0659 (Endoscopy/polyp surveillance: colonoscopy interval for patients with a history of adenomatous polyps—avoidance of inappropriate use) [38].

The lack of outcome measures for gastroenterology has been cited as a concern with the existing measures. In response, CMS has contracted with Yale New Haven Health Services Corporation/Center for Outcomes Research and Evaluation (CORE) to develop administrative claims-based, risk-adjusted measures of high-acuity care

Table 8.3 2013 physician quality reporting system (PQRS) measures related to colorectal cancer (CRC) screening

Measure #	National quality strategy domain	Description
113	Clinical process/effectiveness	Preventive care and screening—colorectal cancer screening (percentage of patients aged 50 through 75 years who received the appropriate colorectal cancer screening)
185	Care coordination	Endoscopy and polyp surveillance: colonoscopy interval for patients with history of adenomatous polyps—avoidance of inappropriate use (percentage of patients aged 18 years and older receiving a surveillance colonoscopy with a history of a prior colonic polyp(s) in previous colonoscopy findings, who had an interval of 3 or more years since their last colonoscopy)
320	Care coordination	Endoscopy/polyp surveillance: appropriate follow-up interval for normal colonoscopy in average risk patients (percentage of patients aged 50 years and older receiving a screening colonoscopy without biopsy or polypectomy who had a recommended follow-up interval of at least 10 years for repeat colonoscopy documented in their colonoscopy report)
321	Care coordination	Participation in a systematic clinical database registry that includes consensus endorsed quality (participation in a systematic qualified clinical database registry)

visits after an outpatient colonoscopy or endoscopy procedure. High-acuity care visits are defined as inpatient admissions, observation stays, or emergency department visits, and may represent complications due to outpatient procedures [39]. A technical expert panel was convened in 2013, with the objective of developing measures by 2014 that can be used to measure and improve the quality of care provided to Medicare beneficiaries, and to potentially submit these measures to the National Quality Forum for endorsement.

In addition to process measures of quality, government programs have begun to transition to value-based incentive programs. As gastrointestinal endoscopic procedures as a whole make up the largest percentage (32.7%) of ambulatory surgical center (ASC) claims in Medicare, gastroenterologists will have a key stake in this process through the development of Medicare's value-based purchasing program for ASCs. The American Society for Gastrointestinal Endoscopy (ASGE) proposed three gastroenterology-specific measures for this program: (1) Appropriate follow-up interval for normal colonoscopy in average risk patients, (2) colonoscopy interval for patients with a history of adenomatous polyps—avoidance of inappropriate use, and (3) comprehensive colonoscopy documentation [40].

Commercial

As with government programs, commercial entities are focusing on value over cost or quality alone. Most commercial programs use physician designation programs based on physician quality and cost to evaluate physicians and incentivize patient behavior. A sample of these programs is represented in Table 8.4. All of the programs reviewed, start with quality designation and augment designation based on cost. These programs use proprietary software to group claim data into episodes of care when considering cost. The criteria for meeting quality and cost designations vary among programs and several entities rely on commercial vendors with proprietary ranking technology to calculate claim-based measures.

Very few commercial payor programs include gastroenterology in their rankings and even fewer contain measures specific to CRC screening. For example, the Aetna Aexcel Program uses expected rate of readmissions and hospital complications for satisfying claim-based measures of quality in gastroenterology [43]. Cigna Care Designation has more robust quality measures for inflammatory bowel disease and Hepatitis C but none for CRC screening specific to gastroenterology [44]. The BlueCross BlueShield of Massachusetts Alternative Quality Contract measures CRC screening rates, but does not specifically rank gastroenterologists [45]. One of the only programs to specifically address colonoscopy quality is the BlueCross BlueShield of North Carolina Tiered Provider Network [46], which uses a commercial software vendor to calculate postcolonoscopy complication rates and requires attestation of a quality management program for colonoscopy through either GIQuIC (http://giquic.gi.org/) or the AGA Digestive Health Recognition Program (http://www.gastro.org/practice/quality-initiatives/aga-digestive-health-recognition-program).

The impact of commercial designation programs on improving the quality or lowering the cost of care has not yet been publicly reported. As quality benchmarks remain crude in many clinical areas, these programs have an impact primarily by increasing competition on cost; this competition will vary based on market penetration. The proportion of physicians in a particular market who have designation ranking can vary based on program and market. As an example, the percent of designated physicians for the Cigna Care Designation Program ranges from a low of 15.1 % in Northern California to a high of 61.3 % in Pittsburgh [44].

Regional

As with commercial measures, most existing regional evaluation systems for healthcare quality focus on screening rates as the primary measure of quality in CRC screening. For example, the Wisconsin Collaborative for Healthcare Quality (http://www.wchq.org) has measured CRC screening rates at the hospital, group, and clinic level since 2005. This program reported a statistically significant improvement in CRC screening rates between 2006 and 2009; although this improvement was not beyond what would have been expected by looking at comparative groups [47].

Table 8.4 Commercial physician designation programs

Program	Description	Include GI	Peer group	Case-mix adjusted	Quality of care	Cost efficiency
United Health Care Premium ® Designation [41]	Physicians or centers that earn designation are (1) identified in a directory and (2) considered for financial incentives	No	National for quality; physician specialty and geographic location for cost	Yes, for certain quality metrics and all costs	Claims-based; augmented by physician participation in BTE, NCQA, or ABIM programs	Percentile rankings of episode costs compared to peer group
Medica Premium Designation [42]	Physicians who receive the two-star designation cost average 10–20% less for patients	No	National for quality; physician specialty and geographic location for cost	Yes, for certain quality metrics and all costs	Claims-based and/or practice data; measure physician performance over 39 months against evidence-based guidelines; must also be board-certified	Percentile rankings of episode costs compared to peer group
Aetna Aexcel ® Program [43]	Practices that receive the designation may be lower cost to insured depending on specific plan	Yes	Physicians of the same specialty in the same Aexcel market or market type if volume is low	Yes, for certain quality metrics and all costs	Specialists must meet at least one of the five criteria for quality: (1) use of technology, (2) alignment with Aetna Institute of Quality, (3) certification from external entity (BTE, NCQA), (4) Board certification, or (5) claim-based measures	Percentile rankings of episode costs compared to peer group

Table 8.4 (continued)

Program	Description	Include GI	Peer group	Case-mix adjusted	Quality of care	Cost efficiency
BlueCross BlueShield of North Carolina Tiered Provider Network [46]	Practices are tiered based on quality and cost parameters; patient co-pay is lower at top tier practices	Yes	Physician specialists in North Carolina	Yes, through indirect standardization against peer practices	Quality measures for gastroenterology include: (1) Colonoscopy: potentially avoidable complications; (2) GERD: potentially avoidable complications; (3) attestation for use of registry	Compare expected versus observed costs for an episode of care over a 3-year period
Cigna Care Designation [44]	Physicians in the upper third compared to peers receive designation; Patients pay lower co-payment or coinsurance	Yes (for IBD and HCV only)	Physician specialty and geographic market	Yes, costs only	Five quality indicators: (1) NCQA physician recognition; (2) Board certification; (3) completion of one or more ABIM practice improvement modules; (4) Certified Bariatric Centers; (5) adherence to claims-based, evidence-based medicine rules	Percentile rankings of episode costs compared to peer group

BTE bridges to excellence, *NCQA* national commission for quality assurance, *ABIM* American board of internal medicine, *IBD* inflammatory bowel disease, *HCV* hepatitis, C virus

Through a survey of program participants, it was clear that the specific choice of measure and the group's performance on this measure relative to peers prioritized quality improvement efforts by any one medical group. A number of other nonprofit entities measure CRC screening rates such as Minnesota Community Measurement (http://mncm.org), Massachusetts Health Quality Partners (http://www.mhqp.org), and the New York City Colon Cancer Control Coalition (http://www.nyc.gov/html/doh/html/living/cancer-colon-provider-coaltion.shtml).

One unique regional effort to use CRC quality measures for physician evaluation is Quality Quest for Health (http://www.qualityquest.org/). Through this initiative, a group of gastroenterologists, pathologists, and surgeons developed a Colonoscopy Best Care Index that incorporates eight components of a high-quality colonoscopy: (1) appropriate indication, (2) pre-procedure medical risk assessment, (3) bowel preparation, (4) complete examination, (5) photo-documentation of the cecum, (6) complete polyp information recorded, (7) withdrawal time recorded, (8) appropriate follow up recommended, and (9) no serious complications. The index score and adenoma detection rates are publically reported for participating physicians in central Illinois.

Integrated Delivery Systems

The largest integrated health-care delivery system in the USA is the Veterans Health Administration (VHA). The VHA's current assessment of CRC screening quality includes HEDIS measurement of screening rate reported at the facility level [48]. In contrast to the government, commercial, and regional programs, the VHA's program also tracks timeliness of care in CRC screening, including time from positive fecal-occult blood test (FOBT) to colonoscopy [49]. More robust measurement systems for colonoscopy quality are currently under development [50].

Kaiser Permanente of Northern California is a large integrated health delivery system with an organized CRC screening and evaluation program in place since the 1960s [51]. The current CRC screening evaluation system is focused at the medical center level and reports on: (1) CRC screening rates, (2) colonoscopy access times, (3) FOBT follow-up rates, and (4) cancer incidence, stage at diagnosis and survival [52]. The latter is unique among health-care systems given its focus on truly impactful outcomes. Individual process measures such as adenoma detection rates are also available for physicians performing endoscopy in each of these facilities. Additional colonoscopy-specific process measures are currently under development [53].

Limitations of Evaluation Systems

Over 15 years ago, McGlynn described six challenges to developing a quality monitoring strategy in health care (Table 8.5) [54]. Many of the same challenges to quality measurement in health care continue to exist today, illustrating the difficulty in

Table 8.5 Challenges to quality measurement in health care. (Based on data from [54])

Challenge	Key questions
Balance competing perspectives	Purchasers—What is the return on our investment?
	Patients—How responsive is the care to my needs?
	Physicians—Was my care consistent with community norms, and have I improved the patient's health?
Develop accountability framework	What is the appropriate lever—Accreditation standards versus public reporting?
	What is the appropriate level of accountability—provider, practice, or health plan?
Establish explicit clinical criteria	What is the strength of evidence required?
	When is professional consensus appropriate?
	Structural, process, or outcome-based measures?
Select indicators for reporting	Are measures relevant (important and actionable)?
	Are measures scientifically sound (reliable, valid, adjustable)?
	Are measures feasible (statistical power, resources required)?
Minimize conflict between financial and nonfinancial objectives	How do actions taken to meet quality goals increase cost?
	How should investments in health-care quality be incentivized among purchasers?
Develop information systems to support quality monitoring	How to make detailed clinical information accessible?
	How to collect patient-centered data (satisfaction, self-management success, impact of illness measures)?
	How to develop standard data definitions?

overcoming these challenges. Specific examples in CRC screening are illustrative. As an example of the difficulty in establishing clinical criteria, clinical guidelines for CRC screening differ between medical societies. Guidelines released by the US Preventative Services Task Force, the Multi-Society Task Force, the American College of Gastroenterology, and the American College of Physicians among others differ in their recommendations in a number of parameters (see Chap. 2). It is very difficult to hold providers, health systems, or populations accountable for the quality of screening when recommendations regarding screening differ. Even more problematic are the issues raised by Walter et al. relating to the difficulty of converting practice guidelines into performance measures [55]. Guidelines do not consider important issues such as illness severity, provider judgment, or patient preference in determining appropriateness of care. As such, selecting indicators for reporting must be separated from the guideline writing process.

Another challenge outlined by McGlynn is the selection of appropriate indicators for reporting. In CRC screening, one of the most difficult challenges to overcome is the inability to measure clinically relevant outcomes, namely CRC incidence, because of the difficulty in linking screening data with outcome data. Kaiser Permanente of Northern California is one of the few programs that overcame this challenge by systematically including CRC incidence in its evaluation of medical centers within its system.

Kaiser's evaluation system highlights the importance of developing robust information systems to support quality monitoring. When these data systems do not exist, is it acceptable to use process measures as proxies for the outcome of interest? In CRC screening, the use of adenoma detection rate (ADR) has been widely promulgated as a process measure for CRC screening quality. Recent evidence has linked ADR with CRC incidence [56], although it remains unclear if this relationship holds at all levels of ADR [57]. Even more challenging is when the optimal, evidence-based process measure (i.e., ADR) cannot be used due to inadequate data systems and physician evaluation relies on more feasible proxy measures (e.g., polyp detection rate).

Another potential limitation of evaluation systems relates to the issue of accountability as outlined by McGlynn. As discussed above, although most evaluation systems focus on the health system or provider group as the level of accountability, individual physician performance is increasingly targeted for evaluation. Physician concerns regarding legal liability as a result of performance measurement may limit enthusiasm for this level of accountability, although likelihood of the use of these measures in medical malpractice cases is low [58]. Physician resistance to evaluation will limit the usefulness of a voluntary system and perhaps corrupt a mandatory system through the avoidance of the sickest patients [28].

These challenges confront ongoing efforts to develop quality management programs in CRC screening and the sustainability of any particular program depends on the extent to which it can overcome these challenges. In their perspective piece, Conway et al. outline several critical steps to overcome these challenges and maximize the benefit of quality measurement. These include: first, a reduction in the complexity and burden of clinical data measurements; second, the creation of automated data collection systems for patient-reported outcomes; third, improved interoperability of data so that traditionally unstructured data such as laboratory data or pathology reports can more easily be queried; finally, improved consistency among electronic health records in calculating quality measures [8].

Conclusions

At present, the majority of quality management programs in CRC screening focus on maximizing the proportion of a given population undergoing screening tests. Of less importance is the quality of that individual test, perhaps reinforcing the adage widely quoted in gastroenterology circles: "The best test for CRC screening is the one that gets done" [59].

Moving beyond process measures of procedure utilization and focusing more on the quality and value of those services is critical to creating an agile, broad-based, feasible, impactful, and vertically aligned quality measurement system that supports provider feedback. Furthermore, understanding the impact of quality measurement on practice will also ensure that unintended consequences of reporting quality are appropriately managed or avoided. These steps will require collaboration between physicians, health system administrators, government agencies, industry representatives such as electronic health record and endoscopy report writer vendors and payors. Integrating patients into the process can be equally important in understanding how to create measures that are truly impactful.

GI societies are optimally positioned to coordinate this collaboration through a number of actions that mirror the recommendations of Conway et al.: first, support the development of scientifically sound quality metrics, including patient-reported outcomes and cost measures; second, advocate for the interoperability of information systems, including endoscopy report writers, pathology databases, and patient-feedback systems; third, continue development of agile registries with low barriers to entry that respond to immediate needs of physicians and provider groups; finally, to support the development of decision-support tools for process improvement. Through these collaborations, we can move CRC screening closer toward a truly learning health-care system [60].

References

1. Lieberman D. Quality in medicine: raising the accountability bar. Gastrointest Endosc. 2011;73(3):561–6.
2. Dorn SD. Gastroenterology in a new era of accountability: part 2. Developing and implementing performance measures. Clin Gastro Hep. 2011;9(8):660–4.
3. Scanlon DP, et al. The role of performance measures for improving quality in managed care organizations. Health Serv Res. 2001;36(3):619–41.
4. Teleki SS, et al. Providing performance feedback to individual physicians: current practice and emerging lessons. 2006 August 10, 2013. http://www.rand.org/content/dam/rand/pubs/working_papers/2006/RAND_WR381.pdf. Accessed 17 Sept 2014.
5. National Committee for Quality Assurance (NCQA). The state of health care quality: reform, the quality agenda, and resource use; 2010. http://www.ncqa.org/Portals/0/State%20of%20Health%20Care/2010/SOHC%202010%20-%20Full2.pdf. Accessed 17 Sept 2014.
6. National Committee for Quality Assurance (NCQA). The state of health care quality 2012: focus on obesity and on medicare plan improvement; 2012. http://www.ncqa.org/Portals/0/State%20of%20Health%20Care/2012/SOHC_Report_Web.pdf. Accessed 17 Sept 2014.
7. Holden DJ, et al. Enhancing the use and quality of colorectal cancer screening. In: Evidence reports/technology assessments, no. 190. Agency for Healthcare Research and Quality; 2010.
8. Conway P, Mostashari F, Clancy C. The future of quality measurement for improvement and accountability. JAMA. 2013;309(21):2215–6.
9. Ivers N, et al. Audit and feedback: effects on professional practice and healthcare outcomes. Cochrane Database Syst Rev. 2012;6:CD000259.
10. Sabatino SA, et al. Interventions to increase recommendation and delivery of screening for breast, cervical, and colorectal cancers by healthcare providers: systematic reviews of provider assessment and feedback and provider incentives. Am J Prev Med. 2008;35(Suppl 1):S67–74.

11. Brouwers MC, et al. What implementation interventions increase cancer screening rates? A systematic review. Implement Sci. 2011;6:111. doi:10.1186/1748–5908–6–111.
12. Corley DA, Jensen CD, Marks AR. Can we improve adenoma detection rates? A systematic review of intervention studies. Gastrointest Endos. 2011;74(3):656–65.
13. Barclay RL, Vicari JJ, Greenlaw RL. Effect of a time-dependent colonoscopic withdrawal protocol on adenoma detection during screening colonoscopy. Clin Gastro Hep. 2008;6:1091–8.
14. Kahi CJ, et al. Impact of a quarterly report card on colonoscopy quality measures. Gastrointest Endos. 2013;77(6):925–31.
15. Coe SG, et al. An endoscopic quality improvement program improves detection of colorectal adenomas. Am J Gastroenterol. 2013;108(2):219–26.
16. Ryan AM, Damberg CL. What can the past of pay-for-performance tell us about the future of value-based purchasing in medicare? Healthcare. 2013;1(1–2):42–9.
17. VanLare JM, Blum JD, Conway PH. Linking performance with payment: implementing the physician value-based payment modifier. JAMA. 2012;308(20):2089–90.
18. Scott A, et al. The effect of financial incentives on the quality of health care provided by primary care physicians. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD008451.
19. Jha AK. TIme to get serious about pay for performance. JAMA. 2013;309(4):347–8.
20. Johnson DA. Pay for performance: ACG guide for physicians. Am J Gastroenterol. 2007;102(10):2119–22.
21. Hewett DG, Rex DK. Improving colonoscopy quality through health-care payment reform. Am J Gastroenterol. 2010;105(9):1925–33.
22. Lansky D. Improving quality through public disclosure of performance information. Health Aff. 2002;21(4):52–62.
23. Joynt KE, Blumenthal DM, Orav EJ, Resnic FS, Jha AK. Association of public reporting for percutaneous coronary intervention with utilization and outcomes among medicare beneficiaries with acute myocardial infarction. JAMA. 2012;308(14):1460–8.
24. Smith MA, et al. Public reporting helped drive quality improvement in outpatient diabetes care among Wisconsin physician groups. Health Aff. 2012;31(3):570–7.
25. Fung CH, et al. Systematic review: the evidence that publishing patient care performance data improves quality of care. Ann Intern Med. 2008;148(2):111–23.
26. Ketelaar NA, et al. Public release of performance data in changing the behaviour of healthcare consumers, professionals or organisations. Cochrane Database Syst Rev. 2011; (11):CD004538.
27. Casalino LP, et al. General internists' views on pay-for-performance and public reporting of quality scores: a national survey. Health Aff. 2007;26(2):492–9.
28. Werner RM, Asch DA. The unintended consequences of publicly reporting quality information. JAMA. 2005;293(10):1239–44.
29. Sarfaty M, Myers RE. The effect of HEDIS measurement of colorectal cancer screening on insurance plans in Pennsylvania. Am J Manag Care. 2008;14(5):277–82.
30. Klabunde CN, et al. Health plan policies and programs for colorectal cancer screening: a national profile. Am J Manag Care. 2004;10(4):273–9.
31. Cartwright-Smith L. Fair process in physician performance rating systems: overview and analysis of Colorado's Physician Designation Disclosure Act. 2009. http://www.rwjf.org/content/dam/web-assets/2009/09/fair-process-in-physician-performance-rating-systems. Accessed 13 Aug 2013.
32. Hurley RE, Strunk BC, White JS. The puzzling popularity of the PPO. Health Aff. 2004;23(2):56–68.
33. Attorney General of the State of New York. Agreement concerning physician performance measurement, reporting and tiering rograms; October 2007. http://healthcaredisclosure.org/docs/files/NYAG-CIGNASettlement.pdf. Accessed 12 Aug 2013.
34. Adams JL, et al. Physician cost profiling—reliability and risk of misclassification. New Engl J Med. 2010;362(11):1014–21.
35. Physician Quality Reporting System and Electronic Prescribing (eRx) Incentive Program. 2011. Reporting Experience, Centers for Medicare & Medicaid Services.

36. ASGE Advocacy Newsletter. http://www.asge.org/advocacy/advocacy.aspx?id=16649. Accessed 14 Aug 2013.
37. Lieberman DA, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143(3):844–57.
38. National Quality Forum. NQF endorses gastrointestinal measures. Washington, DC; 2013. http://www.qualityforum.org/News_And_Resources/Press_Releases/2013/NQF_Endorses_Gastrointestinal_Measures.aspx. Accessed 17 Sept 2014.
39. Centers for Medicare & Medicaid Services. Technical expert panels: welcome to the quality measures call for technical expert panel members page; 2014. http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/MMS/TechnicalExpertPanels.html. Accessed 17 Sept 2014.
40. U.S. Department of Health and Human Services Report to Congress: Medicare Ambulatory Surgical Center Value-Based Purchasing Implementation Plan. http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ASCPayment/index.html?redirect=/ascpayment/. Accessed 2 Sept 2013.
41. United Healthcare. UnitedHealth premium physician designation program: detailed methodology; 2014. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Unitedhealth%20Premium/Detailed_Methodology_2013–2014.pdf. Accessed 17 Sept 2014.
42. Medica. Premium Designation Program. https://member.medica.com/C0/PremiumDesignation/default.aspx. Accessed 15 Aug 2013.
43. Aetna. Understanding Aexcel; 2009. www.aetna.com/docfind/pdf/aexcel_understanding.pdf. Accessed 15 Aug 2013.
44. Cigna. Cigna care designation and physician quality and cost-efficiency displays 2013 methodologies whitepaper; 2013. http://cigna.benefitnation.net/cigna/CCN.pdf. Accessed 15 Aug 2013.
45. Chernew ME, et al. Private-payer innovation in Massachusetts: the 'alternative quality contract'. Health Aff. 2011;30(1):51–61.
46. BlueCross BlueShield of North Carolina. Tiered network product; 2013. http://www.bcbsnc.com/content/providers/quality-based-networks/tiered-network.htm. Accessed 15 Aug 2013.
47. Lamb GC, et al. Publicly reported quality-of-care measures influenced Wisconsin Physician Groups to improve performance. Health Aff. 2013;32(3):536–43.
48. Long M, et al. Colorectal cancer testing in the National Veterans Health Administration. Dig Dis Sci. 2012;57(2):288–93.
49. Gellad ZF, et al. Time from positive screening fecal occult blood test to colonoscopy and risk of neoplasia. Dig Dis Sci. 2009;54(11):2497–502.
50. Personal communication with Jason Dominitz, MD MHS, National Program Director for Gastroenterology, Department of Veterans Affairs, August 2013.
51. Levin TR, et al. Organized colorectal cancer screening in integrated health care systems. Epidemiol Rev. 2011;33(1):101–10.
52. Levin TR. Organized cancer screening in a U.S. healthcare setting: what works. In: Centers for Disease Control and Prevention (CDC) Public Health Grand Rounds. 2013.
53. Personal communication with Doug Corley, MD PhD, Kaiser Permanente of Northern California, July 2013.
54. McGlynn EA. Six challenges in measuring the quality of health care. Health Aff. 1997;16(3):7–21.
55. Walter LC, et al. Pitfalls of converting practice guidelines into quality measures: lessons learned from a VA performance measure. JAMA. 2004;291(20):2466–70.
56. Kaminski MF, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med. 2010;362(19):1795–1803.
57. Gellad ZF, et al. Colonoscopy withdrawal time and risk of neoplasia at 5 years: results from VA Cooperative Studies Program 380. Am J Gastroenterol. 2010;105(8):1746–52.

58. Kesselheim AS, Ferris TG, Studdert DM. WIll physician-level measures of clinical performance be used in medical malpractice litigation? JAMA. 2006;295(15):1831–4.
59. Inadomi JM. Why you should care about screening flexible sigmoidoscopy. New Engl J Med. 2012;366(25):2421–2.
60. Greene SM, Reid RJ, Larson EB. Implementing the learning health system: from concept to action. Ann Intern Med. 2012;157(3):207–10.

Chapter 9
Sedation Issues in Colonoscopy: Quality and Economic Considerations

Karen J Wernli and John M Inadomi

Introduction

The use of moderate sedation during colonoscopy has long been the standard US gastroenterology clinical care. Used in >98% of endoscopy procedures [1], the primary purpose is to alleviate patients' discomfort and anxiety. Moderate sedation is routinely a benzodiazepine and narcotic. However, over the past decade, since the US Preventive Services Task Force recommendation for use of colonoscopy for routine screening in 2002 [2], the use of propofol and deeper sedation has increased in magnitude [3, 4] and varies regionally in the incorporation into clinical practice [4, 5]. Understanding how the use of propofol affects known risks of colonoscopy and overall costs are important considerations in the future of US endoscopy practice, and importantly, in population health screening for colorectal cancer.

Medication Used for Colonoscopy Sedation

Midazolam has emerged as the most commonly administered benzodiazepine for colonoscopy sedation. Other less commonly used benzodiazepines include alprazolam, bromazepam, brotizolam, clotiazepam, diazepam, etizolam, flunitrazepam, lorazepam, oxazepam, and triazolam. Similarly, fentanyl is the narcotic most often used for colonoscopy sedation and has eclipsed meperidine and morphine for this indication. Total procedure time has been demonstrated to be shorter with fentanyl

K. J. Wernli (✉)
Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101, USA
e-mail: wernli.k@ghc.org

J. M. Inadomi
Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_9

compared with meperidine [6]. Moreover, the combination of midazolam with a narcotic has been demonstrated to reduce recovery time compared with the use of narcotic alone [7]. Greater patient satisfaction has been shown with the use of a combination of midazolam and fentanyl, perhaps based on the amnestic qualities of midazolam. For these reasons, the combination of midazolam and fentanyl has become the standard of traditional endoscopic sedation in the USA.

Propofol is a sedative–hypnotic drug without analgesic effects. It has a rapid onset of action and a short recovery period of 10–20 min after discontinuation. The main drawback of propofol sedation is the narrow margin between moderate and deep sedation, requiring administration by health care providers skilled in maintaining ventilation and airway support. Propofol sedation, however, has been associated with lower overall complication rates compared to traditional sedation with narcotic and benzodiazepine [8]. It should be noted that propofol sedation is often performed in combination with small doses of opiates or benzodiazepines so the term "propofol sedation," "monitored anesthesia care (MAC)," or "anesthesia-professional administered sedation" may refer to a combination of propofol plus opiate and benzodiazepine.

Quality

Overall Risks

The most common risks associated with routine colonoscopy include sedation-associated cardiopulmonary adverse events, perforation, and hemorrhage [9, 10]. Hence, it is important to understand whether these risks and others change with the use of propofol or deep-sedation anesthesia because it alters the clinical practice of endoscopists, propofol elicits different side effects, or other rationale. Cooper et al. evaluated complications associated with use of sedation services comparing overall colonoscopy complications [11]. In this analysis and other claims-based analyses, billing codes indicated as MAC serve as a proxy for propofol medication; moderate sedation is built into the reimbursement for routine colonoscopies and the addition of these billing codes with a colonoscopy indicates anesthesia services with propofol. The study population was US adults >65 years in a noncancer cohort of linked Surveillance, Epidemiology, and End Results SEER-Medicare Linked Database of national colonoscopies performed from 2000 to 2009. The total study population included 165,527 colonoscopy procedures in 100,359 individuals, representing a 5% random sample of the eligible population. Significant patient factors associated with receipt anesthesia services included older age, more recent receipt of colonoscopy, having a colonoscopy in an ambulatory setting, and colonoscopies performed in the South, Midwest, and most especially, Northeast. Colonoscopy complications of interest included aspiration pneumonia, colonic perforation, and splenic injury.

Study results demonstrated that overall 30-day mortality rates were similar between the two groups of colonoscopies performed with (0.32%) and without anesthesia (0.29%; $p=0.29$). The overall complication rate was 0.22% in the anesthesia group compared to 0.16% in the nonanesthesia group. In multivariable logistic regression models adjusted for age, sex, race, procedure year, comorbidity score, facility type, and geographic region, the use of anesthesia services was associated with a 46% increased risk of overall complications (1.09–1.94), in particular aspiration pneumonia [0.14% (95% CI 0.11–0.18%) in anesthesia services group compared to 0.10% (95% CI 0.08–0.12%) in nonanesthesia services group].

Similarly, Domintz et al. also evaluated risks associated with anesthesia services in 20% sample of Medicare data of colonoscopies performed in 2003 only ($n=382,426$ outpatient colonoscopies) [5]. Complications of interest including gastrointestinal bleeding, perforation, emergent hospitalization within 30 days, and emergency room visits within 30 days, regardless of indication. In multivariable adjusted models, the use of anesthesia services was not associated with statistically significant increased risks of any of the a priori outcomes of interest: bleeding (OR = 0.98, 95% CI 0.84–1.13), perforation (OR = 1.11, 95% CI 0.78–1.57); emergent hospitalization (OR = 0.98, 95% CI 0.91–1.06); and emergency room visit (OR = 0.97, 95% CI 0.91–1.04).

Perforation

Adeyemo et al. evaluated perforation rates at a single tertiary gastroenterology institute. From 2003 to 2012, gastroenterologist performed 118,004 colonoscopies in adults (≥18 years older) [12]. Type of sedation was available and the authors could distinguish the use of propofol, rather than relying on billing codes. The type of colonoscopy performed was classified as diagnostic or therapeutic (where a biopsy or polypectomy was done). Overall rates of perforation were 4.1/10,000 colonoscopies, quite similar to other reports [9, 10]. However, the perforation rate in colonoscopies which used propofol was statistically significantly higher (6.9/10,000) compared to colonoscopies that did not use propofol for sedation (2.7/10,000) ($p=0.0015$). In multivariable models adjusting for age, and sex, the use of propofol was associated with 3.4-fold (95% CI 1.60–7.34) increased risk of perforations among those who had therapeutic colonoscopy (biopsy or polypectomy) compared to all other colonoscopies performed.

Other studies have found no association between propofol use and increased perforation rates [5, 11, 13]. Cooper et al. reported that the incidence of perforation was similar between anesthesia- and nonanesthesia-performed colonoscopies [11]. Dominitz detected an 11% increased risk of perforation; however, this result was not statistically significant. One last study from Spain found no difference in perforation, but this has been published only in abstract form [13].

Polyp Detection Rates

Only a few studies have evaluated polyp detection rates among colonoscopies performed with propofol compared with moderate sedation. Again, using the US Medicare population, Dominitz et al. detected no differences in the polyp diagnosis (OR = 1.04, 95% CI 0.99–1.09), diagnostic biopsy (OR = 1.03, 95% CI 0.97–1.10), and polypectomy (OR = 1.00, 95% CI 0.95–1.05) comparing colonoscopies performed with anesthesia services to procedures with no anesthesia services.

The only randomized controlled trial comparing polyp detection rates in colonoscopies with varying sedation compared midazolam and pethidine at increasing doses to achieve moderate to deep sedation. Paspatis et al. [14] evaluated 520 adults aged 50 and older who presented for screening or surveillance of prior polyps. Participants had a colonoscopy performed at a single institute in Greece between June 2009 and October 2009 and were randomized to receive either moderate or deep sedation. The investigators detected no differences in prevalence of patients with ≥ 1 polyp, ≥ 1 large polyp, or ≥ 1 polyp in the right colon with deep compared to moderate sedation.

Procedure Monitoring

Few studies have evaluated the cardiac risks associated with propofol administration. Friedrich et al. evaluated ventilation, oxygen saturation, and cardiac events in an outpatient endoscopy practice in Germany [15]. The study population included 10,000 individuals with an endoscopy procedure performed between October 2006 and January 2012. Outcomes of interest included episodes of apnea, hypoxemia, bradycardia, and hypotension. Among colonoscopy procedures, there was no significant difference in these adverse events between propofol- and nonpropofol-sedated colonoscopies ($p = 0.809$).

Issues in Quality

In 2011, Singh et al. published a review of propofol for sedation evaluation risks during colonoscopy [16]. The overall conclusion was that the propofol poses no increased harm to patients above the moderate sedation protocols already the standard of care. However, in terms of harms from colonoscopies, many of these events are very rare occurrences that require very large sample sizes to have sufficient power to detect significant risks. Many of the conclusions from the Cochrane evaluation were based on single institution studies, few with samples sizes above >500 colonoscopies; however, the available evidence might still not be sufficient to fully address harms from colonoscopy and overall quality, such as for perforations. Further,

while studies have attempted to address confounding, even large claims-based data analyses are not immune to potential bias due to uncontrolled confounding [17].

Is it plausible that during a deeply sedated colonoscopy, endoscopists continue to advance the colonoscope despite meeting intestinal resistance? It has been hypothesized [11, 17] that in the absence of feedback about the pressure felt while completely sedated, that endoscopists miss the feedback needed about when to stop[11, 17]. The use of propofol during colonoscopy does not seem to decrease overall procedure time [16], and could present an opportunity to extend the withdrawal time without additional consequences.

Overall, the use of propofol compared with traditional colonoscopy sedation appears to be associated with minimal, if any increased risks and on a population-level evaluation this would result in harm to few additional patients. However, literature to definitively eliminate significant differences in colonoscopy quality and harm to patients is lacking. Additional research is needed to further address harms in all-age eligible individuals not those individuals >65 years, to move the research beyond single institution studies and compare and contrast across regions, systems, and practitioners; to appropriately ascertain the use of propofol to avoid misclassification of sedation agent, and adequately control for patient characteristics which could influence the use of propofol in different settings, and finally to understand the use of propofol in more contemporary settings as the diffusion in practice has reached potential plateau in some US regions.

Economic Considerations

There are several key economic issues surrounding propofol use for patients undergoing colorectal cancer screening by colonoscopy that include increased patient expectations, throughput, increased revenue, and payer reimbursement.

The total cost of the colonoscopy with anesthesia services increases the total overall cost of colorectal cancer screening to payers and patients [18]. Use of propofol increases procedure costs largely because of the additional medical personnel and the facility conducting the procedure. With the mandate requiring administration of propofol by an anesthesiology professional, there might be some attenuation in short-terms harms, but the improvement in short-term outcomes is likely small relative to the large increase in overall cost of colonoscopy. The question remains whether the additional costs are worth the benefit? Gastroenterologists report that their primary use of propofol is for rapid recovery times and to reduce discomfort from the colonoscopy [19]. However, perhaps the discussion could be framed in the manner proposed by Agrawal and Rockey [19] to determine whether a patient should be asked to pay more for a colonoscopy in which optional use of anesthesia professional's services are provided.

Patient Expectations

Market forces driving the use of propofol for colonoscopy include patient preferences for sedation [20]. Many patients knowledgeable of the differences between traditional moderate sedation with narcotics and benzodiazepines versus propofol request or insist upon the use of the latter. Advantages of propofol include the hypnotic/amnestic qualities that provide consistent diminution of recollection of the procedure including any unpleasant sensations, such as pain and bloating. The rapid resolution of the sedative effects of propofol is also desired by patients. Mean recovery time among patient who receive propofol is about 15 min less compared to moderate sedation [16]. Increased time available allows more rapid return to normal mental function, although the requirement for supervised exit from the endoscopy unit is not rescinded. In certain markets, the patient preferences are highly developed to the point where the lack of propofol use in one unit may adversely impact market share for endoscopists practicing in that unit, particularly in the Northeast where the market is near saturation on the use of propofol with colonoscopy. Certainly, the geographic variation in the use of propofol for endoscopic procedures is believed to be due in part to the effect of patient preference.

Throughput

One of the important rationales used by endoscopy units to justify the use of propofol for routine colonoscopy screening is the reduction in recovery time that allows a greater throughput of patients within the constraints of the fixed space of an endoscopy unit. Several analyses of optimal endoscopy operations note the limitations of recovery space as a major bottleneck for efficient colonoscopy services. Due to the prolonged recovery time resulting from traditional sedation with a combination of narcotic and benzodiazepine, the ratio of endoscopy rooms to recovery bays is 1:2 or more [21, 22]. Use of propofol reduces the need for recovery space due to its rapid restoration of effect. Throughput for colonoscopy with propofol compared with traditional sedation increases by 76% [23]. Reductions in space costs (rent) are accompanied by and augmented by reductions in personnel costs (recovery personnel). Business models have demonstrated that the increased cost of propofol administration can be offset by increased efficiency of operations that increase endoscopy volume per unit time. In the hospital outpatient endoscopy setting, the break-even point for the cost of a rapid recovery sedation agent such as propofol was US$ 71 (95% confidence interval US$ 38–106) and US$ 61 (US$ 41–109) in the ambulatory surgical center setting [23].

Revenue for Endoscopy Practices

In addition to the improvements in endoscopy operations based on increased throughput, there are direct revenue opportunities for endoscopy units based on anesthesia services. The average Medicare reimbursement for an anesthesia professional for the administration of sedation for colonoscopy is about US$ 103 more than a colonoscopy procedure without anesthesiologist involvement [4]. Current models of ambulatory surgery units include employment of anesthesia professionals (certified registered nurse anesthetists or anesthesiologists). This employment model is highly dependent upon the reimbursement policies of the payers and the willingness of patients to participate in the cost-sharing (co-payment) for screening procedures.

Reimbursement Decisions (Payers)

The focus on the high costs of health care in the US has centered on colonoscopy [18, 24]. Greater awareness of the variation in the charges for colonoscopy regionally and nationally has resulted in payer decisions impacting reimbursement for endoscopic sedation. Highmark (Pennsylvania) made a coverage decision denying reimbursement for anesthesia professional's services provided for routine colonoscopy; however, implementation of this policy change was delayed at the time of this chapter construction and sparked controversy [25]. While this may be an isolated case, it does represent a shift in the support previously held for universal reimbursement for propofol in routine endoscopy that will spread to other regions throughout the country. Indeed, the dramatic variation in use of propofol across the country also reflects payer reimbursement practices (in addition to patient preferences, above) that also widely vary across the US.

Studies of the Economics of Propofol

It is difficult to conduct a properly designed study that isolates the components that drive the variation in the use of propofol. Instead, we rely upon observations in differential use of traditional sedation and propofol across various subsets of populations in the US to derive hypotheses that may explain these variances. We have demonstrated the rapid rise in the prevalence of anesthesia-professional-assisted sedation for colonoscopy over the past decade through the use of insurance claims databases [3]. While anesthesia professionals may use general anesthesia, the vast majority of cases involve MAC with propofol and perhaps small amounts of a narcotic and/or benzodiazepine. The proportion of colonoscopies performed with

anesthesia professionals rose from 9% in 2003 to 25% in 2007, and is projected to reach 53% by 2015. More interestingly, there was great geographic variation in the use of anesthesia professionals: in 2007, 11.7% of colonoscopies performed in western US states had anesthesia billing compared to 40% of cases in northeastern states. The rate of rise mirrored these findings, with projected growth rates between 2007 and 2015 ranging from 44% in the West compared to 145% in the Northeast, with the South growing at 129% and the Midwest at 119%. The variances were also associated with patient's per capita income, race, and health care utilization; factors implicating reimbursement practices may be a major factor in the decision to utilize anesthesia services.

In a study by Liu and colleagues [26], the variation in the use of anesthesia professionals for colonoscopy sedation was confirmed in a dataset that combined 1 million Medicare fee for service and 5.5 million commercially insured patients. Combining both upper endoscopy with colonoscopy, the proportion of procedures with anesthesia services increased from 13 to 30% (Medicare) and from 13 to 35% (commercially insured) between 2003 and 2009. Importantly, the proportion of anesthesia services associated with endoscopy performed in patients at low risk for adverse events (ASA class 1–2) was 64% (Medicare) and 84% (Commercial) in 2009. Based on the number of procedures and the proportion associated with anesthesia services delivered in this population, the investigators calculated that this "discretionary" use of anesthesia accounted for US$ 2.65 million per 1 million CMS enrollees and US$ 7.05 million per 1 million enrollees. On a national level, this equated to US$ 1.1 billion in nonessential spending in 2009. Overall findings reveal that the volume of anesthesia services has continued to increase, with a parallel increase in overall Medicare expenditures among fee-for-service patients. Moreover, the volume and expenditures representing potential overuse of anesthesia for routine colonoscopy continues to rise (Fig. 9.1).

Additional studies have provided similar conclusions. Medicare claims between 2001 and 2006 revealed an increase in the use of anesthesiology professionals with screening colonoscopies from 11 to 23% during this period [4]. Surprisingly, comorbidity was not associated with an increase in the use of anesthesiologists; however, anesthesia professionals' use increased as patients' income increased, but was significantly reduced among Blacks compared with Whites. The authors calculated that the additional sedation costs due to anesthesia involvement in screening colonoscopy during this time period totaled US$ 20 million but would have reached US$ 120 million had anesthesia services been provided for all screening colonoscopies.

Can Propofol be Administered by Nonanesthesia Professionals?

It is clear that addition of anesthesia services to provide sedation increases the cost of colonoscopy. The economics of sedation, therefore, revolve around the

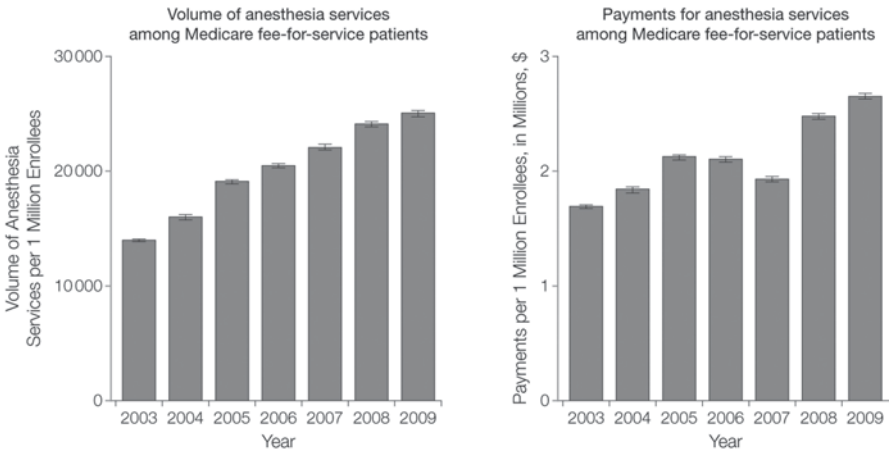

Fig. 9.1 Volume of potentially discretionary anesthesia service use and associated payments among medicare fee-for-service patients during 2003–2009. (Reprinted from [26]. With permission from American Medical Association)

requirement for propofol to be administered by an anesthesia professional. Several studies have demonstrated the safety of nonanesthesia professional administered propofol (NAAP) for gastrointestinal endoscopic procedures. A systematic review of randomized controlled trials comparing NAAP with traditional sedation in patients undergoing routine upper endoscopy and colonoscopy found no significant difference in hypoxemia, bradycardia, or hypotension [27]. The American Gastroenterological Association Position Statement on NAAP for GI endoscopy concludes that the safety profile of NAAP is equivalent to that of standard sedation with respect to the risks of hypoxemia, hypotension, and bradycardia for upper endoscopy and colonoscopy. Further, NAAP sedation improves practice efficiency compared to standard sedation and the use of anesthesia-administered sedation for healthy, low-risk patients undergoing routine GI endoscopy results in higher costs with no proven benefit with respect to patient safety or procedural efficacy [28].

There are now alternatives in the manner in which propofol may be administered during routine colonoscopy. A computer-assisted sedation system integrating propofol delivery with patient monitoring has been approved by the FDA to enable endoscopists and nurses to administer propofol without an anesthesia professional. In a multicenter randomized study, 496 patients undergoing routine colonoscopy or upper endoscopy were randomized to receive sedation using the computer-assisted sedation system versus traditional sedation with narcotic and benzodiazepine [29]. Oxygen desaturation was significantly lower in the computer-assisted sedation system arm and the overall incidence of adverse events was not significantly different (5.8 % computer-assisted sedation versus 8.7 % traditional sedation).

Summary

Who gains when propofol is administered during colonoscopy? The efficiency of an endoscopy unit may improve with propofol sedation due to increased throughput. Patients may have greater satisfaction with colonoscopy and perhaps may be motivated to repeated screening and surveillance due to reduced anxiety and fears of colonoscopy. While some studies highlight a concern that adverse events such as perforation could be increased due to limited patient feedback with deep sedation, this is not a consistent finding. There is no evidence, however, that anesthesia administration of sedation improves colonoscopy quality metrics such as adenoma detection rates.

In the absence of clear evidence demonstrating harm or benefit, the gastroenterology and anesthesia communities should determine whether the benefit from anesthesia services is worth the financial costs, particularly in population screening for colorectal cancer where the emphasis is on less-expensive tests to increase access and cost-effectiveness. The economic debate should also focus on the scientific basis for the requirement that propofol and similar sedation agents be administered by anesthesia professionals. In addition to clinical studies demonstrating safety of propofol administration by nonanesthesiologists, there are technological advances that may allow these drugs to be safely delivered in a setting sufficiently monitored so as to mitigate the potential risks of deep sedation with these agents.

References

1. Cohen LB, Wecsler JS, Gaetano JN, et al. Endoscopic sedation in the United States: results from a nationwide survey. Am J Gastroenterol. 2006;101(5):967–74.
2. U. S. Preventive Services Task Force. Screening for colorectal cancer: recommendation and rationale. Ann Intern Med. 2002;137(2):129–31.
3. Inadomi JM, Gunnarsson CL, Rizzo JA, Fang H. Projected increased growth rate of anesthesia professional-delivered sedation for colonoscopy and EGD in the United States: 2009 to 2015. Gastrointest Endosc. 2010;72(3):580–6.
4. Khiani VS, Soulos P, Gancayco J, Gross CP. Anesthesiologist involvement in screening colonoscopy: temporal trends and cost implications in the medicare population. Clin Gastroenterol Hepatol. 2012;10(1):58–64e51.
5. Dominitz JA, Baldwin LM, Green P, Kreuter WI, Ko CW. Regional variation in anesthesia assistance during outpatient colonoscopy is not associated with differences in polyp detection or complication rates. Gastroenterology. 2013;144(2):298–306.
6. Robertson DJ, Jacobs DP, Mackenzie TA, Oringer JA, Rothstein RI. Clinical trial: a randomized, study comparing meperidine (pethidine) and fentanyl in adult gastrointestinal endoscopy. Aliment Pharmacol Ther. 2009;29(8):817–23.
7. Hayee B, Dunn J, Loganayagam A, et al. Midazolam with meperidine or fentanyl for colonoscopy: results of a randomized trial. Gastrointest Endosc. 2009;69(3 Pt 2):681–7.
8. Qadeer MA, Vargo JJ, Khandwala F, Lopez R, Zuccaro G. Propofol versus traditional sedative agents for gastrointestinal endoscopy: a meta-analysis. Clin Gastroenterol Hepatol. 2005;3(11):1049–56.

9. Levin TR, Zhao W, Conell C, et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med. 2006;145(12):880–6.
10. Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DS. Adverse events after screening and follow-up colonoscopy. Cancer Causes Control. 2012;23(2):289–96.
11. Cooper GS, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. JAMA Intern Med. 2013;173:551–6.
12. Adeyemo A, Bannazadeh M, Riggs T, Shellnut J, Barkel D, Wasvary H. Does sedation type affect colonoscopy perforation rates? Dis Colon Rectum. 2014;57(1):110–4.
13. Jimenez-Perez J, Pastor G, Aznarez R, Carral D, Rodriguez C, Borda F. 3351 Iatrogenic perforation in diagnostic colonoscopy related to the type of sedation. Gastrointestinal Endoscopy. 2000;51(4, Pt 2):AB68.
14. Paspatis GA, Tribonias G, Manolaraki MM, et al. Deep sedation compared with moderate sedation in polyp detection during colonoscopy: a randomized controlled trial. Colorectal Dis. 2011;13(6):e137–44.
15. Friedrich K, Stremmel W, Sieg A. Endoscopist-administered propofol sedation is safe—a prospective evaluation of 10,000 patients in an outpatient practice. J Gastrointestin Liver Dis. 2012;21(3):259–63.
16. Singh H, Poluha W, Cheung M, Choptain N, Baron KI, Taback SP. Propofol for sedation during colonoscopy. Cochrane Database Syst Rev. 2008;4:CD006268.
17. Wernli KJ, Inadomi JM. Anesthesia for colonoscopy: too much of a good thing? JAMA Intern Med. 2013;173(7):556–8.
18. Rosenthal E. The $ 2.7 Trillion Medical Bill: Colonoscopies Explain Why the U.S. Leads the World in Health Expenditures. N.Y. Times 2013.
19. Agrawal D, Rockey DC. Propofol for screening colonoscopy in low-risk patients: are we paying too much? JAMA Intern Med. 2013;173:1836–8.
20. Johannes L. The patient's perspective—patients should be made aware of the options of sedation or no sedation and have a choice in screening colonoscopy. J Interv Gastroenterol. 2011;1(1):42–4.
21. Cono M, Dawson KA. Determining the size of the gastroenterology division expansion using simulation: a case study. Paper presented at: Proceedings of the 1993 Annual HIMSS Conference; 1993.
22. Glick SN. Cost-effectiveness of colorectal cancer screening. [letter; comment.]. JAMA. 2001;285(4):407–8.
23. Vargo JJ, Bramley T, Meyer K, Nightengale B. Practice efficiency and economics: the case for rapid recovery sedation agents for colonoscopy in a screening population. J Clin Gastroenterol. 2007;41(6):591–8.
24. Anesthesia Business Consultants. Anesthesia business consultants comments on colonoscopies—reducing the cancer toll, with or without anesthesia. Wall Street J. 2013 June 6.
25. Fabregas L. Highmark might not cover colonoscopy anesthetic drug. The Pittsburgh Tribune-Review. 2014 May 29.
26. Liu H, Waxman DA, Main R, Mattke S. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003–2009. JAMA. 2012;307(11):1178–84.
27. McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointest Endosc. 2008;67(6):910–23.
28. Vargo JJ, Cohen LB, Rex DK, et al. Position statement: Nonanesthesiologist administration of propofol for GI endoscopy. Gastroenterology. 2009;137(6):2161–67.
29. Pambianco DJ, Vargo JJ, Pruitt RE, Hardi R, Martin JF. Computer-assisted personalized sedation for upper endoscopy and colonoscopy: a comparative, multicenter randomized study. Gastrointest Endosc. 2011;73(4):765–72.

Chapter 10
Role of Pathology in Quality of Colonoscopy

Lawrence J. Burgart, Patrick M. O'Reilly, Kenneth P. Batts, Jason A. Daniels, H. Parry Dilworth and Schuyler O. Sanderson

Introduction

Pathology plays an important role in the completeness and accuracy of diagnostic information derived from colonoscopy. Optimization of this microscopic interpretive process requires close communication between the laboratory team and the colonoscopy team, as well as rigorous processes to maintain appropriate identification of patient materials. Clear, open, and direct communication between the pathologist and gastroenterologist is also essential to timely and clinically useful diagnoses. This chapter will explore a number of specific factors—divided into prelaboratory, intralaboratory, and postlaboratory timeframes—which greatly influence the quality of diagnostic information derived from endoscopic tissue biopsies.

Prelaboratory

Pathologists play an important role in educating colonoscopists and their endoscopy support team regarding the critical nature of labeling specimens appropriately. Given the demands on the colonoscopy team's time and their attention to the patient's

L. J. Burgart (✉)
Minnesota Gastroenterology, University of Minnesota College of Medicine, Mail Route 20207, 2800 10th Ave S, Suite 2200, Minneapolis, MN 55407, USA
e-mail: Lawrence.burgart@allina.com

P. M. O'Reilly
Minnesota Gastroenterology, PA, St. Paul, MN, USA

K. P. Batts · J. A. Daniels · S. O. Sanderson
Minnesota Gastroenterology, Minneapolis, MN, USA

H. P. Dilworth
Department of Pathology, Hospital Pathology Associates, Allina Health, Minnesota Gastroenterology, Minneapolis, MN, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_10

intraprocedural welfare, patient safety issues related to labeling may become of second-tier importance. It is well documented that in this potentially hectic environment significant identification errors can and do occur [1]. These errors result in specimens from different anatomic locations within one patient being shuffled or, of a much more serious nature, one patient's tissue being labeled as coming from an unrelated patient. Often in the pursuit of efficiency, patient-identifying labels are generated and sometimes even put on formalin-filled specimen containers in advance of the patient entering the procedure room. If this is done at the beginning of the day, multiple patients' labels and/or containers are present in the room for any given patient. It is critical that labels and labeled containers present in any procedure room be specific to the patient within that room. Any unused labels and/or labeled specimen containers should be discarded promptly at the end of a procedure and the staff should start fresh with unlabeled bottles and freshly printed patient labels at the beginning of each procedure. The colonoscopy team must develop a system of communication such that tissue being retrieved by the colonoscopist and placed in a formalin-filled bottle is labeled with the appropriate anatomic location. A cancer-containing polyp labeled as coming from the left colon when actually obtained from the right colon can lead to significant surgical morbidity.

Bringing the laboratory's perspective to the endoscopy team has proven very powerful in our practice. We have developed "boot camp" presentations regarding specimen labeling and the endoscopy–pathology axis. These lectures, specific to support staff or endoscopists, also provide literature-based biopsy protocols for each site and indication (i.e., number of biopsy fragments and/or separate specimen containers for inflammatory bowel disease (IBD) surveillance, exclusion of microscopic colitis, or evaluation of polyps) [2]. The boot camp, approximately 60 min long, is provided by a gastrointestinal (GI) pathologist to all new caregivers and endoscopy support staff in our broad medical system.

Pathologists and gastroenterologists in practice together should discuss data-based evaluation protocols. In addition to literature-based sampling protocols alluded to the above, appropriate utilization of ancillary studies within the laboratory should be agreed upon as data driven and clinically meaningful. Two examples of such reflex testing include: (1) immunohistochemistry for DNA mismatch repair enzymes in all biopsy samples of new colorectal cancers as endorsed by a Centers for Disease Control and Prevention (CDC)-sponsored expert panel [3], and now endorsed by the National Comprehensive Cancer Network (NCCN) and (2) immunohistochemistry for cytomegalovirus (CMV) in IBD patients with moderate or severe disease activity [4].

A key component to clear communication between the pathologist interpreting biopsy tissue findings and the gastroenterologists managing the patient is *consistent terminology*. A GI pathology team should use standard language across all cases with the same diagnosis. Gastroenterologists should not be put in a position of deciding whether variability in terminology is clinically meaningful or a creative expression of individual pathologists! Standard diagnostic templates used by all members of the pathology team are key to consistent communication back to the caregivers and have been demonstrated to improve the quality of reporting [5].

Standard templates with "pick-lists" which account for the vast majority of microscopic findings in any given clinicopathologic scenario optimize communication and streamline-reporting workflow. In addition to optimizing clarity of communication, templated reports minimize the transcription and proofreading errors, shorten the time to a final report, and minimize the need for transcription resources. In unusual cases, pathologists will still need to add specific comments regarding the diagnoses and clinical correlation, but these comments become more powerful due to the fact they are present in only a small minority of reports.

From the gastroenterologists' viewpoint, consistent terminology in reporting is the most important factor in high-quality communication between the pathologist and clinician, the factor that most likely has the biggest impact on clinical outcomes for the patient. From this perspective, the quality and improved outcomes come from a close relationship with the gastroenterologists so there can be agreed upon patient management sequences which predictably follow from specific diagnoses. For example, if a mixed serrated–adenomatous polyp is diagnosed and selected from the report-generating pick-list, standard language which has previously been agreed upon by the gastroenterologists and pathologists will be deployed that reminds the gastroenterologist to schedule a follow-up colonoscopy at a short interval (e.g., 3 months) to confirm complete resection of this potentially aggressive lesion.

Laboratory

Entry of the specimens into the laboratory allows another important opportunity to assure the integrity of patient identification and biopsy site information. In most laboratories, patient information must be re-entered into a laboratory information system which is distinct from the clinical electronic medical record (EMR). We are fortunate in our laboratory to have the pathology reporting software built into the clinical EMR, eliminating the need for data reentry. In this situation, the patient information and biopsy site designations on the specimen containers are checked against the EMR-based endoscopy report to assure correlation.

For typical laboratories requiring the accessioning of patient information into the laboratory information system, there are technological solutions that have been shown to markedly decrease patient identification and biopsy site errors due to data entry mistakes. These solutions include application of radio frequency identification devices (RFIDs) or bar codes to link the information from the endoscopy suite EMR to the laboratory information system, via a third-party database, with no opportunity for human error at the time of accessioning the samples into the laboratory for processing. A study of the effect of an RFID system in one high-volume GI endoscopy–pathology system showed the rate of serious misidentification rates drop from 0.09 % baseline to 0.02 % with the system in place [1]. Given the high volumes in most laboratories, the documented rate of serious misidentification errors, and the potentially devastating effects to patients of these errors, such safeguards seem warranted.

It may seem tangential to dwell on patient identification integrity in this discussion of colonoscopy quality, but the pathology laboratory is a very different setting than the clinic. A recent study of labeling errors *within* a pathology laboratory estimated a 0.25% rate of specimen misidentification, and noted that "most errors occurred with small biopsy specimens from endoscopy and dermatology" [6]. In this study, the preponderance of errors was made at the "grossing" bench where tissue fragments are moved from specimen containers into the tissue-processing environment. When it comes to tissue biopsies from the GI tract, they mostly look alike. Although these biopsies arrive in sample containers carefully labeled at the patient's bedside, the tissue fragments are transferred from those bottles into plastic processing cassettes. The appropriate transfer of the tissue fragments from the specimen container to the processing cassette is critical in maintenance of information integrity. We designed a unique safeguard in our laboratory—a surveillance camera of the grossing bench—which has been a key quality control tool in our laboratory and has allowed for critical troubleshooting into potential causes of specimen misidentification. The camera is of the type used to monitor a retail store door or a casino table. It records the hand actions of the technician transferring the tissues for processing. The camera is not routinely monitored but the tape loops are retained for a period of time. If a problem is suspected based on the histologic findings or correlation of histology and clinical information, the tape can be reviewed to assure the tissue from a given specimen container was placed in the appropriately labeled processing cassette. In a typical laboratory, where this visual review is not available, it is never clear if a crossover of tissues occurred within the endoscopy suite or in the laboratory, clouding potential quality improvement discussions.

The tissue-processing steps, transforming tissue from an aqueous basis to a paraffin-embedded dehydrated state ideal for sectioning and staining, take place within a vacuum chamber with solutions transferred in and out in a proscribed order. The same chemical sequence is used for pathologic processing of essentially all human tissues. The time required for each solution to be in contact with the tissue is dependent upon the size of the tissue fragments. There is a great time advantage in a pathology laboratory dedicated to GI biopsy specimens, as specimens under 0.5 cm, which includes most GI cancer biopsies and many polyp specimens, can go through the chemical processing in approximately 65 min. Given the accessioning, tissue transfers, tissue embedding, tissue sectioning, and staining steps, which occur in addition to the chemical processing before histologic analysis, the entire laboratory process can be performed in approximately 4 h. This allows tissues delivered to the laboratory by noon to be microscopically evaluated at 4 p.m. with a final diagnosis in the patient's medical record on the same day as the procedure was performed. Larger tissue fragments, including a significant minority of polypectomy specimens, will require overnight processing.

The steps following chemical processing also deserve mention as the quality of diagnoses is dependent upon the quality of slides available for review, and the quality (training and experience) of the pathologists reviewing the slides.

After the chemical processing, professional histotechnologists embed the biopsy fragments into paraffin in preparation for microtome sectioning. These specialized

technologists are credentialed by the American Society of Clinical Pathology (ASCP) based on training and demonstration of technical competence. Dedicated GI pathology laboratories have the advantage that the histotechnologists become experienced in handling these relatively small tissue samples, sectioning to the appropriate depth to demonstrate all changes while preserving adequate tissue in the paraffin block for any potential ancillary stains (e.g., *Helicobacter pylori* immunohistochemical stain). All laboratories use a routine stain consisting of hematoxylin and eosin (H&E stain), and most laboratories will have sufficient case volumes for an automated staining system, which saves manpower and has the added benefit of decreasing staining variability.

Over the course of approximately 4 h, the GI biopsy tissues have been transformed from floating in formalin to 5-μm-thick cross sections adherent to a glass slide, stained for a pathologist's medical interpretation. As with any medical examination, the quality of interpretation—including both accuracy and completeness—is dependent upon training and experience. And as with any medical examination, training and experience is optimized in the setting of subspecialization. While there is no specific board certification for GI pathology, widely recognized fellowship training programs have been available in recent decades. The pathology workforce contains a sufficient corps of subspecialty GI pathologists now to provide leadership in any group handling a significant number of GI biopsies. Not every colonoscopic biopsy specimen need be personally examined by a GI pathologist, but all such specimens will be optimally interpreted by a pathology group with strong on-site leadership by a subspecialty GI pathologist with a capacity for real-time consultation on unusual or difficult cases.

In addition to the routine processing that occurs in all GI biopsy material, ancillary testing is also important to clinical management in a minority of pathology specimens. In the arena of colonoscopy and neoplasia management, the assessment of DNA mismatch repair enzyme expression by immunohistochemistry, and molecular assessment of kras and/or braf mutations are of most importance. Immunohistochemistry should be available in any high-volume GI pathology laboratory. Molecular assays will routinely be sent to an outside vendor. Residual paraffin-embedded tissue available after routine processing and diagnostic steps are complete is typically adequate for these ancillary analyses.

The literature is clear regarding the subjective nature of certain clinically important data elements in GI pathology, leading to the appropriate recommendation for review by two pathologists. The diagnosis of dysplasia in IBD falls into this category [7]. Not all dysplasia surveillance biopsies from IBD patients will be a "double read" as the majority of these biopsies are clearly and definitively negative. If these biopsies do show dysplasia or microscopic changes suspicious for dysplasia, the biopsy should automatically be evaluated by two pathologists before reporting an interpretation. The gastroenterologist should not be tasked with getting a second opinion on these critical diagnoses.

External consultations on exceptionally unusual cases (i.e., rare processes typical of other organ systems occurring in the colon) may be rarely needed, and should be sought in such instances.

Timely reports with impeccable patient identification integrity are critical for patient management. But, of course, the most obvious mission-critical element in a pathology report is the diagnosis. Too many pathology reports provide descriptive histologic information in the place of a diagnosis. An optimal GI pathology report will correlate the microscopic findings with the clinical and endoscopic findings to relay specific diagnostic information, which will allow the gastroenterologist to optimize patient management. Having direct access to medical record information at the time of microscopic tissue assessment is necessary to provide integrated diagnostic information.

Critical results, such as diagnoses of new malignancies or clinically unexpected findings, should be communicated directly to the care team in addition to the standard reporting mechanism so as not to get delayed in routine workflow. The most effective means of such communication is a direct exchange between the pathologist and the care team. Faxed or email notification would only be adequate if there is a prearranged mechanism for timely action based on the transmission.

Postlaboratory

Before discussing implementation of standard quality pathology measures to a GI pathology laboratory, it is worthwhile to describe a relatively unique patient care benefit of having a dedicated GI pathology team working specifically with a dedicated gastroenterology group in a single EMR: *identification of unexpected trends*. Expected parameters, such as adenoma detection rate, will be followed by the gastroenterology group as discussed elsewhere in this book. Unexpected public health or practice-specific trend identification is greatly facilitated by a dedicated pathology team due to the concentration of cases. While a trend may be too dilute to notice across six-dozen gastroenterologists, the concentration of the unusual finding among six pathologists is less likely to be missed. Once noticed by the pathologists, a rapid evaluation of objective evidence from the electronic medical record will confirm or dispel the concern of a trending issue. A concrete example is provided here [8]:

A large gastroenterology group modified its colonoscopy preparation regimen based on current standards in an attempt to reduce patient volume intake and optimize colon readiness for evaluation. Over the ensuing weeks, the pathologists believed they were seeing a small increase in the number of ischemic colitis biopsies in unexpected patients. After consultation with the gastroenterologists' clinical practice committee, data were pulled from the EMR comparing ischemic colitis rates to different colonoscopy preparation regimens. A small but statistically significant increase in ischemic change (predominantly asymptomatic) was noted in cancer screening patients correlating with an increase in the standard preparatory dulcolax (bisacodyl) dosage. This rapid assessment allowed the preparatory regimen to be changed after minimal time had passed.

Standard pathology QA programs are well described by Dr. Raouf Nakhleh, a leader in general pathology quality. Dr. Nakhleh lists a number of important quality

steps important in "surgical" pathology which also apply to "medical" pathology such as GI pathology [9]. His multifaceted approach, strongly endorsed in our GI laboratory include: (1) retrospective review of randomly selected cases, (2) focused internal review of specific case types, (3) interdepartmental conferences, (4) intradepartmental QA conferences, (5) evaluation of cases incidentally reviewed at an outside institution, and (6) review of previous case material at the time of a new biopsy.

The standard retrospective case audit is performed by the laboratory medical director, a fellowship-trained GI pathologist, or his designee and consists of a set number of cases monthly. The case list is randomly generated, but in a way which accrues cases from each of the several endoscopy sites, and covers both morning and afternoon endoscopy procedures. The review includes microscopic reevaluation of the biopsy tissue, appropriateness, and completeness of the pathology report, and review of the endoscopy report to assure availability of information needed for clinicopathologic correlation within the pathology report. Direct feedback is given to pathologists regarding irregularities or variability in diagnoses and report content. This review is another way to pick up clinical practice trends, although that is more likely to happen in real time if the endoscopy report with clinical information is appropriately reviewed at the time of microscopic examination of in every case.

Focused internal review happens in our practice prospectively and includes a second pathologist independently evaluating all new malignancies and the diagnosis of dysplasia, or changes indeterminate for dysplasia, in IBD.

Interdepartmental conferences, such as tumor boards or IBD practice group meetings, provide excellent opportunities for diagnostic material to be presented as part of clinical care discussions. This allows additional correlation of microscopic diagnoses and patient management, and has the potential to further diminish any barriers to timely communication between pathology and the clinical care team. This interaction positively impacts pathology diagnostic services by allowing the pathologists to understand more fully what microscopic information set is critical to patient care, and allows the gastroenterologist or surgeon to get a more complete understanding of what clinical information may impact pathologic evaluation.

Intradepartmental conferences should help periodically to evaluate latest practices and minimize variability. These conferences should also include open communication about any errors or "near-miss" scenarios which have been discovered through the other forms of review.

Incidental outside reviews of pathology material occur when a patient seeks treatment at a different health system, typically for a tertiary care issue. It is good, and relatively standard, medical practice to review biopsies from other medical systems when a new patient presents. When biopsies from our GI pathology laboratory are reviewed elsewhere for these purposes, a copy of that pathology report is then received in our laboratory and compared to our original interpretation. If there is any difference in interpretation, we rereview the material and resolve the difference either internally or with the outside institution.

An additional source of directed quality review is serial biopsies within a given patient. Especially in inflammatory issues such as IBD, providing direct comparison

data between previous and current biopsies may be informative in patient management. Certainly, not all previous biopsy material need to be reviewed in every patient (reviewing serial adenomas over years is very unlikely to be helpful) pathologists need to be aware of all previous material within their laboratory and have ready access to those slides for review as indicated by discrepant findings or evolving disease conditions.

Finally, open communication with the gastroenterologists is imperative after a pathology diagnosis is rendered. There should be no barriers to any patient-care team member calling the pathologists and asking, "What about…?" All experienced pathologists have been humbled by the subtlety of amyloid, viral inclusions, or other unnoticed histologic findings which come to light on review after a clinical suspicion or hunch is shared. These subtle findings often require additional cytochemical or immunohistochemical stains which may be performed only in certain clinical settings, so keep those lines of communication open!

Summary

High-quality GI pathology diagnoses and resultant optimum patient management are dependent upon open communication among all stakeholders, as well as attention to high-fidelity patient/sample identification integrity. Pathologists should be involved in patient sample handling before the specimen arrives in the laboratory and implement a multifaceted QA program which includes interdepartmental presentation.

References

1. Francis DL, Prabhakar S, Sanderson SO. A quality initiative to decrease pathology specimen-labeling errors using radiofrequency identification in a high-volume endoscopy center. Am J Gastroent. 2009;104:972–5.
2. ASGI Standards of Practice Committee, Sharaf RN, Shergill AK, Odze RD, Krinsky ML, Fukami N, Jain R, et al. Endoscopic mucosal sampling. Gastrointest Endosc. 2013;78:216–24.
3. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009;11:35–41.
4. Al-Zafiri R, Gologan A, Galiatsatos P, Szilagyi A. Cytomegalovirus complicating inflammatory bowel disease: a 10-year experience in a community-based, university-affiliated hospital. Gastroenterol Hepatol. 2012;8:230–9.
5. Casati B, Bjugn R. Structured electronic template for histopathology reporting on colorectal carcinoma resections: five-year follow-up shows sustainable long-term quality improvement. Arch Pathol Lab Med. 2012;136(6):652–6.
6. Layfield LJ, Anderson GM. Specimen labeling errors in surgical pathology, an 18-month experience. Am J Clin Pathol. 2010;134:466–70.

7. Eaden JA, Abrams KR. Inter-observer variation between general and specialist gastrointestinal pathologists when grading dysplasia in ulcerative colitis. J Pathol. 2001;194:152–7.
8. O'Reilly PM, Burgart LJ, Vargo PM. High dose bisacodyl as part of a colonoscopy preparation may cause colon ischemia. Gastrointest Endosc. 2009;69:AB134.
9. Nakhleh R. What is quality in surgical pathology? J ClinPathol. 2006;59:669–72.

Chapter 11
Managing Quality in Ancillary Services

Michael Frist, Marc Sonenshine and Steven J. Morris

Introduction

The traditional role of the gastroenterologist has changed over the years, as it has for many medical and surgical specialties. In taking care of patients, not only the professional part of care is rendered but also the doctor has assumed the ability to offer many of the components that are ancillary but critical to the totality of service provided. When the physician assumes this role, he/she also carries the responsibility to make certain that the quality provided meets or exceeds all applicable or expected standards. Quality alone is not enough in today's market place, and, if the doctor is to undertake the role of providing ancillary services, we must also look at the value proposition created.

A crucial principal in a free market is that the consumption of goods or services will only occur when the value is created. In health care, the value is determined by the ability to access quality care as a function of its cost. At some threshold, poor quality or extraordinary cost leads to diminishing value, whereby the benefits of care to the patient no longer exist. Over the years, the field of gastroenterology adapted to create significant value for both patients and their payers. In this chapter, we will discuss specific ancillary services provided by many gastroenterologists and how to assure the quality and value.

Colorectal Cancer Screening

Study after study reemphasizes the benefits of screening colonoscopy for reduction of morbidity and mortality related to colorectal cancer. The United States Preventive Services Task Force and numerous society guidelines recommend screening

S. J. Morris (✉) · M. Frist · M. Sonenshine
Atlanta Gastroenterology Associates, LLC, 550 Peachtree St. NE, Atlanta, GA 30308, USA
e-mail: steven.morris@atlantagastro.com

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_11

for appropriate patients. Despite the various options for screening, colonoscopy remains the gold standard as it has the greatest diagnostic ability through enhanced detection and tissue sampling of simple and complex dysplastic growths. Further, colonoscopy has the potential for curative therapeutics by the means of polypectomy, thus making colonoscopy the premier modality for screening.

Ambulatory Surgical Centers

Historically, hospitals were the main sites for colonoscopies, as it was perceived that an invasive procedure requiring patient sedation could only safely be performed in a hospital setting. But, over the years, growth in ambulatory surgical centers (ASCs) specializing in a variety of minimally invasive surgeries and endoscopic procedures has exploded. The utilization of ASCs for colonoscopy benefits all parties—payers, patients, and providers. Often owned by groups of physicians, services provided by an ASC are provided to patients and their payers at a marked reduction of the costs compared to the hospital setting; physician ownership is appealing as it allows the doctor to maintain operational control and ownership of a profitable asset, two clear incentives to run an efficient process.

However, to ensure value, besides just lowering cost, the safety and quality of the colonoscopy performed must not be compromised. If patient safety was compromised, no value could be gained. In 2011, Dr. Azrak's article illustrated safety at ASCs; a 15-year review of a random sample of 174,000+patients showed no statistical difference in associated complications (morbidity) or mortality of Medicare patients receiving colonoscopy in a hospital versus an ASC [1]. To further solidify the safety in ASCs, Centers for Medicare and Medicaid Services (CMS) require certification and/or accreditation by state regulatory commissions or registered societies. These governing bodies ensure a specific level of conditions for coverage—essentially minimal standards necessary to ensure safety. However, state and society guidelines are typically even more stringent and demanding. Centers only need approval from either the state or an accrediting body, but most ASCs now are obtaining both. The three accrediting bodies registered through CMS include the American Association for Accreditation of Ambulatory Surgical Facilities, the Accreditation Association for Ambulatory Health Care, and the Joint Commission on Accreditation of Healthcare Organizations. Surveys of the facility do not just occur at the opening of the center, but periodically to ensure standards are consistently met, with even unscheduled "surprise drop-ins."

With demonstration of safety at the facility and necessary oversight in place, and the case for cost squarely in the ASC corner, the only remaining question remains the quality of the procedure. The standards of colonoscopy remain the same, regardless if performed in a hospital or in an ASC. The gastrointestinal (GI) community at large has quickly identified specific quality indicators. Furthermore, many centers track and grade individual physicians by these standards, specifically adenoma detection rate (ADR), cecal intubation rates with photography documentation of

landmarks, withdrawal times, and complication rates. Centers concentrating on care are also tracking appropriateness of repeat intervals based on guidelines, and documentation of prep quality.

However, what separates a single purpose ASC from a hospital is its focus. While the expertise is definitely still present, a provider whose sole concentration is a small cluster of procedures clearly outweighs having to be a part of a diverse offering. The ASC procedural technicians and nurses also benefit from this same practice; hospitals often find themselves pulling staff to cover other areas. Experienced GI techs working solely in one center with just a handful of physicians leads to understanding the style of practice and habits. This familiarity improves the working relationship between team members in the endoscopy suite leading to improved quality, patient care, and experiences.

Finally, with physician ownership in an ASC, there is a financial incentive to keep costs low. Lower costs can be obtained through volume, efficiency, appropriate staffing, and improved buying power/negotiation as physicians cooperate on standardization of equipment. There is also a freeing up from burdensome and expensive hospital regulation and requirements that may make sense for inpatients with greater acuity of illness but often add to cost without benefit for the ASC setting. Frankly, many argue that physician ownership creates conflict of interest, in particular, the possibility of inappropriate over-usage. However, this same interest also leads to a better patient experience as the physician's reputation and business relies on providing a top-quality patient encounter. Also, the differential between ASC cost and more expensive hospital settings is not just fractional but can vary up to 4–8 × for the same procedure, a fact that seems to be poorly understood and is hard to justify in any system where value must be offered.

Anesthesia Services in Colonoscopy

Clearly, screening colonoscopy saves lives. Thus, all barriers which prevent access to the test must be removed. Besides patient displeasure with the colonoscopy preparation, a major limitation to access remains patient's fear of discomfort during the procedure. Though no causative data exist, there is no surprise that the utilization rate of colonoscopies is increased as the access to anesthesia services for colonoscopy has improved.

Moderate sedation with narcotics and benzodiazepines remains the cheapest method for providing comfort. However, significant drawbacks to physician directed moderate sedation exist. First, delivery of moderate sedation requires a registered nurse and an ordering physician, typically the endoscopist [2]. Performing a high-quality examination for colonic abnormalities (polyps, etc.) should be the endoscopist's primary objective, not the constant monitoring of a patient's cardiopulmonary status and their comfort. Furthermore, recovery time from moderate sedation by the patient is much longer than that of propofol sedation, the most common anesthetic used for colonoscopy through monitored anesthesia care. Delayed recovery times

decrease efficiency in an endoscopy suite and thus access is affected. Additionally, though moderate sedation is effective, patients across the board describe their experience with propofol much more pleasantly than that of moderate sedation—in particular, the procedure and recovery process—as nausea and grogginess is much less.

The argument against widespread use of propofol is the cost of the drug and the need for a monitoring and delivering provider [2].A black-box warning dictating a provider with skill in airway management (i.e., anesthesia provider) essentially limits a gastroenterologist from giving the medicine. Also, as Irvani has articulated: "The bottom line is that no matter how precise of a control is exercised over sedation depth, in a large patient series, there will be incidences in which unintended deep sedation…is reached" [3]. Gastroenterologists clearly do not possess the necessary airway management skills to deal with these circumstances. Hence, the clear need for trained anesthesia professionals. The cost can be offset by the fact that the vast majority of the cases (>95%) can be electively done in the ASC's outpatient, the low-cost setting. Further, physicians, by controlling the ASC, should ensure that the anesthesia services are negotiated for as in-network contracts (as are the ASC facility fees). Plus, lower cost is driven by improving center efficiency with greater access and throughput in the center with lower recovery times. In addition, with the gastroenterologist not having to worry about patient comfort or cardiopulmonary monitoring, an endoscopist can concentrate on polyp identification and removal. No study has evaluated whether cost may be saved by changing the location of the majority of procedures and greater detection of colorectal cancer early and thereby preventing therapies associated with later detection and treatment.

To ensure quality with monitored anesthesia care and propofol, an appropriately trained provider must be administering the drug with easy access to all necessary equipment should patients require prompt attention for undesired depth of sedation and associated cardiopulmonary compromise. Thus, constant monitoring with appropriate vital sign monitoring equipment including capnography must be available. Furthermore, airway management tools including nasal trumpets, ambu bags, and endotracheal tubes need to be within every patient room. Processes in cases of patient deterioration need to be clear to not just the anesthesiologists/anesthetists and the endoscopists, but to all members of the endoscopy suite staff with periodic refresher courses/training on their role and how to assist, even if it is to simply remain calm and out of the way. Finally, another advantage of a physician-run endoscopy center is that the anesthetists/anesthesiologists are completely dedicated to the GI service. In a hospital, the anesthetists/anesthesiologists typically rotate through other service lines; with their availability and dedication to the GI patients in question.

Pathology

Gastroenterologists rely heavily on the expertise, accuracy, and efficiency of the consulting histopathologist. Incorrect or delayed pathologic assessments result in clinical errors and patient dissatisfaction, which renders the services provided and associated fees wasteful. Thus, all endoscopists must assume the responsibility of

delivering a dependable strategy to manage pathology specimens along each step, from acquisition to patient notification. Three critical components exist in the chain: labeling at the time of acquisition, expert evaluation of the specimen, and patient and referring physician notification of results and follow-up instructions.

First, partnership with the technicians assisting the endoscopist is necessary to ensure the tissue removed for evaluation is labeled appropriately and placed in the correct specimen container. As in most areas, communication is a critical step and should not be overlooked. Throughout the procedure and at its terminus, ensuring the jars holding the specimen are correct minimizes the likelihood of a clinical error. Every endoscopist should match his procedure note to the labeling of tissue prior to allowing the specimens to leave the endoscopy suite. A read-back system/double-check system is used by many laboratories. Providing a description of the tissue, associated clinical history, and specific diagnoses entertained by the endoscopist will assist the pathologists once they receive the tissue.

Second, and probably most obvious, an accurate evaluation of the tissue is critical. A specially trained GI pathologist is definitely preferable to a general pathologist who switches between multiple fields. Many options to obtain a GI pathologist exist, whether through a large GI pathology group which contracts with endoscopists throughout the country (Gastrocor, GIPath, Endochoice, etc.) to endoscopists creating their own laboratory and thus hiring their own pathologist. A specially trained GI pathologist will not only improve turnaround time but also understands the intricacies of GI pathology and the implications of the results (i.e., dysplasia in esophageal intestinal metaplasia or inflammatory bowel disease, hyperplastic versus serrated adenoma in the right colon).

Finally, systems to notify patients and their referring physician of the results must not be minimized. Optimal management depends on patient and physician comfort levels. Many endosocpists require office visits for face-to-face discussions with patients to discuss the results; this clearly allows for better understanding, but is also with significant costs to the system and the patient. Other physicians call patients, but again, challenges in reaching patients and assessing understanding exist. Letter notification or access through electronic portals to notify patients creates challenges too. Nonetheless, whatever system chosen, it should meet the following standards: assurance patients are provided the diagnosis, an avenue to easily ask questions to assure understanding and associated implications, documentation for medico-legal purposes, a clear plan of action on how to act from the results, and a system to ensure the appropriate follow-up or surveillance is in place. Finally, other physicians in the care of the patient should receive copies of the results and recommendations.

Gastrointestinal suites produce many anatomic pathology specimens each day, and a management plan for the samples must be identified. The two components of pathology include the technical component (preparing the specimen) and the professional component. Each component can be insourced or outsourced, each of which have positive and negative factors. The plan for how to handle pathology depends on the finances as well as local and federal laws, specifically the Stark laws and Medicare anti-markup law. No matter the arrangement, the solution must be precise, reproducible, and efficient.

For each specimen jar produced, a technical component (TC) and professional component (PC) is generated. Thus, the more specimens removed, the greater the cost. A CMS review revealed a large increase in the number of specimens being performed in all procedures (dermatology, urology, and GI), and thus in 2013 a significant 35 % reduction in the technical component ensued with a slight 2 % increase in the professional component [4]. In deciding on the optimal strategy, understanding the average monthly volumes produced for a laboratory will help generate a proforma to understand the revenue.

Three options exist as to how to handle pathology:

1. Insource entirely—a practice can build its own laboratory constrained by strict laws and collect both the professional and technical components (88305).
2. Outsource entirely—send all specimens to a pathology service which bills and collects for the entire TC/PC
3. Split the TC/PC—contract with a pathology service to prepare the slides and thus collect the technical fee while providing or contracting a pathologist to evaluate the slides.

Each strategy has significant pros and cons. For insource purposes, direct fixed overhead costs are significant, as the necessary equipment for accessioning and preparing the specimens for evaluation is expensive, not to mention the cost of acquiring a Clinical Laboratory Improvement Act (CLIA) certificate and building the laboratory to meet necessary specifications (heating, ventilation, and air conditioning (HVAC), etc.). A modest estimate of initial overhead costs is US$ 500,000, not to mention the cost of hiring experienced, expert histopathology technicians [5]. Once up and running, internal controls with frequent quality checks are also necessary.

Complete outsourcing is easy to arrange, as many private GI pathology groups exist and are eager for the business. However, in choosing this route, an endoscopist relinquishes some control as the quality of the slide preparation, turnaround time, and expertise of the pathologist is left in a third party's control. Some may argue that such control is better left in a practice whose entire focus is pathology, while others maintain a relationship built with local physicians may improve results.

The third option is a split TC/PC. This plan allows for a pathology company to solely prepare the slides (and thus recoup the declining technical component) and allows the GI group to contract out or hire a pathologist (and collect the professional fee). This option is considered a hybrid of the two above; it allows for the endoscopist to maintain more control over which pathologist evaluates the specimen while reducing the associated costs and issues of maintaining a laboratory .

Infusion Centers

Centers for infusion of intravenous medications are another ancillary service many physicians build to improve patient experience and increase revenue. In-office infusion centers can create significant financial rewards for the physicians while also

keeping costs for patients low and access easy—true value. Just like ASCs provide a significantly reduced cost to a patient for a colonoscopy compared to a hospital, physician-owned infusion centers or infusion rooms as part of the office setting are much less expensive than hospital-based infusion centers, not to mention typically easier to access (parking, less walking through a hospital, etc.).

Infusion centers have low overhead to establish. Beyond the actual real estate space, patient chairs, four poles, vital signs machines, and personnel, the costs to establish an infusion center are minimal, and many physicians even use a simple office room with a few reclining chairs as their center.

Revenue is generated in two ways. First, a fee is collected for delivering the medications, which in GI are drugs typically for inflammatory bowel disease patients (biologics for active inflammation, ferrous gluconate for nonabsorbing iron deficiencies, and bisphosphonates for nonabsorbing osteoporosis). Second, and sometimes controversial, is the cost of the drug itself. Physicians typically buy the drug and are reimbursed at a higher cost through the payers providing a margin for physicians. Even though the office setting may save insurers' very large sums versus hospital-based infusion, the margins are often very slim, and with inventory costs high, the practice must be careful to properly run the infusion component or face losses negating their ability to continue to provide this ancillary service. Centers which do the purchasing of the medication directly with resale to the patients through provider reimbursement are more profitable than allowing the patient (and their insurance carrier) to buy directly from other pharmacies or the company itself and then bring the medicine to the center for infusion (and just a nurse administrating fee is collected). This latter model may be hard to justify from a financial view and may be run as a break even for the practice, but a valuable, quality service for patients.

Understanding the patient volumes requiring infusion medications for a practice is the critical component of whether a practice should offer an infusion center. Many infusion centers try to recruit patients from other specialties which the same meds are offered by most GI infusion centers to grow the patient base to help make a center profitable—i.e., rheumatologists, hematologists, and endocrinologists. Also, beyond cost and access, physicians often offer internet access (Wi-Fi), individual televisions, and snacks to help patients pass the time. Finally, being tied to the ordering physician's office improves communication between the provider and the patient; so, outcomes typically are better because problems which arise are more quickly delivered to the doctor than relying on a hospital staff member who has no allegiance to the doctor.

Diagnostic Imaging

As groups of gastroenterologists have merged in many areas of the country, the capability to purchase equipment and provide diagnostic imaging services to patients has become a reality. The high cost of computed tomography (CT) scanning and even ultrasound examinations in a hospital setting allows the gastroenterologist to

now provide an in-office alternative at a much better price point. But, once again, places the responsibility for achieving and maintaining quality on the practice.

While regulations may vary from state to state, this chapter gives the reader an outline of what a typical approach is. An application will need to be submitted to the State Department of Human Resources for state certification of both the scanner and the proposed CT suite. The application will include an initial evaluation by an approved physicist of both the radiation safety of the scanner and the lead lining of the CT suite. A quality assurance program must be submitted along with this evaluation and then usually annually to maintain certification.

After state certification, obtaining accreditation through one of the several Medicare approved bodies must occur. Currently, the options include the American College of Radiology, Joint Commission, or Intersocietal Accreditation Commission. As part of the process, the following is required to be submitted:

- Images for each of the scan types offered (abdomen, pelvis, chest)
- Scan protocols
- Clinical protocols:
  - Contrast administration
  - Contrast reactions
  - Contrast extravasation
  - Radiation safety management of women of child-bearing age
  - Contrast administration during breast-feeding
- Policies and procedures:
  - Radiation safety for both patients and staff
  - Reporting and follow-up
  - Documentation
  - Quality assurance for both technologist and radiologist
  - Adverse event management and reporting
  - Incident management and reporting
  - Employee orientation and training program
  - Medical record retention and confidentiality

For quality assurance, there are programs such as the ACR's peer review program, RADPEER. The technologists receive quarterly quality evaluations for technical competency. Most GI groups will find it more efficient and less costly to subcontract out the readings to a local radiology group. Also, most gastroenterologists use one of their group's doctors as the head of the division to ensure all protocols, regulations, and quality measures are meeting or exceeding expectations.

Conclusions

Over the years, gastroenterology practices have evolved from strictly offering physician cognitive services to become a procedure and consultative profession. Further, change has seen many practices assume control of various ancillary services

to provide a wider range of care options for patients. Many gastroenterologists have financially benefited from these additional revenue streams beyond their typical professional fees, but an added burden of responsibility has coincided with these decisions. Quality, safety, ethical utilization, and cost must never be compromised. The field of GI has been a leader in self-regulation, and gastroenterologists continue to find new methods in order to deliver premium patient care, with the highest standards, while driving costs down and improving access to all. In addition to the surgical centers, anesthesia, pathology services, imaging and infusion centers, gastroenterologists continue to push the envelope by expanding their scope of care. Some practices are investing in specialty clinics (motility, hepatology, inflammatory bowel disease, and research) typically only offered at large urban academic centers, telecommunication consults to rural communities, and online second opinions for complicated cases. No matter what the offering, the issue of delivering quality will always be first and play a key role in both how the care is delivered and whether it can be judged successfully.

References

1. Voelker R. Ambulatory centers match hospital safety for outpatient colonoscopy. JAMA. 2011;305(24):2508–9.
2. Liu H, et al. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending. JAMA. 2012;307(11):1178–84.
3. Iravani M. On computers, nurses, and propofol: further evidence for the jury? Gastrointest Endosc. 2008;68(3):510–1.
4. Schneider M. Medicare cuts payment for pathology code. GI & Hepatology News Digital Network; 2012.
5. Sarles Harry. Incorporating a GI pathology laboratory into your practice. Gastroenterology and Endoscopy News. 2011;1–4.

Chapter 12
Medical Legal Aspects of Quality Improvement

Kayla Allison Feld, Sarah Faye Blankstein and Andrew D. Feld

Basic Legal Concepts Relevant to Quality Improvement

The tort of negligence is the basis for most medical malpractice suits, and thus it is important to understand the elements of a negligence claim [1]. To succeed in a claim against a doctor for malpractice, plaintiff's attorneys must prove four elements:

1. Duty: the physician owed a duty of care to the plaintiff.
2. Breach: the duty was violated by practice below the applicable standard of care.
3. Causation: the substandard practice was a direct and proximate cause of the harm asserted.
4. Harm: the plaintiff suffered compensable damages.

The existence of a doctor–patient relationship generally suffices to establish the first element of a malpractice claim—that the physician owed the plaintiff a duty of care. To prove the second element, breach, the plaintiff ordinarily must prove that the physician did not provide the level of care that a reasonable and prudent member of the medical profession would undertake under the same or similar circumstances [2].[1] Breach may be established by showing that the treatment itself

[1] Hood v. Phillips, 554 S.W.2d 160, 165 (Texas 1977).

Disclaimer: This chapter is written for educational purposes, and should not be construed to provide specific legal advice; for that the reader will need to consult his/her own health-care attorney

A. D. Feld (✉)
Department of Gastroenterology, University of Washington, Group Health Cooperative, 125 16th Ave East CSB-2, Seattle, WA 98112, USA
e-mail: afeld@uw.edu

K. A. Feld · S. F. Blankstein
Seattle, WA, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_12

was substandard or that the physician failed to obtain informed consent for the procedure from the patient. With respect to substandard treatment, the traditional method for establishing current standards of care is by expert witness testimony. However, with increasing frequency, courts rely upon respected national guidelines and quality measures to define standards of care. With respect to informed consent, a physician violates his/her duty to the patient and subjects himself/herself to liability when he/she fails to disclose facts necessary for the patient to form intelligent consent to proposed treatment.[2] The third element, causation, may be established by showing that the physician's substandard medical care directly led to the harm experienced by the plaintiff. Finally, plaintiffs must prove the fourth element, damages, by showing that they experienced some form of compensable harm. Once the plaintiff has established all of the above elements, the defendant physician (or insurance carrier) is required to pay all damages suffered by the plaintiff, even if it is surprisingly great in scope.

The amount of damages a plaintiff could recover explains why some types of malpractice cases are brought with significantly greater frequency than others. For example, an actuarial assessment of malpractice risk [3] has revealed that delayed diagnosis of CRC is the most frequent and serious lawsuit against gastroenterologists. CRC is a serious illness that produces significant harm, which can be associated with a large financial damages award. The potential for a large financial settlement or court judgment is enough to justify the expense of bringing a case. If the plaintiff's attorney believes the critical elements of a negligence claim can be met—particularly a breach of standard of care or informed consent—he/she may front the expenses necessary to bring the claim forward and take the case on a contingent fee basis. This arrangement makes it more likely the claim will be pursued. On the other hand, if the gastroenterologist has practiced within the standard of care and with appropriate informed consent, then, despite the patient's damages, the plaintiff's attorney may be concerned that the element of breach cannot be proved. In that situation, it is risky for the plaintiff's attorney to take a contingency fee case in which the law firm could lose substantial money spent on expert witnesses, depositions, court fees, etc. if the jury decides in the physician's favor. A gastroenterologist practicing within established quality measures is, therefore, a harder malpractice target.

The Use of Clinical Practice Guidelines and Quality Measures to Define Standard of Care

The overarching aim of quality measurement and improvement with regard to performance of colonoscopy is to enhance the health value of the examination by reducing the risk of missed cancers, avoiding delays in diagnosis or treatment, and minimizing procedural complications.

[2] Salgo v Leland Stanford Jr. University Board of Trustees 317 P.2d 170 (California 1957).

Clinical Practice Guidelines

Clinical Practice Guidelines (CPGs) are developed to assist practitioners determine preferable approaches to treat specific clinical problems [4].[3] CPGs are created with the goal of improving the quality and reducing the cost of care delivered by consolidating pertinent scientific developments and expert opinions, providing guidance on the use of medical devices, and recommending specific treatment [5]. CPGs are developed by a spectrum of groups: primarily medical societies that use data drawn from randomized, controlled trials, peer-reviewed studies, and expert consensus[4] but also third-party payers, malpractice insurance carriers, and others [6].

Although CPGs are useful to promote effective and efficient care, they have certain limitations. First, they may quickly become outdated and no longer represent the generally accepted level of care (see [7]). Physicians are still required to follow and apply advancements in medicine, regardless of the outdated status of the guideline.[5] Second, CPGs may limit physician autonomy to apply individualized treatment because they recommend only general approaches. Third, CPGs are created using a variety of methodologies for diverse purposes. The result is that various CPGs dealing with the same medical practice may conflict [6, 8]. This poses particular difficulty for courts attempting to use CPGs as a standard of care.

Practice guidelines have no inherent legal significance, but may acquire such import if designated by a statute[6] or applied by courts as the standard of care in determining breach of a physician's duty to his/her patient. CPGs can be applied in establishing the second element of a negligence claim, to show whether the physician applied the accepted standard of care that would be used by a reasonably prudent physician practicing in the same geographic region. While in most fields the standard of care is defined by governmental agencies or professional licensing boards, this has not been the case in medicine [9]. In malpractice cases, the standard of care is determined through a variety of sources, including expert testimony, scientific studies, and CPGs that can demonstrate what may be considered "standard practice" [5].

Courts do not automatically equate deviation from CPGs with negligence, unless that particular deviation was of the type which no doctor of ordinary skill and care

[3] Committee to Advise the Public Health Service on Clinical Practice Guidelines, Institute of Medicine, Clinical Practice Guidelines: Directions for a New Program, at 8 (Marilyn J. Field and Kathleen N. Lohr eds., 1990)

[4] I.e., the ACG in its guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee, using expert opinion and data available at the time. The ACG then seeks the approval of the governing boards of the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American Association for the Study of Liver Diseases. See id.

[5] See May v. Moore 424 So 2d 596 (Ala 1982) ("there is no tenable policy reason why a physician should not be required to keep abreast of the advancements of his profession.").

[6] Some states, including Maine, Florida, Kentucky, and Minnesota have created statutes to permit physicians to use adherence to CPGs as an affirmative defense in malpractice actions.

would make. Nor will adherence to a CPG automatically protect a physician from liability. However, guidelines remain influential in malpractice cases either to shift the burden of proof or because a jury could easily consider them to reflect standard practice. Clinical guidelines may be used to supplement and enhance expert testimony or influence a jury as to the appropriate standard of care in situations where practices vary and more than one standard may exist. Courts have used CPGs both directly as the standard of care and indirectly as evidence that the physician adhered to customary practice, adhered to the custom of a "respectable minority,"[7] used "reasonable prudence" in deciding on treatment strategy,[8] or followed acceptable practice [10]. The majority of states will admit guidelines as relevant evidence but do not give them determinative weight in assessing negligence (see p. 665 in [11]). The admissibility of and weight accorded to CPGs depends on their reliability and their relevance to the particular case.[9] The more respected the medical society, the greater the likelihood the court will consider the guideline to reflect mainstream professional practice.

Courts may, and increasingly do, rely on guidelines even when the guidelines explicitly state they have been developed to enhance clinical care and not for legal purposes [2]. Legal scholars predict this trend will become even stronger [11]. Guidelines distributed by medical societies typically include disclaimers affirming they do not function as a standard of care. For example, the American Gastroenterology Association (AGA) writes, "these documents are not to be construed as standards of care. All decisions regarding the care of a patient should be made by the physician in consideration of all aspects of the patient's specific medical circumstances."[10] Similarly, the American College of Gastroenterology (ACG) writes, "guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems…. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated" [4]. Despite the disclaimers, guidelines remain influential in malpractice cases, and courts consistently refer to them in establishing the standard of care.

[7] See Hood v Phillips, 554 S.W.2d 160, 165 (TX, 1977) ("A physician is not guilty of malpractice where the method of treatment used is supported by a respectable minority of physicians, as long as the physician has adhered to the acceptable procedures of administering the treatment as espoused by the minority").

[8] See Helling v. Carey (519 P.2d 981 Wash. 1974).

[9] See, e.g., Frakes v. Cardiology Consultants, PC, 1997 Tenn App 597 (Tenn Ct App 1997) (holding that the guidelines at issue, which were promulgated by the American College of Cardiology and American Heart Association, were recognized by a majority of experts as the standard of care for the profession and therefore were relevant and had authoritative power as substantive evidence in malpractice litigation).

[10] American Gastroenterological Association, Guidelines, *available at* http://www.gastro.org/practice/medical-position-statements.

Quality Measures

Quality measures allow users to evaluate the quality of a selected aspect of care by comparing it to an evidence-based criterion that specifies what constitutes high-quality care [12]. The goal is to increase the quality of patient care by encouraging physicians to meet the standards specified in the quality measures. In the context of colonoscopy, quality measures may be used to enhance the health value of the exam by reducing the risk of missed cancers, avoiding delays in diagnosis or treatment, and minimizing procedural complications. Similar to CPGs, quality measures are based on recommendations provided by large organizations with expertise in the area described. For colonoscopy, groups such as the ACG, the American Gastroenterology Association, and the American Society for Gastrointestinal Endoscopy provide evidence and consensus-based standards for improving overall quality of gastrointestinal (GI) procedures [13–15] and reducing the variability of performance.

Quality measures may appear on the surface different from clinical guidelines. However, expert witnesses may cite quality measures in the same manner as clinical guidelines. Little imagination is required to understand how a jury could be persuaded that quality measures should be regarded as standards of care. Influential texts such as "To Err is Human: Building a Safer Health System" [16] and "Crossing the Quality Chasm: A New Health System For The 21st Century" [17] have only heightened public concern about medical error and the quality of medical care. Medical societies are responding with a multitude of programs, task forces, and quality measures to help achieve clinical quality [13–15]. It will be increasingly necessary for the practicing gastroenterologist to be aware of those measures and adopt those that are likely to be construed as standards of care, or face challenges in the event of a negligence claim. While these measurements may theoretically put a physician at risk by showing the physician conducted a low-quality examination, they will more often play a useful role in demonstrating that the physician did comply with an accepted standard of care.

Effect of Failure to Adopt and Monitor Compliance with CPGs and Quality Measures

Adopting quality standards is likely to benefit patients, help marketing and business efforts, and benefit the practitioner in the event of a legal malpractice challenge. Conversely, failure to adopt and measure physician compliance with CPGs and quality measures will not protect physicians from liability for not complying with those standards. Sufficient data exist about quality practices such that a plaintiff's attorney can often build a case against even those who elect not to measure quality. For instance, in a malpractice action against a gastroenterologist, the plaintiff was able to prove substandard colonoscopy technique with inadequate withdrawal time even though the physician did not measure withdrawal time. The case against the

gastroenterologist was based on the physician's use of photo documentation during colonoscopy. The view of the cecum was timed, as was the retroflexed rectal view, which occurred 1 min after the cecal view. If a gastroenterologist consistently fails to monitor recommended quality standards, a court might instruct physicians who do not track adenoma detection rates to comply with a discovery request from the plaintiff's attorney for that rate by going through records and calculating it retrospectively. The difficulty of such a process would not necessarily dissuade the court, which places a high premium on accurate discovery.

Quality Assurance and Peer-Review Protections

A key liability issue in the collection of quality assurance data and benchmark comparisons is whether they will be protected as peer-review product in the event of litigation. This is important, because if plaintiffs are allowed to access quality assurance data, they could selectively use unflattering data against hospitals and physicians in litigation. Although there are no guarantees that courts will respect the confidentiality of quality data, carefully structuring quality assurance programs to comply with the requirements of peer-review statutes offers the best chance of protection.

All 50 states and the federal government have passed statutes protecting the peer-review process[11] with the goal of encouraging physician candor in peer-review proceedings. The peer-review statutes vary substantially by state, but they generally share two common elements. First, they provide peer-review participants with some degree of immunity from lawsuits arising out of their participation in the review process. Second, they make documents produced and information gathered as part of the peer-review process "privileged" and/or "confidential." Confidentiality provisions broadly prevent disclosure of peer-review information to third parties, whereas privilege provisions are tied to the existence of litigation and bar only the discovery and use of peer-review materials at trial. Confidentiality and privilege provisions both promote open participation in peer review by preventing information disclosed to a peer-review committee from being used against participating physicians or hospitals in later litigation.

Peer-review statutes protect data related to health-care quality improvement when certain requirements are satisfied. Confidentiality and privilege protections are generally limited to information prepared for or gathered by well-defined peer-review committees, including quality assurance and quality improvement committees [18].[12] Thus, disclosure and analysis of quality measures in an organized

[11] See Virmani v. Novant Health, Inc., 259 F.3d 284, 290 (4th Cir. 2001) ("[A]ll fifty states and the District of Columbia have recognized the [peer review] privilege."); Health Care Quality Improvement Act of 1986 (HCQIA), 42 U.S.C. § 11101 *et seq.*

[12] See also generally Bredice v. Doctors Hosp., Inc., 50 F.R.D. 249–50 (D.D.C. 1970); Claypool v. Mladineo, 724 So. 2d 373, 388 (Miss. 1998); Cruger v. Love, 599 So. 2d 111, 114–15 (Fla.

peer-review context generally will be protected. Disclosure and analysis of quality measures outside of an organized peer-review context, on the other hand, generally will not be protected. Many states also require proof that a document was created exclusively for peer review or quality improvement purposes in order to be protected. For example, courts in Iowa, Ohio, and Nevada have held that documents prepared in the ordinary course of business as part of a hospital's risk management policies—such as incident reports—are discoverable, even if the documents were utilized in peer-review proceedings.[13]

In order to maintain confidentiality and privilege protections, therefore, healthcare professionals should take care to ensure that data related to quality improvement are prepared for and utilized only by an organized peer-review committee. Since many peer reviews take place at regular subspecialty meetings, this may require structuring and formally titling a section of these meetings as engaging in "peer review" as defined by the applicable state statute. Care must be taken to ensure that quality data discussed in such meetings are not discussed or disclosed outside of the meeting, which may void peer-review protections. This severe restriction on data disclosure may conflict with institutional goals of transparency. An institution deciding to disclose specific individual quality data to enhance its reputation for quality and transparency will likely lose peer-review protection for at least that specific data and perhaps more. This may also promote disagreement between the physicians and the administrators of the institution. Hospitals looking to share and utilize peer-review data more broadly should work with legal counsel to maintain the greatest amount of peer-review protection consistent with the hospital's goals.

Specific Aspects of CRC Screening which Entail Liability Risk

This section addresses specific aspects of CRC screening which have given rise to malpractice lawsuits. These malpractice areas include: (1) lack of informed consent, (2) missed diagnosis due to substandard screening technique or failure to notify patients about results or follow-up, (3) failure to properly address patient's use of anticoagulation medication, (4) improper management of sedation issues, (5) failure to warn patients about possible genetic risk for CRC, and (6) missteps related to open access colonoscopy. In each of these high-risk areas, it is crucial that gastroen-

1992); Trinity Med. Ctr., Inc. v. Holum, 544 N.W.2d 148, 155 (N.D. 1996); Young v. Saldanha, 431 S.E.2d 669 (W. Va. 1993); Moretti v. Lowe, 592 A.2d 855, 857 (R.I. 1991); HCA Health Servs. of Virginia, Inc. v. Levin, 530 S.E.2d 417, 420 (Va. 2000); Glover v. Griffin Health Servs., No. X06CV055001692S, 2007 WL 3173658 at *4 (Conn. Super. Oct. 11, 2007).

[13] Orgavanyi v. Henry County Health Center, 2010 WL 5394785 (Iowa Ct. App. Dec. 22, 2010); Legg v Hallet, No. 07AP-170 (Ohio Ct. App. Dec. 11, 2007); Columbia/HCA Health Care Corporation v. Eighth Judicial District Court, 936 P.2d 844 (Nev. 1997).

terologists keep up with quality measures, guidelines, and other potential standards of care in order to provide good patient care as well as manage malpractice risk.

Informed Consent

The ethical and legal requirement to obtain informed consent [19] before performing colonoscopy derives from the concept of personal (patient) autonomy.[14] Using this approach, the competent patient, after receiving appropriate disclosure of the material risks of the procedure, and understanding those risks, benefits, and alternative treatments, makes an informed and voluntary decision whether to proceed [20]. A physician violates his/her duty to the patient and subjects himself/herself to liability when he/she fails to disclose facts necessary for the patient to form an intelligent consent to the proposed treatment.[15] Malpractice suits involving the doctrine of informed consent generally rely upon one of two causes of action: (1) the provision of treatment without obtaining prior consent for that treatment and (2) the failure to disclose sufficient information that would allow the patient to make a truly informed decision when giving consent [21]. Because the latter is more easily proven, cases involving incomplete disclosure are more commonly argued.

Courts apply two different standards to determine the physician's obligation to disclose certain information to a patient: the reasonable person standard and the prudent physician standard. The former requires that physicians disclose what a reasonable person would find significant in deciding about a treatment. Under the prudent physician approach, the information disclosed must comply with that which a reasonable physician in similar circumstances would disclose. Which standard applies depends upon the state in which the gastroenterologist practices.

The physician's legal and professional obligation to obtain consent from the patient serves as more than a procedural requirement to obtain a signature, but rather constitutes a comprehensive process that allows the physician and the patient to achieve a mutual understanding of the risks, alternatives, and goals of the proposed treatment. The physician must ensure that the patient is capable of making an informed and voluntary decision about whether to undergo the proposed treatment. This includes ensuring that the patient has an understanding of the possible material risks associated with the procedure and the availability of alternate treatment options. Material risks[16] are determined by the nature, magnitude, probability, and imminence of the risk that they represent. Although CPGs inform physicians of the type of information they should provide patients when obtaining consent, the level of detail will vary by situation.

Most state laws specify that obtaining informed consent is a non-delegable duty (i.e., it must be performed by the physician and cannot be delegated to one's staff

[14] Schleondorff v Society of New York Hospital, 211 N.Y.125, 105 N.E. 92 (1914), New York.

[15] Salgo v. Leland Stanford Jr. University Board of Trustees 317 P.2d 170, California.

[16] Canterbury v. Spence 464 F.2d 772(D.C. Cir. 1972).

or endoscopy nurse). However, consent is a process, and if sufficient and thorough information is provided, the final portion (in which the physician finalizes consent before the procedure and asks if questions remain) may be very brief. This standard is particularly important for the success of an open access (OA) process, so that OA patients have already received information and have been given the opportunity to ask questions to satisfaction before the preparation for the procedure.

In order to reduce the risk of liability for failure to obtain informed consent, gastroenterologists should adopt an intake/preparation process by which the patient is mailed or verbally given information about the CRC screening procedure. This should cover the purpose, description of the procedure, risks, benefits, and alternatives. It would be useful to document the patient's receipt of information and if any concerns or questions occur after having read it. Further, one should instruct office staff to be alert to patients who appear uncertain, have many questions, or are worried about proceeding and have staff arrange a pre-procedure consultation. The thoroughness of the information packet or process can make it hard to convince a jury that the patient received insufficient information or was coerced even if the final immediate pre-procedure discussion with the physician was limited [19]. On the day of procedure, the physician can fulfill his/her legal obligation by summarizing the information.[17]

Missed Diagnosis of Colorectal Cancer

Missed and delayed diagnoses account for more malpractice lawsuits than any other error [22]. Delayed diagnoses are not typically caused by a single misstep, averaging about three contributing factors in each case [23, 24]. Common problems triggering liability for delayed diagnosis include failure to conduct an initial screening with the appropriate level of care, failure to notify patients about abnormal test results, and failure to ensure that patients complete follow-up appointments [25].

Liability for Substandard CRC Screen

Failure to exercise an appropriate level of care in an initial CRC screen can lead to missed or delayed diagnosis of colon cancer. This situation carries significant liability risk for the gastroenterologist and is devastating for the patient and his/her family [26]. The legal issue hinges on whether the standard of care during performance of the colonoscopy was breached. Two questions are central to final legal resolution. First, was the cancer newly developed since the examination because it was fast growing? Second, was the procedure performed with good technical qual-

[17] One possible example: "The information you received noted that no test is perfect, including this endoscopy, and our staff have reviewed the risks of colonoscopy, including bleeding, perforation, infection, heart or respiratory complications, missed diagnosis, incomplete procedure, and sedation risks. Do you have any questions for me?"

ity, defined as a level of talent that a reasonable physician in similar circumstances would have applied? The latter implies that the average gastroenterologist would not have detected the cancer at first colonoscopy.

The general public usually does not realize that even the most careful endoscopist cannot guarantee a 100% detection rate of CRC. Since 100% detection is not achievable, even a highly skilled physician still may face legal action if he/she fails to understand and document using protocols recommended by medical literature. As discussed more thoroughly elsewhere in this book, a list of generally acceptable components of complete documentation for colonoscopy could include the following: (a) photographic recording of the cecum and landmarks; (b) description of the colon preparation (with a recommendation for early repeat when the prep is inadequate; (c) slow and careful withdrawal with adequate clearing of residual pools of liquid; (d) compliance with the informed consent process, including mention of the possibility of missed diagnosis; (e) an established process for managing post-procedure patient inquiries or complications; (f) a secure method to notify patients and referring physicians of procedure results (including pathology and recommendations for further examinations); and (g) some system to monitor procedure quality and results [27].

Liability for Non-notification of Abnormal Test Results

Failure to notify patients of abnormal test results from a CRC screen may lead to missed or delayed diagnosis, triggering malpractice liability. Non-notification of abnormal test results is a widespread problem [28]. This is especially true for the results of colorectal, breast, cervical, and prostate cancer screenings. Hundreds of thousands of these screenings are requested and completed each year, with the typical primary care provider ordering over a thousand tests each week [29]. This creates an enormous volume of data that must be reviewed, making it more likely that the results from such screenings will be overlooked and not reported to patients.

Lack of patient notification of abnormal test results due to forgetfulness, lost laboratory reports, belief that the results were trivial, or other reasons has resulted in substantial malpractice awards [30–32]. Although failure to notify a patient of abnormal test results does not itself give rise to a claim for malpractice, if the lack of notification leads to a missed or delayed diagnosis, the physician will be liable for failing to send the patient his/her results. Therefore, it is crucial that physicians report all abnormal test results to patients in a timely manner.

To best avoid malpractice liability, gastroenterologists should report all results from CRC screens to patients, including normal results. This avoids the problem of patients being falsely reassured by not hearing from their physician, when they mistakenly were not notified of abnormal results [30]. To ensure that test results are actually reported to patients, office staff should be trained to track, file, and report test results. As a failsafe, physicians should also ask patients to contact the office if they have not received their test results by a specified date.

Liability for Missed Follow-Up Appointments

A physician's duty to his/her patients extends to posttreatment follow-up. Physicians face substantial malpractice liability when patients miss follow-up appointments. Physicians may be held liable for (1) failure to stress the necessity of the appointment to the patient, (2) failure to send an appointment reminder, and (3) failure to track whether follow-up was completed and contact the patient after a missed appointment.

In delayed diagnosis lawsuits involving missed appointments, the patient often argues lack of informed refusal. Namely, the patient argues that the physician failed to explain the importance of returning for the follow-up appointment, and the patient skipped the appointment because he/she was not sufficiently informed about the risks of nonattendance. This often arises in malpractice lawsuits where a patient failed to appear for a scheduled colonoscopy, and the patient developed colorectal cancer [33]. In order to avoid malpractice liability, physicians must be careful to inform patients about the importance of returning for follow-up [34]. Physicians should also document this discussion with the patient for use as evidence in possible future litigations.

In addition to stressing the importance of coming in for follow-up, physicians should also send reminders to patients to schedule and/or return for scheduled follow-up appointments. Physicians' legal responsibility to send reminders has not been clearly defined by the courts [30]. Nevertheless, physicians still may be liable for missed or delayed diagnosis where the patient missed his appointment and the physician had not sent a follow-up reminder [30]. It is, therefore, prudent to have an automated reminder system in place to avoid the risk of malpractice liability [35].

Lastly, physicians must have a system in place to track whether patients have completed follow-up and contact patients who have missed scheduled follow-up appointments. The failure to track patient follow-up and contact patients after missed appointments creates a substantial liability risk in malpractice lawsuits for missed or delayed diagnosis [33, 34]. In a survey of 723 patient care sites by liability insurer, The Doctors Company, the most frequent risk management issues were failure to track and contact patients after missed appointments [33]. In order to avoid liability, physicians should set up an automated tracking system which alerts them on the date that the patient should have been in for an appointment or results from a referral appointment should have been received. Upon being alerted that the patient failed to complete the scheduled follow-up, the physician's office should contact the patient by phone or letter to reschedule the appointment [34]. All communications with the patient should be documented for evidentiary use in potential future litigation. Mistakes made by office personnel who fail to communicate physician-directed information may leave the physician liable under the legal theory of vicarious liability (the wrongdoing is extended to the person on whose behalf the wrongdoer acted) [1]. A process should be established within a practice policy manual for future notification of patients for follow-up examinations, requiring that patients be informed of the importance of follow-up examinations (including the risks of ignoring advice) and specifying the extent to which the practice will go to find the patient

when a follow-up examination is due. The responsibility for notification should be clear to the patient, specialist, and primary care physician.

Anticoagulation

Patients taking anticoagulant medication require additional consideration by the physician. In some instances, temporarily taking the patient off medication may prove necessary to prevent internal bleeding during or after the CRC screening procedure. However, one must weigh the risks of thrombosis or cardiac stent occlusion with risks caused by discontinuing anticoagulation or antiplatelet therapy. These risks must be explained to the patient and his/her consent documented. Treating physicians have been found liable in a wrongful death suit where the patient was instructed to stop anticoagulant medication for what was concluded to be an excessive period of time.[18]

Sedation

The physician's duty to identify and manage medical circumstances that require special attention applies directly to issues concerning sedation. Physicians should identify prior sedation issues, a medical status that could complicate sedation (e.g., emphysema, cardiomyopathy, obstructive sleep apnea, use of home oxygen, or continuous positive airway pressure, CPAP) and medications that might render certain sedatives ineffective (chronic narcotics and anxiolytics). For patients with increased risk, physicians might elect to perform the procedure within a hospital setting and consider having an anesthesiologist administer sedation. Failure to document whether these issues were considered and managed in a generally acceptable manner could result in malpractice liability [36].

Genetic Risk

Certain high-risk genetic conditions give rise to a duty to warn patients and inform them of their need to warn family members of a possible inherited CRC risk. Physicians traditionally do not have a duty to third parties such as family members who have not established care with the physician. However, with regard to conditions such as a Lynch syndrome, hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis (FAP), courts have found physicians at fault for not documenting a clear explanation about the condition and the need for a patient to warn his/her relatives of a potential inherited risk [37, 38].

[18] Mitchell v. United States, 141 F3d 8; 49 (1st Cir 1998).

The most serious concern for the colonoscopist results from a failure to obtain and document sufficient family history for a reasonable provider to identify a familial risk. A plaintiff's attorney may argue the patient presented for CRC risk reduction (which includes both screening and management of future risk), not merely a single colonoscopy. Thus, when a genetic risk is not recognized and managed, this could be construed as negligence. An intake process for open access colonoscopy patients that will identify potential genetic risk may mitigate legal risk and help patients and their families make informed health decisions.

Open-Access Colonoscopy

Open access (OA) has become a well-established practice in gastroenterology, whereby a patient presents for the procedure having received instructions but not having had a pre-procedure clinic visit for an in-person discussion of the procedure. It fulfills multiple business[19] and medical goals, including patient convenience, cost reduction, facilitated access to screening, and increased ability to meet patient/provider requests.[20] It is, therefore, an important part of meeting public health goals in CRC screening. OA has been widely accepted and is considered to fall within the standard of care for gastroenterology [26, 39].

However, when relying on OA, physicians must use caution to avoid several potential problems inherent in this approach. These problems, many of which are noted in practice guidelines,[21] include mismatched patient/provider expectations, inadequate pre-procedure screening for indications and safety, vicarious liability, and lack of informed consent[22] or follow-up. In particular, patients too ill to safely undergo the procedure or those who require special attention as a result of anticoagulation or sedation issues, may present a problem for the proceduralist who is unaware of those issues or becomes aware only at the last moment. If a procedure is performed in cases where it would have been inadvisable, legal challenges may result. Pre-procedural screening (and effective communication between physicians) is therefore necessary to evaluate whether the patient is healthy enough to undergo the examination and whether any special precautions need to be addressed. Notably, the gastroenterologist performing the procedure could still be held liable if he/she failed to prevent an inappropriate examination, even if the referring physician failed to adequately supply the necessary information.

[19] OA is financially rewarding for practices.

[20] i.e., accomplishing screening colonoscopy in a single visit.

[21] See, e.g., ASGE Practice Guidelines on Open Access Endoscopy, available at http://www.asge.org/assets/0/71542/71544/04fc88121fec40b6b99883384beb5cf6.pdf.

[22] Informed consent is particularly important and the patient must be given sufficient time before the procedure to ask questions or inform the physician of additional concerns or complications the patient might have. The informed consent process as it relates to OA will be detailed in section c., infra.

Pre-procedure screenings must therefore be sufficient to prevent inappropriate examinations. They should include a sufficient medical history of advanced pulmonary or cardiac disease, allergies, medications (chronic narcotic and anxiolytics), and presence of internal devices that might complicate the procedure (e.g., automatic cardiac implantable defibrillators, pacemakers, cardiac stents, home oxygen, and continuous positive airway pressure machines). Appropriate decisions can be made during remote or telephone triage regarding the need for bridging anticoagulation or use of anesthesiologists, procedure performance in a hospital facility, or other deviations from normal procedure. Interestingly, despite the numerous complicated considerations providers must keep in mind, guidelines on the subject merely alert the physician of the desirability for obtaining sufficient information without detailing what that information entails.

Use of Financial Incentives to Promote Quality Measures and Benchmarks

As discussed in Section II, quality measures may be used in colonoscopy to reduce the risk of missed or delayed CRC diagnosis and minimize procedural complications. One way to encourage physicians to meet quality measures and benchmarks is to institute a pay-for-performance program. Under such a program, physicians' salaries are increased or decreased based on meeting or failing to meet specified quality measures. Many hospitals in the USA and in other countries have begun to institute pay-for-performance programs based on a variety of quality measures (see [40–42]), including gastroenterology measures. For example, Gastrointestinal Associates in Knoxville, Tennessee has implemented a pay-for-performance program, which uses two different benchmarks to measure physician performance: 10-year follow-up for an average risk patient with a normal screening colonoscopy, and five-year follow-up for non-high-risk patients with fewer than three adenomas [43]. Studies of the effectiveness of pay-for-performance programs have yielded mixed results, but generally suggest that well-designed incentive programs can successfully drive quality improvement [44, 45].

Although pay-for-performance programs provide a promising method for improving quality of care, hospitals and providers should take steps to avoid possible unintended side effects of these programs. Such side effects include distortion of physician effort to meet quality measures, risk to physicians' job security and professional reputation, and the rise of malpractice actions based on misuse of quality measures.

One major side effect of tying financial incentives to quality measures is distortion of physicians' efforts to meet the quality measures. Participating physicians may focus only on the measures of quality tied to the financial incentive, ignoring the aspects of quality care not included in the pay-for-performance program (see [40]). Additionally, physicians may attempt to maximize measured results by refusing to treat less healthy or less compliant patients (see [40]). To avoid this problem,

the ACG recommends adopting quality measures which account for disease severity and demographic bias [46].

Pay-for-performance programs may also unintentionally harm participating physicians, if physicians are discharged due to failure to meet quality indicators. The goal of pay-for-performance programs is to improve care and not eliminate providers. But, because hospitals will be retaining explicit and possibly accessible data on the quality of their physicians, they may face increased malpractice liability exposure for credentialing underperforming physicians [47]. As a result, hospitals may preemptively terminate physicians who do not meet the quality measures in the pay-for-performance program [47]. Thus, even if a physician meets 11 out of 12 nationally proposed quality indicators, but the hospital administration picked only 2 for the pay-for-performance program, one of which the physician did not meet, the physician may still be terminated. Because of this risk to participating physicians, physician contracts should provide for a hearing process to challenge the results of performance evaluation and termination decisions [25].

Another risk of instituting pay-for-performance is that the misuse of quality measures tied to economic incentives may endanger patient safety and expose participating physicians and hospitals to malpractice liability. Hospitals must exercise care to avoid setting and incentivizing physicians to meet inappropriate quality measures. The ACG recommends that measures be rapidly responsive to changes in clinical guidelines so that payment policies do not promote outmoded standards of care [46].

Case Study: Misuse of Quality Measures Tied to Economic Incentives

A hospital's administration wishes to promote a quality measure and proposes tying compensation to achieving a high cecal intubation rate of 99%. The administration would like to increase salary by 5% for those gastroenterologists who meet this quality measure. What are the potential liability problems for the administration if it implements this plan?

To begin with, cecal intubation rate is an appropriate quality target for colonoscopy. However, the rate of 99% is out of line with national and expert suggestions. Published literature suggests that lower rates are appropriate for cecal intubation quality measures—about 94–95% [48, 49]. This is because attempting to reach the cecum is not always appropriate. Some colons have anatomic issues such as diverticular narrowing which increase the risk of perforation from efforts to achieve cecal intubation.

Setting the cecal intubation measure inappropriately high and tying that measure to an economic incentive poses a risk of harm to patients and exposes physicians and the hospital to liability. If there is an incentive to achieve a 99% cecal intubation rate, providers may be tempted to push excessively to reach the cecum in every case, assuming that it is appropriate and trying to avoid being found deficient for the salary augmentation. This could lead to

perforation in difficult colonoscopies where the gastroenterologist should not attempt to achieve cecal intubation. From a liability standpoint, if a diagnostic perforation colonoscopy were to occur and lead to a malpractice action, the hospital's creation of a financial incentive to push to cecum at an arguably inappropriate target rate puts both the performing gastroenterologist and the hospital at an increased risk of liability.

Risk Management Programs

A risk management program can be developed to mitigate legal risk in colonoscopy given some of the quality issues discussed. A risk management program is intended to mitigate legal risk through prevention and implementation of proactive strategies. These programs involve estimation of actual risk by analysis of malpractice data so that a risk reduction strategy can be developed based on empirical data. Exact data are frequently difficult to find, so physicians should understand the concept of reasonable risk, based on legal theory. For instance, realizing that physicians have a duty to warn patients and families with high genetic risk of CRC will lead risk management programs to develop policies to ensure appropriate patient warnings.[23] Such programs endeavor to clarify areas where legal risk occurs and introduce strategies to anticipate and manage risk without contributing unduly to costly defensive medicine [50].

Elements of a risk management program in the area of CRC screening may include [26]: (1) a codified peer- review process, which may include reviews of complications, cecal intubation rates, polyp or adenoma detection rates, colon withdrawal times, and sentinel events; (2) unit reviews, with monitoring of infection control steps, adequacy of clinical triage for OA, and adequacy of reminder systems and results notification with documented follow-up recommendations;[24] (3) use of guidelines and plans surrounding anticoagulation and sedation risks, adequacy of colon preparations, and discharge instructions; and (4) documentation of practices (i.e., a written policy for responding to post-procedure patient concerns or complications) and documentation of physician practice (such as sedation recovery) [51].

Certain information, such as complication rates and discussions, should be identified as covered within a formal peer-review process, so that mandatory disclosure is limited. However, groups may choose to make some practice (or even physician-level data) public to highlight their concern and openness regarding quality issues. Unless discoverable data show persistently uncorrected substandard performance, openness should not put the physician at increased liability risk. Indeed, it may reflect self-confidence, concern for quality, and acceptable quality performance.

[23] Safer v. Pack, 677 A2d 1188, cert. Den'd, 683 A2d1163 (New Jersey 1996).

[24] (see the article by Greenwood elsewhere in this issue).

Another important aspect of a quality improvement program is the use of methods to update both physician and unit reviews as new information becomes available. Patient registries have become a useful and important epidemiologic tool for learning about quality issues, especially those requiring large sample sizes. Many contain de-identified data. The legal risk of contributing to a registry is low if the registry has acceptable processes for de-identifying critical patient information and is compliant with the 1996 Health Insurance Portability and Accountability Act (HIPAA). Information needed for malpractice discovery would be obtained by disclosure requests made directly to the gastroenterologist's office and not to a formal registry.

Summary

The use of quality improvement tools such as clinical practice guidelines and quality measures can improve patients' clinical outcomes and reduce the incidence of adverse events. In addition to improving patient care, properly structured quality improvement policies can also reduce physician liability for two reasons. First, if fewer patients experience harm, fewer cases will result in litigation. Second, if a physician is sued for malpractice, proof that the physician complied with a guideline or quality measure will help prove lack of fault for a negative outcome.

However, guidelines and quality measures are double-edged swords. As quality measures and guidelines become established, courts increasingly adopt them as de facto standards of care. In this situation, physician noncompliance with the quality measures and guidelines may lead to malpractice liability. Given the increasing court reliance on quality measures and the public attention to the improvement of quality in healthcare, it will not be possible to ignore quality measures. Trends toward transparency will also likely mean access to, and therefore utilization of, quality measures by insurance companies, the federal government, and competing medical institutions.

The careful gastroenterologist will need to keep up with quality measures both to provide good patient care and to manage malpractice risk—particularly in the highly litigated areas of informed consent, CRC screening technique, and test results notification and follow-up. Ideally, these efforts should be codified into a risk management program which is structured to obtain peer-review protections for individual quality measurement data. In addition, medical practices and hospitals should adopt policies encouraging gastroenterologist compliance with guidelines, quality measures, benchmarks, and other potential standards of care. In doing so, hospitals and medical practices must be careful to avoid misusing financial incentives to encourage physicians to meet quality measures, which could risk patient safety and expose both the hospital and its physicians to liability.

References

1. Feld AD, Moses RE. Most doctors win: what to do if sued for malpractice. Am J Gastroenterol. 2009;6:1346–51.
2. Moses RE, Feld AD. Legal risks of clinical practice guidelines. Am J Gastroenterol. 2008;103:7–11.
3. Gerstnberger PD, Plumeri PL. Malpractice claims in gastrointestinal endoscopy: analysis of an insurance industry database. Gastrointest Endosc. 1993;39:132–8.
4. American College of Gastroenterology. Diagnosis, treatment, and surveillance for patients with colorectal polyps. Am J Gastroenterol. 2000;95:3053–63. http://gi.org/guideline/diagnosis-treatment-and-surveillance-for-patients-with-colorectal-polyps/.
5. Finder JM. The future of practice guidelines: should they constitute conclusive evidence of the standard of care? Health Matrix. 2000;10:67–77.
6. Kozlick D. Clinical practice guidelines and the legal standard of care: warnings, predictions, and interdisciplinary encounters. Health Law J. 2011;19:125–133.
7. Shekelle PG, et al. Validity of the agency for healthcare research and quality clinical practice guidelines: how quickly do guidelines become outdated? J Am Med Assoc. 2001;286:1461. (finding that three quarters of the reviewed guidelines needed updating, and after 5.8 years 50% of the guidelines were out of date).
8. Sniderman AD, Furberg CD. Why guideline-making requires reform. J Am Med Assoc. 2009;301:429. (noting that as of 2009 the National Guidelines Clearinghouse had registered 2373 guidelines produced by 285 different organizations).
9. Furrow BR, et al. Health Law. 1995;6–2:361–2.
10. Rosoff AJ. Evidence-based medicine and the law: the courts confront clinical practice guidelines. J Health Polit Policy Law. 2001;26:327–38.
11. Mello MM. Of swords and shields: the role of clinical practice guidelines in medical malpractice litigation. Univ Pa Law Rev. 2001;149(3):645, 665. (“many courts have gone so far as to recognize CPGs offered by the plaintiff as establishing a rebuttable presumption of the standard of care.”).
12. Agency for Healthcare Research and Quality (AHRQ). Variety of measures in national quality measures clearing house. http://www.qualitymeasures.ahrq.gov/tutorial/varieties.aspx. Accessed 26 Sept 2014.
13. Brotman M, Allen JI, Bickston SJ, et al. AGA task force on quality in practice: a national overview and implications for GI practice. Gastroenterology. 2005;129(1):361–9.
14. Rex DK, Bond JA, Winawer S, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations for the US multisystem task force on colorectal cancer. Am J Gastroenterol. 2002;97:1296–308.
15. Lieberman DA, Nadel M, Smith RA, et al. Standardized colonoscopy reporting and data system report of the quality assurance task group on the national colorectal cancer round table. Gastrointest Endosc. 2007;65:757–66.
16. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human: building a safer health system. Washington, DC: National Academy Press; 2000.
17. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2000.
18. Miller LK. Protecting and preserving the peer review privilege: solutions for corporate counsel representing hospitals. Health care corporations, and health care providers, DRI defense library series. 2008. (citing *Pardo v. Gen. Hosp. Corp.*, 841 N.E.2d 692 (Mass. 2006)).
19. Feld AD. Informed consent for colonoscopy. In: Waye J, Rex DK, Williams CB, editors. Colonoscopy: principles and practice. Malden: Blackwell Publishing; 2009. p. 79–89.
20. Berg JW, Appelbaum PS, Lidz CW, et al. Informed consent: legal theory and clinical practice. 2nd ed. Oxford: Oxford University Press; 2001.
21. Gatter R. Informed consent law and the forgotten duty of physician inquiry. Loyola Univ Chic Law J 2000;31:557.

22. Davenport J, Lippman H. Sued for misdiagnosis? It could happen to you. J Fam Pract. 2010;59(9):498–508.
23. Gandhi TK, et al. Missed and delayed diagnoses in the ambulatory setting. Ann Intern Med. 2006;145(7):488–96. (In a review of 181 closed malpractice claims for missed or delayed diagnosis, the authors found an average of three contributing errors in each case).
24. Mello MM, Studdert DM. Deconstructing negligence: the role of individual and system factors in causing medical injuries. Georgetown Law J. 2008;96:599–623. (In a review of 889 malpractice cases, not limited to claims for missed and delayed diagnosis, the authors found an average of 3.14 contributing errors in each case).
25. Wahls TL, Peleg I. Patient and system-related barriers for the earlier diagnosis of colorectal cancer. BMC Fam Pract 2009;10:65. http://www.biomedcentral.com/1471-2296/10/65.
26. Feld KA, Feld AD. Risk management and legal issues for colonoscopy. Gastrointest Endosc Clin N Am. 2010;20(4):595–6.
27. Rex DK, Bond JH, Feld AD. Medical legal risks of incident cancers after clearing colonoscopy. Am J Gastroenterol. 2001;96(4):952–7.
28. Schoen C, et al. Primary care and health system performance: adults' experiences in five countries. Health Aff. 2004. (A survey of patients in five countries found that 9 to 15% of adults treated as outpatients received incorrect results or delayed notification of abnormal results).
29. Wahls TL, Peleg I. Patient and system-related barriers for the earlier diagnosis of colorectal cancer. BMC Fam Pract. 2009;10:65. http://www.biomedcentral.com/1471-2296/10/65.
30. Boohaker EA, et al. Patient notification and follow-up of abnormal test results: a physician survey. Arch Intern Med. 1996;156:327–9.
31. Potchen EJ, et al. Mammography and malpractice. Am J Roentgenol. 1991;156:475–80.
32. Berlin L. Malpractice and radiologists. Am J Roentgenol. 1980;135:587–91.
33. Gallegos A. Medical liability: missed follow-ups a potent trigger of Lawsuits. Am Med News. 2013.
34. Giblin EB, Christina MS. Does patient responsibility still exist? AAOS Now 2012. (The authors discuss a 2010 committee opinion of the American College of Gynecology stating that all physicians have a duty to inform patients of the importance of returning for follow-up. The authors state that all physicians must comply with this opinion to avoid malpractice liability, because plaintiffs' lawyers are likely to point to the opinion as evidence of physicians' standard of care).
35. Howard ML. What to do until the lawyers arrive. In: Professional liability handbook. American Academy of Otolaryngology—Head and Neck Surgery; 2001. http://www.entnet.org/practice/upload/professional-liability-handbook.pdf.
36. Cohen LB, DeLegge M, Aisenberg J, et al. AGA institute review of endoscopic sedation. Gastroenterology 2007;133:675–701.
37. Feld AD. Medicolegal implications of colon cancer screening. Gastrointest Endosc Clin N Am. 2002;12(1):171–9.
38. Feld AD. Malpractice risks associated with colon cancer and inflammatory bowel disease. Am J Gastroenterol. 2004;9:1641–4.
39. Mahajan RJ, Marshall JB. Prevalence of open access gastrointestinal endoscopy in the United States. Gastrointest Endosc. 1997;46:21–6. (According to the survey, approximately 60% of respondents use some form of Open Access in their practice).
40. Custers T, et al. Selecting effective incentive structures in healthcare: a decision framework to support healthcare purchasers in finding the right incentives to drive performance. BMC Health Serv Res. 2008;8:66.
41. Rosenthal MB, et al. Paying for quality: providers' incentives for quality improvement. Health Aff. 2004;23:127–41.
42. Baker G, Carter B. Provider pay-for-performance incentive programs: 2004 national study results. San Francisco: Med-Vantage; 2005.
43. Monica J. Smith. Higher reimbursement an added bonus of quality benchmarking program. Gastroenterol Endosc News. 2013;64:8.

44. Li J, et al. Physician response to pay-for-performance: evidence from a natural experiment. National Bureau of Economic Research (NBER) working paper no. 16909; 2011.
45. Lindenauer PK, et al. Public reporting and pay for performance in hospital quality improvement. New Eng J Med. 2007;356(5):486. (In a study of hospitals instituting pay-for-performance, the researchers found that physicians at those hospitals did in fact perform better on a variety of individual and composite quality measures than physicians at non-pay-for-performance hospitals).
46. Johnson DA. Pay for performance: ACG guide for physicians. Am J Gastroenterol. 2007;102(10):2119–20.
47. Cook SL. Will pay-for-performance be worth the price to medical providers? A look at pay-for-performance and its legal implications for providers. Ann Health Law 2007;16:163–80.
48. Deas T, Pike I. Benchmarking to excellence: using quality indicators to improve performance. Endoeconomics. 2010;19:19–20. (using QIQuIC data to suggest a target rate of 94 % for cecal intubation).
49. Petrini J, et al. Quality indicators for colonoscopy. Gastrointest Endosc. 2006;63(4):16–21. (suggesting a target cecal intubation rate of 95 % for CRC screenings in healthy adults, and a 90 % cecal intubation rate for all colonscopy).
50. Pengalis SE, Wachsman HF. American law of medical malpractice. 2nd ed. 1992. p. 49.
51. Petrini DA, Petrini JL. Risk assessment and management for endoscopists in an ambulatory surgery center. Gastrointest Endosc Clin N Am. 2006;16:801–15. (Additional factors include: processes for consent, disclosure, and decision making; and methods to obtain family history and manage high-risk conditions).

Chapter 13
Areas for Future Research

Douglas K. Rex and Ashish K. Tiwari

Introduction

Quality in the technical performance of colonoscopy has dominated the medical literature recently published in colonoscopy. The interest in quality in colonoscopy constitutes a revolution that has developed relatively quickly, as evidence of variable performance of colonoscopy did not begin to appear until the mid-1990s [1], and the first recommendation to measure the adenoma detection rate (ADR) in clinical practice was published only 13 years ago [2]. Operator dependence in colonoscopy performance has been shown for adenoma detection [3–6], detection of serrated lesions in the proximal colon [7, 8], prevention of colorectal cancer among gastroenterologists [7, 8], prevention of colorectal cancer between specialties [9–13], interpretation of bowel preparation quality [14], effectiveness of polypectomy [15], and use of recommended screening and surveillance intervals [16–18]. There is considerable evidence that colonoscopy prevents most cancers and deaths from cancer resulting from left-sided colorectal cancer [19, 20], and a substantial proportion of cancers and deaths from right-sided cancer [13, 21, 22], but protection can be improved by skill in cecal intubation [10], and lesion detection and resection [23]. The goal of improved the quality movement is to maximize the impact of colonoscopy on colorectal cancer prevention by minimizing operator dependence. The basic premise is that every patient deserves to undergo colonoscopy with an

Disclaimer: This report was funded by a gift from Scott and Kay Shurz of Bloomington, IN.

D. K. Rex (✉)
Department of Gastroenterology/Hepatology, Indiana School of Medicine,
IU Hospital, 4100 550 N. University Boulevard, Indianapolis, IN 46202, USA
e-mail: drex@iu.edu

A. K. Tiwari
Department of Internal Medicine, Michigan State University (MSU),
East Lansing, MI 48824, USA

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5_13

adequate bowel preparation, and by an endoscopist committed to a careful examination, and by an endoscopist who is fully trained in recognizing the complete spectrum of precancerous lesions in the colorectum. To achieve this goal, an enormous amount of work must yet be done.

Training

There is likely no aspect of quality improvement in colonoscopy with more opportunities for research than training. A principal area of need is the development of lesion recognition training tools [24]. A logical approach would begin with an atlas of still photographs demonstrating conventional adenomas in each morphology of the Paris classification [25] (pedunculated, sessile, flat, and depressed) as well as the typical appearances of each of the serrated lesions (sessile serrated polyp, hyperplastic polyp, and traditional serrated adenoma). Still photography would be followed by video segments, and then creation of video test segments. The test segments would require creation of colonoscopy video segments in which lesions are detected by an expert operator, but ignored during a first pass through a colon segment or the entire colon, and then the expert would reintubate the colon to remove the lesion. The segments in which polyps were ignored could then be used to test trainees. Such a tool could be used to evaluate gastroenterology trainees, trainees performing colonoscopy in other subspecialties, and practicing colonoscopists.

Since achievement of an adequate ADR is now an expectation for endoscopists performing colonoscopy in clinical practice [2, 26], it seems reasonable to require trainees to demonstrate adequate ADR prior to certification. Assessment of adenoma miss rates by gastroenterology trainees through use of a tandem design has been reported [27], but this approach would be too time consuming for widespread use in academic training programs. Simple measurement of the ADR by the trainees is complicated because adenoma detection reflects both the technical handling of the colonoscope and the lesion recognition skills of the trainees and their attending physician. Alternative approaches would include assessment of video recordings of colonoscopy withdrawals by trainees, or real-time assessment of numbers of inadequately exposed proximal sides of haustral folds, and enumeration of lesions exposed on the monitor but not recognized by the trainees. Observational studies could establish acceptable rates of deviation from high quality withdrawal, and endoscopically exposed, but not recognized lesions for a trainee examination during observation by an attending expert with a proven high-level ADR.

Much of the range of quality recommendations in colonoscopy [2, 26] could be subject to this type of investigation for the trainees. However, probable priorities for investigation should be assessment of bowel preparation quality, lesion detection, polypectomy technique, and use of appropriate screening and surveillance intervals [24]. Cecal intubation is a primary goal of colonoscopy, and improvements in cecal intubation technique have been the major focus of colonoscopy simulators [28], but the impact of simulators has been primarily to improve rates of cecal intubation

very early in the training process [29]. Without the use of simulators, most gastroenterology trainees develop high cecal intubation rates well before completion of their fellowships. Simulators may have their greatest role in training colonoscopists in specialties where volumes of colonoscopy are considerably lower during training. In clinical gastroenterology practice, low cecal intubation does not seem to be the main problem in cancer prevention, although there are almost certainly individual exceptions to this rule among gastroenterologists. Low cecal intubation may constitute a major deficit in colonoscopy performance for other specialties [10].

Measurements of Mucosal Inspection Quality

The ADR, originally proposed by the US Multi-Society Task Force in 2002 [2], and refined by a combined task force of the American College of Gastroenterology/American Society for Gastrointestinal Endoscopy in 2006 [26], is currently defined as the percentage of patients age 50 and older with one or more conventional adenomas documented by endoscopic resection. The targets are at least 30% in men and 20% in women.

When it was first created, the ADR was one of several potential measures of the quality of mucosal inspection, but it appeared to be the one with the best data available to create credible targets [2], and the least likely to be corrupted in clinical practice by gaming behaviors. However, the ADR is imperfect as a quality measure [30]. The biggest practical problem with ADR is that pathology databases and endoscopy databases are typically not linked in a matter that allows automatic or electronic calculation of the ADR. Therefore, endoscopists typically must have information from the pathology report entered manually into an endoscopy database. Future research could make a major contribution to quality by the design of software applications that make this process automatic. Second, the ADR is itself subject to gaming through the process of "one and done" [24, 30]. Thus, the ADR gets equal credit for the detection of a patient with one adenoma compared to a patient with multiple adenomas detected. This phenomenon of "one and done," in which a single adenoma is detected and then subsequent lesions are less likely to be removed, has actually been observed in clinical practice [31]. However, "one and done" is most likely the result of our current reimbursement system, which pays essentially the same amount whether one or multiple polyps are removed during colonoscopy and largely regardless of the complexity of polypectomy. Nevertheless, the one and done phenomenon suggests that a better measure of mucosal inspection quality would be adenomas per colonoscopy (APC). An important area for future research is to define what rate of APC corresponds to various levels of ADR, since much more information is available in the medical literature on ADR than is available for APC. In addition, recent studies with large numbers of observed interval cancers have refined the association between ADR and the risk of interval cancer. An initial Polish screening colonoscopy study found that the original thresholds suggested in 2002 by the US Multi-Society Task Force produce a well-defined sepa-

ration between doctors whose patients were at increased risk of developing colorectal cancer [23]. However, there were few patients of doctors with ADR above 20% who developed colorectal cancer. A more recent study with a much larger number of interval cancers showed continued improvement in prevention of colorectal cancer up to an ADR of 32% [32]. At this time, it is unknown what APCs are associated with interval cancer, and this should become a focus of future research. The major obstacle currently delaying the transition from ADR to APC is insufficient information about optimum targets for APC.

An ongoing controversy is whether an alternative to adenoma detection should be utilized. An optimal approach would be to directly measure the outcome of interval cancer rates for individual endoscopists. For example, an acceptable rate of interval cancer development after adenoma resection might be 1/150 colonoscopies [33]. Problems with this approach are numerous. First, the actual optimal thresholds are unknown. Second, accurate observation of the event in question would require state or national registries or a systematic follow-up by endoscopy centers to identify the events, which might occur years after the colonoscopy in question. Next, large numbers of patients would have to be observed, in order for the confidence interval around the measurement to be sufficiently narrow. Next, there would have to be adjustments for endoscopists with patient populations that have disproportionately increased risk, such as patient populations with Lynch syndrome, where lesions are more likely to be flat [34] and therefore missed, and also more likely to progress when missed [35]. Patients with serrated polyposis [36], and even a patient population that is disproportionately elderly [36, 37], would have higher progression rates to cancer. Finally, waiting for accurate measurement of an interval cancer rate could require years of observation, whereas use of a more easily measured surrogate, such as the ADR or APC, could allow identification of a low-level performer much sooner.

The most commonly discussed alternative to ADR is the polyp detection rate (PDR), measurement of which does not carry the difficulty of manually entering pathology data. Unfortunately, all available data on PDR are retrospective [38–40]. Because it seems highly subject to gaming, prospective studies of PDR would be needed to establish its appropriateness as a substitute for ADR.

Another important area for clarification is whether a serrated lesion detection rate is needed [41]. Serrated lesions are subject to more variability in detection than conventional adenomas [7, 8]. Serrated lesions contribute disproportionately to the occurrence of interval cancers [42]. Additional study must clarify whether the ADR and the proximal colon serrated lesion detection are correlated, as thus far this issue has had mixed results. At least two obstacles will make utilization of a serrated lesion detection rate quite problematic. First, there is poor interobserver variation (this word stays in the sentence in the distinction between sessile serrated polyp from hyperplastic polyp histologically [42]. Thus, an initial serrated detection target, which was recently proposed at a level of 5% for the colon proximal to the sigmoid [41], would likely have to include both sessile serrated polyps and hyperplastic polyps. Prospectively, the need to confine the detection target to

lesions proximal to the sigmoid colon, in order to avoid incentivizing resection of rectosigmoid hyperplastic polyps, will inevitably lead to gaming by removing hyperplastic lesions from the sigmoid and calling them proximal colon when the targets are applied prospectively.

Other reports have discussed the problems associated with other potential targets that appear to be better surrogates for cancer detection and prevention than is overall adenoma detection, such as detection of advanced conventional adenomas (adenomas with villous elements, high-grade dysplasia, or size >1 cm). The problems with actual accurate measurement of these targets are substantial and likely currently insurmountable [24, 30]. Finally, future research should develop schemes for photographic documentation of the ADR and the rates of APC. One downside of the use of APC versus ADR is that it might incentivize placement of each individual polyp in a separate pathology bottle in order to improve documentation of APC, but a practice that would be associated with increased pathology costs. An alternative form of documentation would be a separate photograph of each polyp, which would then become the record of its histology. The photograph would enable the endoscopist to document the basis for shorter surveillance intervals in patients with multiple polyps, without increasing the number of bottles and pathology costs. The ability to store images of the same quality seen during real-time imaging will be essential to the successful development of a resect and discard policy [43].

Correction of Low-Level Detection

Elements of the problem of correcting low-level detection overlap with issues related to training. Tools developed for training might reasonably be employed and tested for their ability to correct low-level detection. In general, the issue of correcting low-level detectors is akin to the general problem of reducing operator dependence. Although reductions in operator dependence are applicable to several issues in colonoscopy, they are probably of greatest importance to issues in detection.

Corley has reviewed in detail efforts to improve adenoma detection [44]. The simple institution of a quality improvement process in which report cards are given to physicians regarding their performance has achieved mixed results [6, 45]. Two studies produced consistent and across-the-board improvements in ADR within a group of gastroenterologists. One of these employed an educational session combined with institution of a timer set to produce a total of 8 min withdrawal, but sounding withdrawal every 2 min at 2 min intervals, with a goal of having examined about a quarter of the colon in each 2 min [6]. A second study used an educational program focused on lesion recognition and withdrawal technique [45]. Effective methods of handling low-level detection must be greatly expanded, systematized, and made widely available to practicing endoscopists.

Polypectomy Technique

In the past years, polypectomy technique was performed in an almost exclusively anecdotal fashion, in which endoscopists tended to use techniques they had learned during training. In recent years, we have finally entered an era of evidence-based polypectomy practice, in which an increasing number of randomized controlled trials have been completed [46–51]. These randomized controlled trials have produced numerous conclusions that can guide practice (Table 13.1). Additional aspects of polypectomy should be subjected to randomized controlled trials ([52]; Table 13.2). These trials will be critical in establishing which polypectomy techniques constitute best practice. In addition, teaching tools will need to be developed that will allow safe dissemination of new techniques, as well as old techniques that have not been employed by practicing endoscopists, and which will be easy for endoscopists to access, study, demonstrate knowledge of, and implement in clinical practice.

Table 13.1 Evidence regarding polypectomy from randomized controlled trials

Detachable snares reduce immediate and delayed bleeding from pedunculated polyps
Epinephrine injection reduces immediate bleeding from pedunculated and sessile polyps
Cold snaring effective and more efficient than hot snaring for small polyps
Hydroxyethyl starch more effective and efficient submucosal injection fluid than saline
D50 associated with increased risk of post-polypectomy syndrome
Cold snaring more efficient and effective than cold forceps for diminutive polyps
Jumbo forceps more effective and efficient than standard forceps for tiny polyps

Table 13.2 Unanswered questions about colonoscopic polypectomy technique: potential targets for controlled investigation. (Modified from Ref. [52]. With permission from Elsevier)

What is the best methodology for testing completeness of polypectomy at the time of resection?
Are the long-term outcomes of ESD and EMR different?
Which electrocoagulation current (e.g., coagulation, blended, microprocessor controlled alternating coagulation/cutting current) is best with regard to safety and effectiveness?
Can clip closure of large EMR defects reduce the risk of delayed complications?
Can cold snaring be effectively applied in piecemeal fashion to any set of polyps?
At what polyp size/shape/histology is electrocautery needed to optimize polypectomy outcomes?
What are the best methods for defining the edges of serrated lesions prior to polypectomy? What are the best techniques for effective resection of serrated lesions? What is the optimal margin of normal tissue to ensure eradication of serrated lesions?
What is the value of ancillary imaging techniques (e.g., dye spraying, magnification, electronic chromoendoscopy)?
Can technical measures such as specialty snares or cap-fitted colonoscopy reduce or eliminate the need for ablative techniques?
Is it still helpful to systematically apply argon plasma coagulation to EMR defects with clear margins as assessed with high definition and ancillary imaging?

EMR endoscopic mucosal resection, *ESD* endoscopic submucosal dissection

Conclusion

The effort to understand and improve quality in colonoscopy is still in its infancy. High-quality evidence to support many routine and investigational practices during colonoscopy and polypectomy is lacking. Many colonoscopy and polypectomy practices were established through anecdotal experience and expert consensus, and warrant controlled investigation. Quality targets must be refined and modified to link them to optimal outcomes. There are many opportunities available to clinical investigators interested in improving and refining quality processes in colonoscopy.

References

1. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterol. 1997;112:24–8.
2. Rex DK, Bond JH, Winawer S, et al. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. multi-society task force on colorectal cancer. Am J Gastroenterol. 2002;97:1296–308.
3. Barclay RL, Vicari JJ, Doughty AS, et al. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med. 2006;355:2533–41.
4. Chen SC, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. Am J Gastroenterol. 2007;102:856–61.
5. Imperiale TF, Glowinski EA, Juliar BE, et al. Variation in polyp detection rates at screening colonoscopy. Gastrointest Endosc. 2009;69:1288–95.
6. Shaukat A, Oancea C, Bond JH, et al. Variation in detection of adenomas and polyps by colonoscopy and change over time with a performance improvement program. Clin Gastroenterol Hepatol. 2009;7:1335–40.
7. Hetzel J, Huang CS, Coukos JA, Omstead K, Cerda SR, Yang S, O'Brien MJ, Farraye FA. Variation in the detection of serrated polyps in an average risk colorectal cancer screening cohort. Am J Gastroenterol. 2010;105:2656–64.
8. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. Clin Gastroenterol Hepatol. 2011;9:42–6.
9. Rex DK, Rahmani EY, Haseman JH, et al. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterol. 1997;112:17–23.
10. Baxter N, Sutradhar R, Forbes DD, Paszat LF, Saskin R, Rabeneck L. Analysis of administrative data finds endoscopist quality measures asociated with post-colonoscopy colorectal cancer. Gastroenterol. 2011;140:65–72.
11. Singh H, Nugent Z, Mahmud SM, et al. Predictors of colorectal cancer after negative colonoscopy: a population-based study. Am J Gastroenterol. 2010;105:663–73.
12. Rabeneck L, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. Clin Gastroenterol Hepatol. 2010;8:275–9.
13. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. J Clin Oncol. 2012;30:2664–9.
14. Mahadev S, Green PH, Lebwohl B. Rates of suboptimal preparation differ markedly between providers; impact on adenoma detection rates. Gastrointest Endosc. 2013;77:AB510–11.
15. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy—results of the Complete Adenoma Resection (CARE) study. Gastroenterol. 2013;144:74–80.
16. Mysliwiec PA, Brown ML, Klabunde CN, et al. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. Ann Intern Med. 2004;141:264–71.

17. Saini SD, Nayak RS, Kuhn L, et al. Why don't gastroenterologists follow colon polyp surveillance guidelines? Results of a national survey. J Clin Gastroenterol. 2009;43:554–8.
18. Schoen RE, Pinsky PF, Weissfeld JL, et al. Utilization of surveillance colonoscopy in community practice. Gastroenterol. 2010;138:73–81.
19. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009;150:1–8.
20. Singh H, Nugent Z, Demers AA, et al. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. Gastroenterol. 2010;139:1128–37.
21. Brenner H, Chang-Claude J, Seiler CM, et al. Does a negative screening colonoscopy ever need to be repeated? Gut. 2006;55:1145–50.
22. Brenner H, Chang-Claude J, Seiler CM, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med. 2011;154:22–30.
23. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. N Engl J Med. 2010;362:1795–803.
24. Hewett DG, Rex DK. Improving colonoscopy quality through health-care payment reform. Am J Gastroenterol. 2010;105:1925–33.
25. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: Gastrointest Endosc. 2003;58:S3–43.
26. Rex DK, Schoenfeld, PS, Cohon, J. et al. Quality indicators for colonoscopy. Gastrointest Endosc. 2015;81:31–53.
27. Munroe CA, Lee P, Copland A, et al. A tandem colonoscopy study of adenoma miss rates during endoscopic training: a venture into uncharted territory. Gastrointest Endosc. 2012;75:561–7.
28. Hill A, Horswill MS, Plooy AM, et al. Assessing the realism of colonoscopy simulation: the development of an instrument and systematic comparison of 4 simulators. Gastrointest Endosc. 2012;75:631–40.
29. Cohen J, Cohen SA, Vora KC, et al. Multicenter, randomized, controlled trial of virtual-reality simulator training in acquisition of competency in colonoscopy. Gastrointest Endosc. 2006;64:361–8.
30. Rex DK, Hewett DG, Snover DC. Detection targets for colonoscopy: from variable detection to validation. Am J Gastroenterol. 2010;105:2665–9.
31. Wang HS, Pisegna J, Modi R, et al. Adenoma detection rate is necessary but insufficient for distinguishing high versus low endoscopist performance. Gastrointest Endosc. 2013;77:71–8.
32. Corley DA, Marks AR, Zhao W, Lee JK, Quesenberry C, et al. Physician adenoma detection rate variability and subsequent colorectal cancer risk following a negative colonoscopy. Gastroenterol. 2013;144:S2–3.
33. Robertson DJ, Lieberman DA, Winawer SJ, et al. Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. Gut. 2014;63(6):949–56.
34. Rondagh EJ, Gulikers S, Gomez-Garcia EB, et al. Nonpolypoid colorectal neoplasms: a challenge in endoscopic surveillance of patients with Lynch syndrome. Endoscopy. 2013;45:257–64.
35. Edelstein DL, Axilbund J, Baxter M, et al. Rapid development of colorectal neoplasia in patients with lynch syndrome. Clin Gastroenterol Hepatol. 2011;9:340–3.
36. Rex DK, Ahnen DJ, Baron JA, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012;107:1315–29.
37. Brenner H, Hoffmeister M, Stegmaier C, et al. Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies. Gut. 2007;56:1585–9.
38. Chen SC, Rex DK. Variable detection of nonadenomatous polyps by individual endoscopists at colonoscopy and correlation with adenoma detection. J Clin Gastroenterol. 2008;42:704–7.
39. Francis DL, Rodriguez-Correa DT, Buchner A, et al. Application of a conversion factor to estimate the adenoma detection rate from the polyp detection rate. Gastrointest Endosc. 2011;73:493–7.

40. Williams JE, Holub JL, Faigel DO. Polypectomy rate is a valid quality measure for colonoscopy: results from a national endoscopy database. Gastrointest Endosc. 2012;75:576–82.
41. Kahi CJ, Li X, Eckert GJ, et al. High colonoscopic prevalence of proximal colon serrated polyps in average-risk men and women. Gastrointest Endosc. 2012;75:515–20.
42. Khalid O, Radaideh S, Cummings OW, et al. Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. World J Gastroenterol. 2009;15:3767–70.
43. Rex DK, Kahi C, O'Brien M, et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc. 2011;73:419–22.
44. Corley DA, Jensen CD, Marks AR. Can we improve adenoma detection rates? A systematic review of intervention studies. Gastrointest Endosc. 2011;74:656–65.
45. Kahi CJ, Ballard D, Shah AS, et al. Impact of a quarterly report card on colonoscopy quality measures. Gastrointest Endosc. 2013;77:925–31.
46. Paspatis GA, Tribonias G, Konstantinidis K, et al. A prospective randomized comparison of cold vs hot snare polypectomy in the occurrence of postpolypectomy bleeding in small colonic polyps. Colorectal Dis. 2011;13:e345–8.
47. Ichise Y, Horiuchi A, Nakayama Y, et al. Prospective randomized comparison of cold snare polypectomy and conventional polypectomy for small colorectal polyps. Digestion. 2011;84:78–81.
48. Draganov PV, Chang MN, Alkhasawneh A, et al. Randomized, controlled trial of standard, large-capacity versus jumbo biopsy forceps for polypectomy of small, sessile, colorectal polyps. Gastrointest Endosc. 2012;75:118–26.
49. Katsinelos P, Kountouras J, Paroutoglou G, et al. A comparative study of 50% dextrose and normal saline solution on their ability to create submucosal fluid cushions for endoscopic resection of sessile rectosigmoid polyps. Gastrointest Endosc. 2008;68:692–8.
50. Lee C, Kim JW, Jang JY. Cold SNARE polypectomy versus cold forceps polypectomy using double biopsy technique for removal of diminutive colorectal polyps: a prospective randomized controlled trial. Orlando: DDW; 2013.
51. Aslan F, Alper E, Vatansever S, Akpinar Z, Camci M, Arabul M, et al. Cold SNARE polypectomy versus standard SNARE polypectomy in endoscopic treatment of small polyps. Gastrointest Endosc. 2013;77:AB561.
52. Kahi CJ, Rex DK. Why we should CARE about polypectomy technique. Gastroenterology. 2013;144:16–8.

Index

A. Shaukat, J. I. Allen (eds.), *Colorectal Cancer Screening,*
DOI 10.1007/978-1-4939-2333-5