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Activity description	Practicing evidence-based medicine (EBM) is important in today's health care environment because this model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These e-newsletters will enable health care professionals (HCPs) to put new EBM into practice.
Learning objectives	• Articulate the evidence and rationale supporting the use of coronary computed tomographic arteriogram (CCTA) as a first strategy for the evaluation of stable chest pain. • Evaluate the use of blood eosinophil counts to determine oral glucocorticoid therapy for chronic obstructive pulmonary disease (COPD) exacerbations. • Examine the benefits and related uncertainties of anticancer drugs. • Demonstrate effective medical management practices, including supporting timely primary care follow-up post-hospital discharge to reduce hospital readmission rates, not utilizing repeat endoscopy for non-erosive gastroesophageal reflux disease, and compare the benefits and drawbacks of common cancer screening and stool-based colorectal cancer screening tests.

Accreditation statement

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In support of improving patient care, this activity has been planned and implemented by Optum Health Education and Optum. Optum Health Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE) and the American Nurses Credentialing Center (ANCC), to provide continuing education for the health care team.

Credit designation statements

Nurses
The participant will be awarded up to 1.00 contact hour(s) of credit for attendance and completion of supplemental materials.

Nurse practitioners
The American Academy of Nurse Practitioners Certification Program (AANPCP) accepts credit from organizations accredited by the ACCME and ANCC.

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PAs
The American Academy of Physician Assistants (AAPA) accepts credit from organizations accredited by the ACCME.

Attendance
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Provided by
This activity is provided by Optum Health Education and Optum.

Commercial support
No commercial support was received for this activity.

Coronary computed tomographic arteriogram as first strategy for the evaluation of stable chest pain

The evaluation and management of stable chest pain has undergone a paradigm change. Stable chest pain can be thought of as the wide range of presentations of suspected coronary artery disease. It excludes unstable angina and the acute coronary syndromes in which urgent management is indicated. Three years ago, we first introduced in the Forum the use of coronary computed tomographic arteriogram (CCTA) with fractional flow reserve (FFR) for the evaluation of stable chest pain. Recall that CCTA was initially unable to differentiate functionally significant stenoses that limited blood flow from those that did not. Software that calculates FFR now allows an accurate estimation of the pressure gradient across a stenotic artery, and therefore can determine functionally significant from non-significant stenoses. FFR only needs to be utilized when visually significant stenoses are observed. The range of studies needing FFR varies between 15%–30%.

Between 2019 and 2023, three large RCTs that compared CCTA/FFR to ischemia testing were published.

- CONSERVE Trial[1] – Over 1,600 patients who had been recommended by their cardiologist to undergo coronary catheterization were randomized to have an initial CCTA/FFR vs. going directly to catheterization. Major adverse cardiovascular events (MACE) were the same in both arms of the trial. However, in the CCTA/FFR patients, there were 78% fewer catheterizations and 45% fewer coronary artery interventions.
- DISCHARGE Trial[2] – Using a similar design to the above trial, over 3,600 patients were randomized to CCTA/FFR vs. coronary catheterization. MACE were non-significantly reduced in the CCTA/FFR patients. Once again in the CCTA/FFR patients, there was a 78% reduction in cardiac catheterization and a 36% reduction in coronary artery interventions
- PRECISE Trial[3] – This trial randomized 1,937 patients to a precision strategy (PS) arm vs. a usual testing (UT) arm. In the PS arm, the lowest risk patients had testing deferred. Those in the higher risk categories received CCTA/FFR. In the UT arm, cardiologists chose their preferred ischemia test and referred for coronary catheterization accordingly. In the PS arm, 20% of patients were classified as minimal risk and had testing deferred. None of these patients had a subsequent MACE. Overall, in the PS arm there was a 75% reduction in catheterizations that did not show obstructive disease compared to the UT arm. Once again, overall MACE was similar in the two arms.

We now have three large well done RCTs showing strikingly similar results. Compared to ischemia testing whether nuclear, stress echo or stress PET, those who have CCTA in lieu of ischemia testing showed a marked reduction in the need for cardiac catheterization, a marked reduction in the “clean cath rate” (those catheterizations that did not show obstructive disease) and similar CV outcomes. Two of the three trials also showed a marked reduction in the need for coronary artery interventions. Based on these accumulated data, in 2021, the American College of Cardiology (ACC/AHA) revised their guidelines on the management of stable chest pain. These guidelines were adapted into our Optimal Care algorithms for the management of stable chest pain, with and without known CAD. These algorithms take into consideration the pretest probability of CAD, and the chart to estimate the pretest probability of CAD is embedded within the algorithm.

Our algorithm for patients with stable chest pain and no known CAD suggests that those patients with a pretest probability of CAD of < 15% should have a coronary artery calcium score with no further testing if the score is zero. The AHA/ACC guideline also states that reassurance with deferral of testing is appropriate for these patients. For those with a pretest probability of > 15%, CCTA will be recommended for most of these patients. In this algorithm, cardiology referral may or may not be indicated based on the result of the CCTA/FFR. Please see the Coronary CT angiography for stable chest pain with no known CAD algorithm for details.

For those patients with stable chest pain and known CAD, if the patient has a known coronary stenosis of > 50% or if they have had a prior coronary intervention, they should be referred to cardiology. If not, they should be treated with guideline directed medical therapy since medical therapy and coronary intervention have equivalent outcomes in stable CAD. If symptoms are not adequately controlled with this approach, a CCTA/FFR should be obtained as the next step with cardiology referral if indicated, based upon the results. Please see the Coronary CT angiography for stable chest pain with known CAD algorithm for details.

The current clean cath rate across Optum Health is ~60%, not significantly different than the national average. With widespread adoption of the new AHA/ACC guideline embedded in our Optimal Care algorithms, we should be able to reduce the rate of unnecessary catheterizations dramatically. In fact, our Optum Health data has shown that as our CCTA utilization increases, our clean cath rate decreases. Lower catheterization rates also equate to lower coronary intervention rates. A recent study by the Lown Institute[4] suggested that 22% of stents were unnecessary with a cost to Medicare of $2.44 billion over three years.

There are several barriers to widespread adoption of the CCTA first strategy:

- While all of our markets have access to the appropriate CT scanners through owned or contracted imaging centers, many care delivery organizations (CDOs) have not yet formalized the referral network for CCTA and/or executed a contract for FFR which is needed for these readings.
- Many cardiologists are unwilling to forgo the revenue associated with ischemia testing and therefore don't prioritize the use of CCTA first.
- This does require a bit more work from the primary care physician (PCP). A referral to cardiology requires only a click or two. Scheduling a CCTA requires checking to see if the eGFR is > 30 ml/min and prescribing a beta blocker to be used pretest,as the HR needs to be in the 60 bpm range for optimal imaging. The beta blocker regimen is simple:
  - If the patient heart rate (HR) is > 70 bpm, prescribe short-acting metoprolol tartrate 100 mg one hour prior to the CCTA.
  - If the patient HR is between 60-70 bpm, prescribe short-acting metoprolol tartrate 50 mg one hour prior to the CCTA.
- CCTA can't be used for patients with atrial fibrillation if they have heart rates much over 60 bpm, a severe contrast allergy or BMI > 40.

We are addressing all of the above. Our newly formed Cardiology Forum, made up of our employed cardiology thought leaders, has created a CCTA sub-committee to strategize on the mitigation of all of the above barriers. Given the compelling evidence of improved patient outcomes, reduced harms of invasive coronary interventions, and reduced cost of care, the use of the CCTA first strategy is one of the chief priorities for the Optimal Care model.

Use of blood eosinophil counts to determine glucocorticoid therapy for COPD exacerbations

Multiple studies have demonstrated that the blood eosinophil count (BEC) should be used to guide inhaled corticosteroid therapy (ICS) in COPD, as reflected in the updated GOLD guideline.[5] This is because it is now well-established that ICS therapy increases the risk for bacterial pneumonia from secondary immunodeficiency due to steroids. In those individuals with an elevated BEC, the improvement in COPD exacerbation rate with ICS use is greater than the risk of pneumonia and therefore ICS use is indicated. Our Optimal Care COPD algorithm therefore recommends ICS use in patients with a BEC >300 cells/ul or for those patients with >100 cells/ul if there are repeated exacerbations.

Similar studies have not been done to evaluate whether the BEC should inform the use of oral glucocorticoids for COPD exacerbations. Although the risks of short-term treatment are low, about 30% of seniors have type 2 DM complicating the use of oral glucocorticoids. A recent study in the British Medical Journal examined the use of BEC informed use compared to the standard of care in COPD exacerbation, using a double blind, placebo-controlled approach.[6] Patients with COPD and at least one exacerbation in the past year were recruited from 14 PCP practices in the U.K. Participants were randomly assigned (1:1) to blood eosinophil-directed treatment (to receive oral prednisolone 30 mg once daily if eosinophil count was high [≥ 2%] or placebo if eosinophil count was low). Prednisolone was used in all of the standard care patients. Treatment was prescribed for 14 days, and all patients also received antibiotics. The primary outcome was the rate of treatment failure, defined as any need for re-treatment with antibiotics or steroids, hospitalization for any cause, or death, assessed at 30 days after exacerbation.

There were just over 70 patients in each treatment group. There were 14 (19%) treatment failures at 30 days post-exacerbation in the BET group and 23 (32%) in the ST group, resulting in a large non-significant estimated effect between BET and ST (RR 0·60 [95% CI 0·33–1·04]; p=0·070) in reducing treatment failures after a COPD exacerbation. Frequency of adverse events was similar between the study groups and hospital admission for COPD exacerbation (2/102 [2%] in BET group and 1/101 [1%] in the ST group) were the two most common adverse events in both groups. No deaths occurred in the study.

Two previous studies looking at BEC to guide glucocorticoid therapy in COPD exacerbations found similar results.[7,8] Given the consistency in these studies, withholding glucocorticoid therapy in COPD exacerbations when the BEC is low seems reasonable, particularly in a patient with type 2 DM who would experience hyperglycemia related to treatment.

Communication of anticancer drug benefits and related uncertainties to patients and clinicians

Research around the accuracy of communication of anticancer drug benefits and toxicities to patients is limited. When patients are receiving cancer drug treatment they need high quality information, including information about the benefits and risks of the drugs that are being offered. This information can support ethical principles of patient autonomy, facilitate shared decision making, and help to ensure that treatment is sensitive to, and meets the needs and priorities of, individuals. Patients with advanced, non-curable cancer can face particularly difficult decisions as they must often weigh a small, or even unknown increase in survival time against the toxicity and expense of treatment. In the U.K. and European Union, it is mandatory for all approved medicines to be accompanied by written information for patients and healthcare professionals that has been approved. This is not the case in the U.S., although the U.S. Food & Drug Administration (FDA) is considering implementing this approach.

A recent study examined the quality of this information in 29 cancer drugs newly approved between 2017 and 2019 for 32 indications.[9] Only 28% of the indications showed benefits on patient-relevant outcomes of survival or quality of life at the time of approval. The remaining 72% of indications lacked evidence that the drug extended survival or improved quality of life. As in the U.S., these drugs were approved on the basis of a surrogate endpoint such as progression-free survival or tumor response. For a quarter of indications, the degree of uncertainty was such that regulatory agency was unable to reach a consensus on whether the benefits of the drug had been shown to outweigh the risks, although they were approved for use.

In the drug leaflet information given to the patients, none of the drugs provided any information on anticipated clinical benefit, overall survival or improvements in quality of life. They also provided no information on how the drug was studied or what outcomes endpoints were used in the approval trials. Recent research suggests that in the absence of explicit information about the strength of the evidence around recommended treatments and interventions, people assume the evidence is of high quality.[10] Patients need to be educated that the surrogate endpoints such as progression-free survival and tumor response do not reliably predict either improved patient survival or improved quality of life. Regulated information sources for anticancer drugs in Europe fail to address the information needs of patients and patient education around new drugs is not currently addressed by the FDA. Until there is effective FDA regulation on this issue, we need to challenge our oncology colleagues to educate our patients about how these drugs will impact the outcomes that matter to them – will I live longer, or will I feel better?

Timely PCP follow-up reduces hospital readmission

Unplanned readmission following hospital discharge is a costly and often preventable outcome. Yet another study highlights the highly significant quality and cost benefits of patients being seen in their PCP office following hospital discharge. In a recent cohort study that included over 345,000 Medicare beneficiaries who were hospitalized with an emergency general surgery (EGS) condition, likelihood of readmission within 30 days was substantially lower in the 45.4% of subjects who had a follow-up PCP visit than those who did not.[11] The median time to a follow up PCP visit was 12 days post discharge. Overall, the adjusted odds ratio (AOR) of readmission was 67% lower in this group who had PCP follow-up (AOR, 0.33; 95% CI, 0.31-0.36). More specifically, those who were treated operatively had 79% reduced odds of readmission (AOR, 0.21; 95% CI, 0.18-0.25) and those treated non-operatively had 64% reduced odds of readmission (AOR, 0.36; 95% CI, 0.34-0.39). The two groups were propensity-matched to minimize risk of bias. Even when adjusting for those who saw their surgeon in follow-up after hospitalization, the benefit of PCP follow-up remained robust (AOR, 0.42; 95% CI, 0.38-0.46). These findings comport with previous studies that show a clear patient benefit of PCP follow-up after hospital discharge,[12,13] reinforcing the importance of care coordination, PCP follow-up, and appropriate hand-off between care teams.

Non-erosive gastroesophageal reflux disease does not require repeat endoscopy to monitor for cancer

A recent large cohort study demonstrated that patients with non-erosive gastroesophageal reflux disease (GERD) are at "average" risk of esophageal cancer and therefore do not need follow-on screening endoscopy.[14] Non-erosive GERD is the most common type. The study included 285,811 patients, median age of 59, 58.7% women, with non-erosive GERD with over 2 million person-years of follow-up. The incidence of esophageal cancer in this group was 11 per 100,000 person-years, which is similar to that of the general population (standardized incidence ratio 1.04 [95% CI, 0.91-1.18]). This is in contrast to a similar cohort (n=200,745) with endoscopically-confirmed erosive esophagitis, who had an incidence rate of esophageal cancer of 31 per 100,000 person-years (standardized incidence ratio of 2.36 [95% CI, 2.17-2.57]). Study participants were from Scandinavian countries (Denmark, Finland, Sweden) from 1987–2019 so findings may not be generalizable to all populations, but they do suggest that for those patients with endoscopically-confirmed non-erosive GERD and no change in signs or symptoms, no additional screening for esophageal cancer is indicated.

Longevity benefits of common cancer screening tests may be smaller than anticipated

Screening programs for common cancers are major public health initiatives in the U.S. and are integral to primary care and preventive healthcare. When detected early, many forms of cancer (CA) are more likely to be amenable to curative treatment and at lower cost and patient discomfort. Successful screening programs for common cancers, when applied to the correct populations of patients, use cost-effective tests with appropriate sensitivity and specificity for conditions that are important to identify and treat before symptoms or signs develop.

A recent meta-analysis of randomized clinical trials examined the impact on longevity of six different CA screening tests: mammography, prostate-specific antigen testing, colonoscopy, flexible sigmoidoscopy, fecal occult blood testing (FOBT), and computed tomography (CT for lung CA screening).[15] 2,111,958 patients were included across all screening tests, with a median follow-up ranging from 10–15 years. Sigmoidoscopy was the only test to demonstrate significant lifetime gain (110 days; 95% CI, 0-274 days). All other tests did not demonstrate significant lifetime gains, with the 95% confidence interval crossing zero days, as shown in the table below. Of note, on average, follow-up did not extend past 15 years for any test.

Table: Lifetime gains for each of six screening tests for common cancers

Test	Lifetime gain (number of days; 95% confidence interval)
Flexible sigmoidoscopy for colorectal CA	110 days; 0–274 days
Colonoscopy for colorectal CA	37 days; -146 to 146 days
FOBT every year or every other year for colorectal CA	0 days; -70.7 to 70.7
Mammography for breast CA	0 days; -190 to 237 days
Prostate specific antigen for prostate CA	37 days; -37 to 73
CT for lung CA	107 days; -286 to 430 days

The current study analyzes a large group and does not address potential individual benefits of early CA detection through screening. Nor do these results address the potential individual harms of CA screening that include direct harms from the test itself (such as perforation during colonoscopy) or indirect harms such as false positive tests with additional testing and patient anxiety. There is little doubt that evidence-based cancer screening programs as promoted by various national bodies such as the USPSTF provide important public health benefits, outside of an estimation of lifetime days gained. Both patients and physicians overestimate the benefits and underestimate the harms of cancer screening. The current study does reinforce the benefits of screening wisely by using the most cost-effective screening modalities and schedules, and adhering to established guidelines and not broadening screening beyond those populations identified.

Expansion of arsenal of stool-based colorectal cancer screening tests

Colorectal cancer (CRC) remains one of the leading causes of death in the U.S., and screening of asymptomatic adults remains one of the most effective ways to identify early disease more amenable to curative treatment. There are many studies reporting on the effectiveness of various screening modalities.

Two recent reports signal additional progress and options for CRC screening. The CRC-PREVENT study is a Phase 3 clinical trial comparing the test performance of a multitarget stool RNA (mt-sRNA) screening test with the fecal immunochemical test (FIT).[16] The BLUE-C trial compared test performance of a multitarget stool DNA (mt-sDNA) screening test with FIT[17] (this test can be thought of as the next generation of the Exact Science Cologuard test). Both trials used screening colonoscopy as the gold standard with which to compare. The mt-sRNA and mt-sDNA both had sensitivities that significantly outperformed the FIT for CRC and for advanced precancerous lesions (APL), although specificity was worse (see Table). Given trade-offs in test performance, frequency, costs, risks, and convenience, clinicians should engage their patients in a shared decision-making conversation to determine which is the most appropriate method for them.

Table: Sensitivity and specificity for CRC and for APL for three stool-based CRC screening tests

	CRC sensitivity	APL sensitivity	Specificity for "no lesions"
mt-sDNA	93.9% (95% CI, 87.1–97.7)	43.4% (95% CI, 41.3–45.6); sensitivity for APL with high-grade dysplasia was 74.6% (95% CI, 65.6–82.3)	93.4% (95% CI, 92.8–93.9)
FIT performance in mt-sDNA study	67.3 (95% CI, 57.1–76.5)	23.3 (95% CI, 21.5–25.2)	96.0% (95% CI, 95.5–96.6)
mt-sRNA	94.4% (95% CI, 81–99)	45.9% (95% CI, 42–50)	87.9% (95% CI, 87–89)
FIT performance in mt-sRNA study	77.8% (95% CI, 61–90)	28.9% (95% CI, 25–33)	95.7% (95% CI, 95–96)

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as Chief Medical Officer from 1995–2020. He now serves as the Executive Director of Translational Research for Optum Care and co-leads the Optum Center for Research and Innovation. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the CDC Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine and School of Pharmacy. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

Joshua Jacobs, MD, FAAFP

With over 20 years of clinical, academic and leadership experience regionally, nationally and internationally, Dr. Jacobs currently serves as primary care engagement lead national Medical Director for Optimal Care within Clinical Performance at Optum Care. He is a Clinical Professor of Family Medicine at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

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Learning objectives	• Describe glucagon-like peptide 1 (GLP-1) receptor agonists mechanism of action, the positive effects in control of diabetes mellitus (DM), obesity/weight loss, cardiovascular, GI, renal, and MSK systems, and the potential complications of treatment. • Discuss the indications and the beneficial effects of dual antiplatelet therapy (DAPT) for transient ischemic attack (TIA) or stroke and the importance of timing the initiation of therapy. • Compare conservative therapies with arthroscopic surgery for meniscal tears. Discuss evidence in support of non-operative treatment for knee pain from meniscal injury or degenerative joint disease. • Explain the role of monoclonal antibody therapy for early Alzheimer's Disease and mild cognitive impairment (MCI). Highlight outcomes of phase III trials using candidate drugs in early Alzheimer's Disease.

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Glucagon-like peptide-1 receptor agonists (GLP-1RA) indications, risks, costs

Several glucagon-like peptide-1 receptor agonists (GLP-1RAs) are available in the United States and share the same mechanisms of action.[1] Examples of these drugs include semaglutide and liraglutide. A third molecule, tirzepatide, has a dual effect combining GLP-1RA with a second mechanism of action via glucose-dependent insulinotropic polypeptide (GIP) agonism.[2]

Mechanism of action and positive effects in control of diabetes mellitus (DM)

These drugs work on receptors in the pancreas to support beta-cells, increasing insulin release and decreasing glucagon release. This leads to lower blood sugar levels but in a glucose-sensitive manner that minimizes risk of hypoglycemia. Additional effects that help treat DM include delayed gastric emptying, increased muscle uptake of glucose, decreased gluconeogenesis and increased satiety. The range of reduction in HbA1c is 0.8%-1.5%.[3]

Mechanism of action and positive effects in obesity or weight loss

Increased satiety and delayed gastric emptying are the predominant beneficial effects when these drugs are used to treat obesity. A significant portion of this increased satiety is related to the direct CNS effects of the GLP-1RAs. Recent trials focused on the use of semaglutide and tirzepatide for obesity in patients without diabetes have demonstrated highly significant median weight loss of 16% with semaglutide at the 2.4 mg weekly dose[4] and 22% total body weight with tirzepatide at the 15 mg weekly dose.[5] Clinically meaningful weight loss effects as well as sustained reductions in HgbA1C have been maintained for over 7 years.[6]

Mechanism of action and positive effects on the cardiovascular, GI, renal and MSK systems

This drug class has positive effects on the cardiovascular system as well, with decreased total cholesterol and blood pressure, and improved left ventricular ejection fraction, coronary artery blood flow, endothelial function, myocardial contractility and cardiac output. It is important to recognize that a class effect of these drugs is an elevation of the heart rate, which may be as much as 6–10 bpm with some drugs in this class.[7] However, adverse effects related to this increased heart rate have not been documented. These beneficial effects are independent of, but may be further augmented by, the glucose-lowering and weight-reduction benefits. Many randomized controlled trials and cohort studies have demonstrated beneficial clinical results of several drugs in these categories in treating DM, DM with cardiovascular disease, diabetic kidney disease, obesity and related complications from adiposity-based chronic diseases such as non-alcoholic fatty liver disease[8, 9, 10] (NAFLD, and metabolic associated fatty liver disease [MAFLD]). Significant and sustained weight loss should reduce severity of hip and knee arthritis as well as the need for hip and knee arthroplasty, and potentially reduce the burden and costs of managing chronic low back pain. Observational studies are ongoing but there are no definitive data at this point.

Potential complications of treatment

Despite the promising results, the side effects and the direct costs of these drugs should temper indiscriminate prescribing. Once started, these drugs may need to be continued indefinitely to maintain any positive results. Data shows the beneficial effects on measures such as BMI, blood pressure and lab results revert to baseline after discontinuation.[11] Side effects include gastrointestinal (GI) upset (nausea/vomiting, constipation or diarrhea and in severe cases, gastroparesis) that commonly results in patient intolerance and discontinuation, with some evidence that over half of patients will stop the medication.[12] These short-term side effects can be managed with slow and careful dose titration and short-term use of ondansetron and laxatives as needed for symptom control. In many patients, the full therapeutic benefit in terms of weight and HbA1c reduction may be obtained at lower than full dose treatment, therefore full dose escalation may not always be necessary.

The positive effects on weight reduction can lead not only to a reduction in adiposity, but to overall weight reduction, including loss in skeletal muscle mass. For example, data from the SURMOUNT-1 tirzepatide study showed that fat mass dropped between 33% and 36% and lean mass by 10% to 11%, depending on the age group. In other words, roughly one-quarter of the weight lost in that study was lean mass. For context, some degree of lean muscle mass loss is normal in most weight loss scenarios, as the body tends to shed both fat and some lean tissue when losing weight.[2] This extreme weight loss, coupled with the benefits outlined above on DM, may also result in a reduced need for other medications, including medications for diabetes and hypertension. If not recognized early and managed with medication adjustments, this can result in hypoglycemia and/or hypotension. Again, slow and careful dose titration is indicated, with concomitant evaluation for reducing or eliminating other anti-diabetic and antihypertensive medications.

Drug cost must be considered when prescribing and may necessitate exploring alternative guideline-directed medical therapies. For example, an article summarized in this issue of the Forum demonstrates the cost of GLP-1RA therapy to avoid one major adverse cardiac event (MACE) over a 3-year period in someone who is obese and with cardiovascular disease is $3.2 million.[13] As a primary CV prevention strategy, this is clearly not feasible and sustainable from a population perspective. However, there is some evidence that for high-risk individuals such as those with DM and cardiovascular disease, drug costs may be offset by reductions in hospitalization costs.[14] Unfortunately, both Novo Nordisc (semaglutide) and Lilly (tirzepatide) priced all doses of their drugs the same, such that dose reduction cannot be used as a strategy to reduce drug costs.

Semaglutide can reduce cardiovascular risk, but at a cost

Glucagon-like peptide-1 (GLP-1) agonists have been shown to reduce major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus and obesity.[15] A recent study published in the *New England Journal of Medicine* demonstrates the benefit of the GLP-1 agonist semaglutide in reducing MACE in obese patients with known cardiovascular disease, even in the absence of diabetes.[16] Based on study findings and the dose prescribed, at the list price of $16,000 per year, the number needed to treat is 66 over 3 years to avoid one event, yielding an approximate price tag of $3.2 million to prevent one event over the 3-year period. If this analysis was extended to a population of patients without preexisting CVD, the costs would be even much higher. From the societal perspective, this is not cost-effective. The study included over 17,000 patients with obesity and evidence of cardiovascular disease, excluding those with diabetes, end-stage renal disease, or advanced heart failure. Half were assigned to the semaglutide group and half to placebo. Primary endpoints examined included death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, and favored the semaglutide group (hazard ratio, 0.80; 95% confidence interval [CI], 0.72 to 0.90; P<0.001). Additional endpoints included heart failure and death from any cause, both also significantly better in the semaglutide group. Serious adverse events were reported in 33.4% in the semaglutide group and 36.4% in the placebo group. Mean change in body weight at 104 weeks after randomization was -9.39% in the semaglutide group and -0.88% in the placebo group.

Although not used in the study, tirzepatide, another GLP-1 agonist with similar properties to semaglutide, is priced about 25% less.[17] If the findings of the study could be replicated with this medication, the cost to avoid one event would drop to roughly $2.4M, still quite high and not meeting accepted criteria for cost-effectiveness.

This drug class shows great promise in safely managing obesity with cardiovascular disease. At present, however, it is priced in a manner to preclude widespread use for the indication of reducing MACE.

DM2 failing metformin – prescription and discontinuation patterns of the non-insulin drug classes

Little is known about the prescribing and discontinuation rates of the various non-insulin drug classes used as second-line therapy in patients with type 2 diabetes mellitus (T2DM) failing metformin monotherapy. Although there are evidence-based recommendations around both improved outcomes and cost-effectiveness for the use the SGLT2i category for patients with heart failure, CAD, and CKD, for other patients the choice of second-line therapy should be a shared decision-making approach with patients including the relative costs and benefits of each drug class. With respect to sulfonylurea use, we know from the CAROLINA trial,[18] that after over 6 years of follow-up, compared to the DPP-IV class which is weight neutral and does not impact MACE, that the short acting sulfonylureas (glimepiride in this case) also had no increase in MACE compared to the DPP-IVs. Moreover, the weight gain at the end of the 6 years was minor at 3.4 pounds. Severe hypoglycemia occurred in approximately 1:200 patient years in the sulfonylurea group.

Added to this body of literature is a new retrospective cohort study that examined claims from over 82,000 patients with T2DM who had failed or didn't tolerate metformin therapy and were initiated on non-insulin therapies between 2013 and 2017.[19] 43% of patients were in commercial health plans and 57% were in Medicare. In terms of which drugs were started as second-line treatment, 52% were sulfonylureas, 24% were DPP-IV, 11.6% were SGLT2i, 8% were GLP-1RA, and 5% were TZD.

38.6% of patients discontinued their secondary drug. With respect to discontinuation by the specific drug class, the highest rate of discontinuation was with the GLP1-RAs, where over half were stopped. The discontinuation rates were fairly uniform for the other drug classes in the range of 35%. The high rate of DPP-IV use is hard to understand given that they are priced at about $5,500 yearly, they are of relatively low efficacy, are not associated with improvements in cardiac or renal outcomes, and don't promote weight loss. On the other hand, given the prevalence of CKD, CHF and CAD in the population of patients with T2DM, it is likely that the SGLT2is were under-prescribed. In the absence of heart failure, ≥ 3 CV risk factors, or CKD, the cost effectiveness of the sulfonylureas supports their high utilization in this study.

Dual antiplatelet therapy for TIA/Stroke

Patients with acute mild ischemic stroke or transient ischemic attack (TIA) have a risk of recurrent stroke of approximately 5% to 10% within 90 days after the onset of the initial event. The timing of initiation of dual antiplatelet therapy (DAPT) is critical as the highest risk of recurrence is immediately following the index event. Prior studies have shown that when aspirin and clopidogrel are initiated within 24 hours, there is a significant reduction in the progression to completed stroke without an increase in severe bleeding.[20] A recent study looked at whether increasing that time window to 72 hours would still result in a reduction of the completed stroke rate.[21] As DAPT is likely to be most effective in those patients with unstable plaque in large vessels, the patient population was those patients with at least 50% stenosis of a major intracranial or extracranial artery, as confirmed by carotid duplex ultrasonography or vascular imaging, that was likely to have accounted for the clinical presentation and cerebral infarction; or acute new multiple infarctions (documented by computed tomography or magnetic resonance imaging of the head) of presumed large-artery atherosclerosis origin, including those with non-stenotic, unstable plaque ipsilateral to the infarction.

6100 eligible patients were randomly assigned in a 1:1 ratio within 72 hours after symptom onset to receive combined clopidogrel plus aspirin or matching clopidogrel placebo plus aspirin. Patients were studied for the incidence of any new stroke, MACE, or significant bleeding occurring within 90 days of randomization. 87% of the patients presented with stroke and 13% with TIA. A new stroke within 90 days occurred in 222 patients (7.3%) in the clopidogrel–aspirin group and in 279 patients (9.2%) in the aspirin group (hazard ratio, 0.79; 95% confidence interval [CI], 0.66 to 0.94; P=0.008). Stroke and/or MACE occurred in 229 patients (7.5%) in the clopidogrel–aspirin group and in 282 patients (9.3%) in the aspirin group (hazard ratio, 0.80; 95% CI, 0.67 to 0.96). Moderate-to-severe bleeding occurred in 27 patients (0.9%) in the clopidogrel–aspirin group and in 13 patients (0.4%) in the aspirin group (hazard ratio, 2.08; 95% CI, 1.07 to 4.04; P=0.03).

These data support extending the window of a beneficial effect to DAPT for TIA or mild ischemic stroke to 72 hours, and in the absence of contraindications to DAPT, this should be considered the standard of care for patients presenting with these conditions.

Arthroscopy for meniscal tears (still) rarely indicated

Previous articles in this Forum for Evidence-Based Medicine as well as the Optimal Care Measure Brief addressing knee arthroscopy in people >35 years have summarized the robust evidence in support of non-operative treatment for knee pain from meniscal injury or degenerative joint disease.[22] Two recent studies extend the evidence in favor of conservative therapies over arthroscopic surgery to include younger patients with traumatic and non-traumatic meniscal tears. The first examined both objective evidence of structural damage as well as subjective evidence of benefit at two years after the index MRI and diagnosis of meniscal tear. This prospective randomized study compared surgery or exercise for meniscal tears in patients aged 18–40 years old.[23] Exclusion criteria were prior surgery of the affected knee, fracture of that knee in the preceding year, complete knee ligament rupture, or participation in supervised exercise within the preceding 3 months. Additionally, patients were excluded if they had MRI-confirmed congenital discoid meniscus or clinical suspicion of displaced bucket handle tear. All other types of tears were included.

The 121 patients were randomized to receive knee surgery (either arthroscopic partial meniscectomy [APM] or meniscal repair, with choice left to the discretion of the surgeon) or to receive supervised exercise therapy two times per week and patient education over a 12-week program. Those randomized to the exercise group had the option to undergo knee surgery later, with 16 of the 61 patients (26%) ultimately having surgery. All patients received an online questionnaire that included KOOS[4] and WOMET (two validated patient-reported outcome measure instruments for knee pain and function[24,25]) at 3, 6, 12 and 24 months. They also had a repeat MRI at 24 months with findings graded based on a validated semiquantitative scoring system (ACLOAS[26]), appropriate blinding, and robust inter-rater agreement of the radiologists. Anatomically, the groups did not appear to differ. Baseline and 2-year MRI findings were essentially the same in both groups with no evidence of worsening cartilage damage or osteochondral damage in the exercise therapy group. There was a trend towards increased osteoarthritis progression in the surgical group (osteophytes present in 17% of surgical patients compared to none in the exercise group), which did not quite meet statistical significance. Patient-reported outcomes also were essentially the same between groups.

The second study demonstrated that physical therapy for traumatic meniscal tears in patients aged 45 and younger was more cost-effective than APM.[27] This study was also of patients with MRI-verified meniscal injury, also with a 24-month follow-up period. It examined costs per quality-adjusted life years (QALY) gained using a healthcare system and societal perspective. Of the 100 patients, roughly half were randomized to undergo APM and half to receive physical therapy, with an option for APM after 3 months. Twenty-one (41%) of the patients randomized to physical therapy eventually underwent surgery during the study period. There was no significant difference in quality of life at 24 months between the two groups, indicating the additional costs of surgery do not add any health benefit.

Two phase 3 trials of gantenerumab in early Alzheimer's Disease

Monoclonal antibody therapy for early Alzheimer's Disease and mild cognitive impairment (MCI) continues to be highly controversial. Multiple phase III trials of candidate drugs have failed to show improvement despite substantial clearing of amyloid plaque on PET/CT. Aducanumab and lecanemab have received FDA approval despite only slight improvements on research cognitive scales, and it is uncertain whether this will translate to meaningful real-world slowing of cognitive decline and clinical improvements. Donanemab is expected to soon be the third drug to receive FDA approval. Amyloid-related imaging abnormalities with edema (ARIA-E) are common, and serious related adverse events have occurred with all drugs in this class.

Recently, two phase III trials of gantenerumab were reported, studying in total close to 2,000 patients with early Alzheimer's Disease or MCI.[28] The results indicated that this was another failed molecule with no significant improvement in cognitive scores despite 27.5% of patients achieving complete amyloid clearance on PET/CT. ARIA-E was seen on imaging in 25% of patients.

Going forward with the approved medications in this drug class, it will be critical to assess whether there is a significant real-world benefit of the small observed reductions in cognitive decline. This along with other measures of effectiveness to include the ability to function independently in the home, assessment of benefits according to caregivers, quality of life, and frequency and severity of side effects needs to be studied. Lilly has planned a phase IV trial of donanemab to address all of the above and many of our neurology practices, in partnership with OCRI, will be participating in this important trial.

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Learning objectives	• Evaluate the role of stool-based tests and emerging technologies in colorectal cancer (CRC) screening. • Analyze the impact of selecting the site of service delivery on cost-effectiveness in physician-administered drugs. • Assess the potential of low-dose aspirin as a treatment for metabolic dysfunction-associated steatotic liver disease (MASLD) and its role within a comprehensive treatment plan for MASLD. • Develop a comprehensive pain management strategy for chronic obstructive pulmonary disease (COPD) patients through a multidisciplinary approach. • Discuss the role of SGLT2 inhibitors (SGLT2i) in managing type 2 diabetes mellitus (T2DM) patients with coronary artery disease. • Describe a comprehensive approach to the diagnosis and management of MASLD, including VCTE as a non-invasive fibrosis assessment tool. • Examine the role of lung-cancer screening based on the National Lung Screening Trial (NLST) guidelines to optimize informed decision-making for patients. • Recognize the potential of bariatric surgery as a cost-effective treatment for type 2 diabetes compared to long-term medical management, considering impacts, potential complications and the importance of shared decision-making for a well-informed approach.

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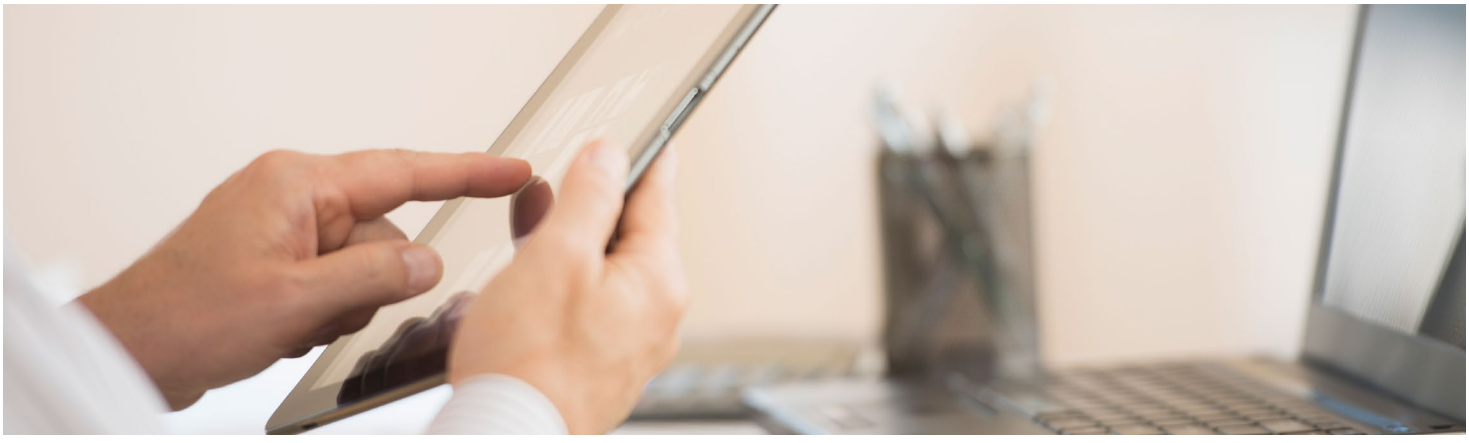
New options for colorectal cancer screening coming soon

Most other wealthy nations around the globe use stool-based testing for colorectal cancer (CRC) screening (predominantly FIT), with colonoscopy used as second line of screening in those with positive stool-based tests. In a recent study, when patients were given shared decision-making information about the risks and benefits of colonoscopy versus stool-based testing, patient selection of stool-based testing went from a baseline of 24% to 67% post-education, and selection of colonoscopy declined from 76% down to 27%.[1] This is important as the overall prevalence of CRC screening in the U.S. for combined noninvasive and endoscopic methods is about 69%, less than the goal of >80%,[2] which may be due, in part, to avoidance of colonoscopy.

Adding to these data are new data suggesting that the reduction in CRC mortality using colonoscopy screening is less than previously thought, casting doubt on whether it should be regarded as the "gold standard" of CRC screening. These data come from the NordICC study, which looked at 28,220 subjects in 3 countries who were invited to participate in colonoscopy screening for CRC and compared them to 56,365 control subjects.[3] This study was criticized due to the low participation rate of 42% and therefore the following statistics reflect the estimated benefit had all invited patients undergone screening. In this best estimation, the risk of colorectal cancer at 10 years was decreased from 1.22% to 0.84% and the risk of colorectal cancer-related death was decreased from 0.30% to 0.15%. Therefore, in this best-case scenario, the risk of dying from CRC using colonoscopy screening was reduced by only 50%. Additional details are available in a previous edition of this newsletter.[4] Most patients believe they are protected from dying from CRC if they have a colonoscopy.

Against this backdrop are 2 new studies looking at alternatives to colonoscopy for CRC screening. The first is the BLUE-C study, which was industry-sponsored and used the next generation of stool DNA markers.[5] It looked at 20,176 subjects over age 40 due for CRC screening. All participants had colonoscopy, stool DNA and FIT. In terms of sensitivity, CRC was detected on colonoscopy in 98 participants (0.5%), of whom 82 (84%) had stage I, II, or III disease. 2,144 participants (10.6%) had advanced adenomas, and 6,973 participants (34.6%) had nonadvanced adenomas. 94% of cancers were detected by stool DNA as were 66% by FIT. 85% of advanced adenomas were detected by stool DNA as were 54% by FIT. In terms of specificity, stool DNA performed at 91% and stool FIT at 97%. These stool DNA results represented a modest improvement in specificity without loss of sensitivity compared to the first-generation test. The ECLIPSE study, also industry-sponsored, used a serum cell-free tumor DNA (cfDNA) test, also known as a "liquid biopsy," to detect genomic alterations, alterations in methylation, and DNA fragment changes.[6] 7,861 participants underwent both colonoscopy and cfDNA testing. The cfDNA assay, as compared with colonoscopy, showed a sensitivity of 83.1% for colorectal cancer and a specificity of 89.6% for advanced neoplasia (defined as either CRC or advanced adenoma), with a 13.2% sensitivity for advanced adenomas. The false positive rate of both the next-generation stool DNA and the cfDNA tests was about 10%.

One other potential benefit to the use of stool DNA (and potentially cfDNA, although not yet studied) is the difference in colonoscopy performance when the colonoscopist is aware of a positive stool DNA test.[7] The performance of colonoscopy in the detection of right-sided advanced adenomas is less than that of left-sided as they are often flat and difficult to detect. When the colonoscopist was aware of the stool DNA findings, the withdrawal time was 6 minutes longer than when blinded to the result. In the "aware" group, the overall polyp detection was 17% higher. The detection of cancers and left-sided advanced adenomas was similar in both groups. However, the detection of flat or slightly raised advanced adenomas in the right colon was 40% in the "aware" group and only 9% in the blinded group.



Importantly, the USPSTF reports the reduction in CRC mortality using colonoscopy, stool DNA, and FIT in their updated guidelines.[8] The mortality reduction per 1,000 patients screened, beginning at age 45, is estimated to be 28 with 10-year interval colonoscopy, 26 with yearly FIT and 25 with 3-year interval stool DNA, placing all 3 modalities within 0.5% of each other in terms of the reduction in CRC mortality. Therefore, considerations other than test performance should heavily influence the choice of tests. As discussed above, when patients understand the risks and benefits of stool-based testing, they preferentially choose this, and the best test for CRC screening is the one that the patient completes. Stool-based testing also reduces low-value surveillance colonoscopy. The presence of 1–2 small tubular adenomas does not increase CRC incidence or mortality.[9] Yet these small adenomas are found in over one-third of patients undergoing colonoscopy, and most of these patients are placed under surveillance more frequently than the 10-year interval that should be indicated based on current data (the Optimal Care CRC screening clinical pathway allows for a 10-year interval colonoscopy in these individuals). In terms of cost-effectiveness, for stool DNA (Exact Sciences Cologuard®), the test is priced about $500. Given the 3-year interval of testing, this would equate to $1,650 over 10 years and therefore in many markets is more expensive than a 10-year interval colonoscopy. When the excess surveillance and complication costs of colonoscopy are considered, the costs of colonoscopy screening increases. Factoring in these 2 costs, a high-level estimate of the break-even for CRC screening costs between colonoscopy and stool DNA would be when the colonoscopy bundle (professional, facility and anesthesia) is in the range of about $1,200. If the FDA approves the cfDNA test, we will need to wait for the pricing to determine the cost-effectiveness.

Hospital price markups for physician-administered drugs for patients with private insurance

Drug costs in the U.S. are more than twice those in other wealthy countries. For physician-administered drugs such as chemotherapy and immunotherapies (part B drugs in the Medicare program), delivery outside of a hospital system is almost always less expensive to the patient, insurer, and healthcare system than those delivered within hospital systems. These hospital systems include both hospital outpatient department (HOPD)/infusion center-administered drugs and those administered by hospital-employed physicians in their offices. To better assess the amount of hospital system profits from the buy-and-bill model of drug administration, a study looked at hospital reimbursement for physician-administered drugs in a commercial insurance population.[10] Using 2020–2021 data, the authors reported the results of a national study of hospital reimbursement-price markups to private Blue Cross Blue Shield (BCBS) insurers, 340B price discounts from drug manufacturers, and hospital revenues obtained owing to drug administration. The study focused on 36 infused drugs used primarily for oncologic conditions, 10 for inflammatory conditions, and 11 for blood-cell deficiency disorders. The 340B program was originally designed to make drugs more affordable, particularly in rural hospital settings. It has since been misused by predominantly large hospitals who buy deeply discounted 340B medicines and then turn around and charge both uninsured patients and insurance companies higher prices, providing a large revenue stream with little to no evidence they use that money to help patients.[11]

The median reimbursements for the non-340B hospitals were 154% to 257% higher than the acquisition prices for the above drug classes. For the 340B-eligible hospitals, the median drug reimbursements relative to acquisition prices ranged from 226% to 319% higher. On the other hand, independent physician practices were reimbursed from a median of 107% to 120% above their acquisition prices. On the high end of the scale, 340B-eligible hospitals were reimbursed as much as 707% above their acquisition prices for oncology drugs, and non-340B eligible hospitals up to 523% above the acquisition prices for oncology drugs. Over one-third of all hospitals and all specialized cancer hospitals are now 340B-eligible and these marked-up profits have fueled the acquisition of oncology, rheumatology and ophthalmology practices, among others, by hospital systems. These excess profits are part of the wasted care in our healthcare system and serve as part of the impetus for our focus on site-of-service efficiencies. Many of us think of site of service as only related to surgical procedures, but as these data underscore, it is also a critical element of our choice of specialists. Choosing a hospital-employed specialist who provides physician-administered drugs may result in payments with the above price markups, and yet the same patient outcomes.

Gabapentin is not a benign drug: Use associated with increased risk of severe COPD exacerbations

Patients with chronic obstructive pulmonary disease (COPD) commonly have chronic pain from one or more conditions including osteoarthritis or other chronic musculoskeletal conditions. [19] Treatment of chronic pain is complex and requires a multidisciplinary approach to address the multiple contributing factors. Gabapentin and pregabalin are often prescribed in primary care when other drugs fail to adequately control chronic musculoskeletal pain. This is considered an off-label use of these drugs, which are anticonvulsants and are associated with sedation and respiratory depression.

A recent population-based cohort study demonstrated those patients with COPD who were initiated on one of these 2 drugs had a higher risk of a severe COPD exacerbation than non-users with COPD (overall HR, 1.39 [CI, 1.29-1.50]).[20] A severe COPD exacerbation was defined as one requiring hospitalization or causing death from respiratory failure. The cohort included patients with COPD with an indication for an anticonvulsant (i.e., epilepsy or neuropathic pain) as well as those started on a gabapentinoid for other chronic pain. The increased risk for severe COPD exacerbation was present in all 3 subgroups compared to the matched control group of patients with COPD, with the increased risk peaking about 6 months after initiation of use. For the subgroup without an indication for an anticonvulsant (the “other chronic pain” group, n=3737, matched 1:1 with 3737 non-users with COPD) the hazard ratio for a severe exacerbation was 1.49 (CI, 1.27-1.73).

Chronic pain is challenging to manage, with limited pharmacotherapeutic options that have been demonstrated safe and effective. A multidisciplinary approach that engages patients to advance pain coping skills, sleep, nutrition, weight management and exercise is ideal. There is not an evidence base to support the benefit of gabapentin for chronic pain and this should be considered low value, potentially harmful care. Off-label use of gabapentin or pregabalin for chronic pain, particularly in those with underlying respiratory disorders such as COPD, should not be initiated

SGLT2 inhibitors and reduced risk of kidney stones: Another potential benefit

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated clinical benefit in the treatment of patients with type 2 diabetes mellitus (T2DM) Various aspects have been covered previously in this newsletter, including several cost-benefit considerations.[21,22,23] Despite the high cost, there are some patient populations for which using an SGLT2i may be indicated, such as those with T2DM and known coronary artery disease.[24]

A recent cohort study of 716,406 patients with T2DM demonstrates yet another consideration for prescribing this drug class: decreased risk of nephrolithiasis.[25] This longitudinal study compared the diagnosis of nephrolithiasis in patients with T2DM who were initiated on SGLT2i versus GLP-1RA, and also compared SGLT2i versus DPP4i. Patients were propensity score-matched and data showed the risk of nephrolithiasis was lower with SGLT2i compared to GLP-1RA (14.9 vs 21.3 events per 1,000 person-years; HR, 0.69 [95% CI, 0.67-0.72]; RD, −6.4 [95% CI, −7.1 to −5.7]) or a DPP4i (14.6 vs 19.9 events per 1,000 person-years; HR, 0.74 [95% CI, 0.71-0.77]; RD, −5.3 [95% CI, −6.0 to −4.6]). In further sensitivity analyses, the authors determined this effect was even more robust for adults aged 70 and above, and was similar by sex, renal disease, obesity, race and ethnicity. These findings in favor of SGLT2i's are consistent with previous research demonstrating this category of drugs lowers serum urate levels and is associated with lower risk of incident gout and gout flares in patients with T2DM when compared to patients taking GLP-1RAs or DPP4i's.[26]

All 3 drug classes have cost-benefit considerations that make them untenable from a population health perspective to use for all patients with T2DM. However, for individual patients in whom one of these medications is indicated, consideration of SGLT2i should include the benefits described.

Low-dose aspirin significantly reduced hepatic fat in patients with fatty liver disease

Fatty liver disease not related to alcohol is widespread, with some estimates >30% of the population worldwide.[12] Previously referred to as non-alcoholic fatty liver disease (NAFLD), the current nomenclature is metabolic dysfunction-associated steatotic liver disease (MASLD). This name change more accurately reflects the metabolic nature of the disease. Likewise, the subgroup of patients with fibrotic liver changes are now referred to as having metabolic dysfunction-associated steatohepatitis, or MASH. Metabolic dysfunction-associated steatosis can progress to MASH, which can progress to cirrhosis and death. Several articles on various aspects of these conditions have been previously published in this newsletter.[13,14,15,16]

A recent prospective randomized double-blind placebo-controlled study provides additional evidence for a straightforward treatment of MASLD: aspirin.[17] In this study, 80 adult patients with a diagnosis of MASLD without cirrhosis were randomized and given 81mg of aspirin once daily (study group) or a placebo (control group) for 6 months. The primary endpoint of mean absolute change in hepatic fat content as measured by MRI was significantly lower in the study group at −6.6% vs 3.6% with placebo (difference, −10.2% [95%CI, −27.7% to −2.6%]; P = .009). There were no patients who experienced bleeding-related adverse events, though one patient in the study group did experience drug-related heartburn. Prior to prescribing long-term low-dose aspirin, clinical assessment of risk factors for gastrointestinal bleeding should be done.[18] Although this was a small study, the relatively safe intervention and significant results suggest consideration of this drug as part of a comprehensive multidisciplinary treatment of MASLD. Larger RCTs need to be performed to confirm both this benefit and safety in large populations of patients with MASLD.

FibroScan® (vibration-controlled transient elastography [VCTE]) for the detection of significant hepatic fibrosis in MASLD

NAFLD, now known as metabolic dysfunction–associated steatotic liver disease (MASLD), is currently the most common chronic liver disease affecting approximately 30% of the worldwide adult population, and up to 40% of the U.S. population,[27] and has been addressed in a previous edition of this newsletter.[28] It is now second behind alcoholic liver disease in causing cirrhosis and the incidence of hepatocellular carcinoma (HCC) related to MASLD is increasing. As addressed elsewhere in this issue of the newsletter, bariatric surgery has been found to be highly effective and the GLP-1RAs and other new pharmacotherapies are showing success in preventing progression of early fibrosis to cirrhosis in these patients. However, most of the natural history leading up to significant fibrosis is clinically silent and we have not done an adequate job of screening our at-risk patients for early fibrosis. The Optimal Care clinical pathway recommends screening patients with obesity, metabolic syndrome, type 2 diabetes, or incidentally found transaminase elevations or steatosis found on imaging. Screening begins with an alcohol use history and a FIB-4 test, easily calculated from the patient's age, ALT, AST and platelet count (mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). In patients with elevated transaminases, labs to exclude other etiologies are recommended as per the clinical pathway. In those patients with an elevated FIB-4 test (>2.67), hepatology referral is indicated. For those with intermediate levels (1.3-2.67) a VCTE (FibroScan® [Echosens SA, Paris, France]) study is indicated. This is an inexpensive, specialized bedside ultrasound that is highly accurate for the measurement of liver fibrosis.

An important new study looked at the correlation of an abnormal VCTE result with future liver-related events (LRE) in 16,603 patients with hepatic steatosis from the U.S., Europe and Asia.[29] Patients were initially screened with VCTE and then followed for a mean of 52 months. LREs were HCC, hepatic decompensation, liver transplant and liver-related death. All patients had the calculation of scores based upon the results of the VCTE. The AGILE 3+ score is derived from the VCTE derived liver stiffness measurement (LSM), ALT, AST, platelet count, diabetes status and age. The AGILE 3+ score performed slightly better than the LSM alone and was found to be predictive of future LREs. Importantly, the results could be followed over time and were highly correlated with improvement or worsening of liver fibrosis. There is an appreciable false-positive rate to the measurements although the false negative rate is very low. An elevated LSM should therefore be repeated prior to the initiation of treatment or a biopsy to confirm the elevation. The calculation of the AGILE 3+ score allows for the assessment of the effect of various interventions both for clinical and research use. These correlations may be more precise than those seen with liver biopsy, suggesting that this may replace the need for liver biopsies for monitoring these patients in both the clinical setting as well as future research studies.

Based on these and other data, we will try to establish a reliable referral source for all of our markets such that when at-risk patients are screened and found to have an intermediate FIB-4, they can easily be referred for VCTE/FibroScan testing to see if further evaluation or treatment is indicated. Elevated FIB-4 tests should be referred for evaluation.

Real-world evidence of downstream procedures and complications associated with lung cancer screening

Current guidelines for lung cancer screening draw from results of the National Lung Screening Trial (NLST).[30] Recommendations are for an annual low-dose CT scan for individuals aged 50–80 with a 20-pack year history of tobacco smoking within the past 15 years.[31] Data from the NLST indicated 17.7% of patients undergoing screening may encounter a complication from screening, with 9.4% suffering a major complication.

A report of a recent retrospective cohort study indicates real-world rates of complications and major complications are much higher than those found in the NLST.[32] The study looked at coding data from records of 9266 screened patients to determine a diagnosis of lung cancer, additional imaging, and invasive procedures within the 12 months following initial screening. The study found that 31.9% of patients had downstream imaging while 2.8% had invasive procedures (e.g., biopsy, bronchoscopy, thoracostomy, etc.). The overall complication rate within 30 days of the procedure was 30.6%, almost twice that found in the NLST, and the major complication rate was 20.6% more than twice that found in the NLST.

Performance of the screening test in this study population was as follows: positive predictive value, 9.5% [95% CI, 8.0% to 11.0%]; negative predictive value, 99.8% [CI, 99.7% to 99.9%]; sensitivity, 92.7% [CI, 88.6% to 96.9%]; specificity, 84.4% [CI, 83.7% to 85.2%]. This comports with the findings of the NLST and speaks to the robustness of the screening. However, the real-world downstream effects may be more harmful than originally indicated by earlier trials, and merit engaging patients in shared decision-making conversations about whether to undergo screening.

Strongly consider bariatric surgery for obesity with type 2 diabetes mellitus

Bariatric surgery in appropriately selected patients with obesity can result in significant and sustained weight reduction with improvement in associated metabolic derangements. A recent report of a pooled analysis of the Alliance of Randomized Trials of Medicine vs Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D) examined health outcomes of 262 patients with T2DM and obesity over 7–12 years of follow-up.[33] Patients were randomized to the bariatric surgery group or to the medical management group. Over the period of study, the group randomized to undergo bariatric surgery required fewer T2DM medications and had a lower HbA1c than the medical management group (-1.5% (95% CI, -2.1% to -0.9%; P < 0.001). The surgery group also had higher rates of T2DM remission (at year 7, 18.2% vs 6.2% in the medical management group (odds ratio, 3.4 [95% CI, 1.3-9.2]; P = 0.02). Lipid profiles were improved in the surgery group compared with the medical management group. There were no differences in death or major adverse cardiovascular events between groups, although the surgery group had more gastrointestinal adverse events, anemia and fractures.

Medical management varied by treatment site, but all were consistent with the Diabetes Prevention Program[34] and Look AHEAD[35] interventions, which are more intensive than usual care. Bariatric surgery included the 3 common procedure types: Roux-en-Y gastric bypass, sleeve gastrectomy or adjustable gastric banding.

Although a comprehensive cost-benefit analysis between these 2 approaches is beyond the scope of this summary, the long-term use of newer antidiabetic medication classes of drugs can be cost-prohibitive and has been covered elsewhere.[36] Bariatric surgery performed on the right population can have profound and lasting beneficial effects and should be strongly considered in obese patients with T2DM.

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Learning objectives	• Discuss approaches to weight loss in obese patients that include lifestyle/behavioral, procedural and pharmaceutical interventions • Describe how using MRI-guided targeted biopsy for prostate cancer detection can result in fewer unnecessary biopsies and reduced diagnosis of insignificant cancers compared to a systematic prostate biopsy approach • Compare atrial fibrillation ablation outcomes in heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved EF (HFpEF) • Identify when spine surgery for degenerative disc disease is indicated as an appropriate intervention • Examine the incidence of periprosthetic joint infection in patients undergoing total joint arthroplasty (TJA) and its association with preoperative and postoperative colonoscopy

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Obesity treatments summarized and compared

Obesity, defined in the United States as excess fat storage and BMI 30 or higher, is present in over 40% of the U.S. adult population.[1] This condition is commonly accompanied by one or more adiposity-based chronic diseases (ABCD). ABCDs, such as type 2 diabetes mellitus, osteoarthritis, sleep apnea, cardiovascular diseases, some cancers, metabolic dysfunction-associated steatotic liver disease (MASLD, also known as NAFLD), and others limit quality of life and longevity, and are associated with enormous health care dollar expenditures and burden of disease.[2] Each ABCD has a host of different treatment options, yet all treatment regimens share a common goal of weight loss to reduce the disease burden, disease progression and complications from disease.

Approaches to weight loss include lifestyle and behavioral, procedural and pharmaceutical interventions. Several aspects have been addressed in previous issues of this newsletter, and updates are provided below.[3,4,5,6,7] Clinically meaningful sustained weight reduction has been ascribed to as little as a 5% reduction.

Lifestyle and behavioral interventions

Lifestyle and behavioral interventions are numerous and may include efforts to improve physical activity, diet, sleep and stress management in both the short and long term. These types of interventions are often necessary, but not sufficient to impact obesity sustainably and substantially. The effectiveness of interventions to address obesity that included increasing physical activity and improving nutrition, and that lasted 6 months or less, has been examined in a recent systematic review and meta-analysis.[8] In this review, 14 randomized controlled trials with a combined total of 2,407 participants were identified who met inclusion criteria. Specific interventions varied, as did level and intensity of engagement (e.g., in-person and frequent, to remote and intermittent). Average baseline weight across individuals in all included studies ranged from 82 kg to 139 kg. The pooled mean difference in weight change was -2.59 kg (95% CI, -3.47 to -1.72). This is less than the ≥ 5% reduction in body weight that is the usual goal of weight loss in obese patients.

Procedural interventions

As recently outlined in the last issue of this newsletter, common bariatric surgery procedure types include the roux-en-Y gastric bypass and endoscopic sleeve gastroplasty (ESG).[9] These procedural interventions have reported efficacy of sustained weight reduction of 13%–26% over a 20-year period. Serious complications are relatively low when performed by experienced surgeons at established bariatric centers.[10]

Sustained benefits have been well described. A randomized controlled trial that compared bariatric surgery plus intensive medical therapy versus intensive medical therapy alone demonstrated significantly better outcomes in quality of life, lipid profile and glucose control over a 5-year period for the surgery group.[11] An observational study of 20,235 patients with severe obesity and type 2 diabetes mellitus showed bariatric surgery was associated with a significantly lower risk of macrovascular diseases at 5 years (2.1% in the surgical group versus 4.3% in the nonsurgical group; hazard ratio, 0.60 [95% CI, 0.42-0.86]), as well as a lower incidence of coronary artery disease (1.6% in the surgical group versus 2.8% in the nonsurgical group; hazard ratio, 0.64 [95% CI, 0.42-0.99]).[12]

More recently, a non-randomized controlled trial followed 2,867 women with obesity for a median follow-up of 23.9 years and found those who underwent bariatric surgery had a significantly lower risk of breast cancer (hazard ratio [HR], 0.68; 95% CI, 0.49–0.94; P = 0.019; adjusted HR, 0.72; 95% CI, 0.52-1.01; P = 0.06).[13] As this protective effect was most pronounced in women with the highest baseline insulin levels, the mechanism of benefit is thought to be related to the decrease in insulin resulting from decreased weight from the surgery. Adverse events of bariatric surgery typically include sequelae related to gastrointestinal malabsorption, refractory esophageal reflux in the ESG group, and reoperation for internal hernias in the roux-en-Y gastric bypass group. Despite the high efficacy and relatively low risks of these types of bariatric surgeries, by some estimates, less than 1% of eligible patients undergo these procedures.[14]

Pharmaceutical interventions

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have garnered much attention in the lay press for use in weight loss and have recently been FDA-approved for not only weight reduction, but also for reducing cardiovascular disease risk.[15] A systematic review and network meta-analysis recently published in the *Lancet* reviews the effectiveness of multiple drug classes for weight loss in obesity.[16] This review examined 132 trials enrolling 48,209 participants and compared effectiveness of drugs to lifestyle modification alone. Phentermine-topiramate was identified as the most effective for achieving ≥ 5% weight reduction (odds ratio [OR] 8·02, 95% CI 5·24 to 12·27; mean difference [MD] of percentage bodyweight change −7·98, 95% CI −9·27 to −6·69) followed by GLP-1RAs (OR 6·33, 95% CI 5·00 to 8·00; MD −5·79, 95% CI −6·34 to −5·25). Findings also revealed semaglutide (a GLP-1RA) had the largest effect (above the 5% threshold), and that phentermine-topiramate had among the highest risk of adverse events leading to medication discontinuation (typically paresthesias, constipation, and/or cognitive complaints). Phentermine-topiramate may be prescribed as its generic components.

The medication classes work in various ways and all result in decreased caloric intake or absorption. Importantly, as weight is reduced, so is energy expenditure.[17] When these medications are discontinued, the balance between weight regulatory hormones such as ghrelin and leptin result in caloric intake returning to "normal" (pre-medication levels) for that individual and, with a decreased energy need, the weight returns. In other words, weight regain is common and expected when any pharmaceutical intervention for obesity is discontinued. This means patients typically need to remain on these medications for life to maintain the weight-reduction benefits unless they significantly increase energy expenditure.[18]

Intervention comparisons

All forms of obesity treatment should include lifestyle or behavioral interventions as costs are reasonable and adverse events rare. Addition of bariatric surgery or pharmaceutical interventions should be done using shared decision-making. A recent cost-effectiveness analysis examined endoscopic sleeve gastroplasty (ESG) versus a GLP-1RA (semaglutide) and found that ESG was far more cost-effective than GLP1-RA therapy, concluding that "ESG is cost saving compared with semaglutide for class II obesity." This finding is due to the increased effectiveness and lower costs of ESG and the increased dropout rates over time with semaglutide. The annual price of semaglutide must decrease by more than threefold to achieve non-dominance with ESG."[19] Pricing analysis was based on information from the Institute for Clinical and Economic Review.[20]

Summary of evidence

Lifestyle and behavioral interventions combined with endoscopic sleeve gastroplasty performed by experienced surgeons at designated bariatric surgery centers appears to be the most cost-effective approach to sustained and clinically meaningful weight loss in obese patients. While GLP-1RAs appear to be effective for weight reduction and are well-tolerated compared with other effective drugs, they are cost-prohibitive when compared with alternative interventions and have a high rate of discontinuation with subsequent weight regain.

Prostate cancer detection using MRI-guided targeted biopsy results in fewer unnecessary biopsies and reduced diagnosis of insignificant cancers compared to a systematic prostate biopsy approach

Prostate-specific antigen (PSA) is a sensitive but not specific serum marker for clinically important prostate cancer. In the U.S., following detection of elevated PSA, a transrectal ultrasound guided systematic (TRUS) prostate biopsy of usually 12 areas in the prostate is the typical approach for suspected prostate cancer.[21] Avoiding unnecessary biopsies for low-risk prostate cancer is important not only to reduce the rate of diagnosis and subsequent ineffective treatment, but also because patients in active surveillance programs for low-risk prostate cancer may opt for more invasive treatment, partially to avoid repeated biopsies.[22]

A recent systematic review and meta-analysis of the use of prebiopsy MRI to help determine the need for, and location of, prostate biopsy highlights the benefits of this approach over the conventional systematic ('blind') TRUS biopsy approach.[23]

- The analysis included more than 80,000 patients from 12 different studies.
- Clinically significant prostate cancer detection rates were not significantly different between PSA screening plus MRI versus PSA screening without MRI (for PI-RADS 3-5, OR 1.02 (95%CI; 0.75-1.37), for PI-RADS 4-5, OR 0.85 (95% CI; 0.49-1.45)).
- Positive predictive value (PPV) for significant cancers, biopsy indication and biopsy adherence were all more favorable for the PSA plus MRI group compared to the PSA without MRI group, with higher PPV, lower biopsy rate and higher biopsy adherence.
- For the MRI group, the odds ratio (OR) for biopsy was 0.28 (95% CI, 0.22-0.36; p≤0.001) and OR for detecting insignificant cancers was 0.34 (95% CI, 0.23-0.49; p=0.002).

In short, prebiopsy MRI following elevated PSA helped identify clinically significant prostate cancer and screened out those clinically insignificant cancers that don't require a biopsy. This approach can result in fewer unnecessary biopsies compared with the traditional approach of PSA plus systematic prostate biopsies. It can also detect many fewer low-risk prostate cancers for which treatment is not recommended, yet are carried out in 40% of men. These recommendations should be incorporated into practice and are consistent with several urological guidelines.[24,25]

Prostate-specific antigen screening and 15-year prostate cancer mortality

The option of screening for prostate cancer using a shared decision-making approach has become the standard of care following the publication of the 15-year outcomes of the European Study of Screening for Prostate Cancer (ERSPC) trial.[26] At 16 years, the benefit of screening was small. The number of men needed for screening to prevent one prostate cancer death was 570. Eighteen men needed to receive definitive treatment to prevent one prostate cancer death. Added to this literature characterizing the magnitude of the screening benefit is the 15-year follow up of the U.K. CAP trial that evaluated the effect of a one-time prostate-specific antigen (PSA) screening invitation in 415,337 men, randomized 1:1 to screening versus no screening.[27] Approximately 34% of the invited men had a satisfactory PSA screen.

At 15 years, the cumulative risk of prostate cancer in the intervention group was 0.47 per 1,000 person years compared to 0.50 per 1,000 person years in the control group, equating to a HR of 0.92. Importantly, clinically insignificant Gleason score 6 cancers were diagnosed at a 37% higher rate at 2.2% of the screened group compared to 1.6% of the control group. The detection rate of intermediate and high-grade cancers was not different in the screened versus control groups. All cause mortality was also not different in the 2 groups (23.2% in the intervention group versus 23.3% in the control group respectively).

In this trial, the overall reduction in prostate cancer death rate was 9 per 1,000 person years, with no reduction in overall mortality. This magnitude of reduction in prostate cancer mortality was smaller than the a priori defined effect size considered important for clinical and public health benefit. This study adds to our understanding not only of the small benefit of PSA screening for reducing prostate cancer mortality, but also the very long-time horizon post treatment needed to see this small benefit. This last point is particularly relevant as the harms from PSA screening in men over the age of 69 will likely exceed the benefit of screening, and we continue to screen this population at a high rate.

Atrial fibrillation ablation outcomes in heart failure with reduced ejection fraction (HFrEF) versus heart failure with preserved EF (HFpEF)

Evidence from randomized clinical trials (RCTs) suggests that catheter ablation may be superior to conventional rate or rhythm control for improving clinical outcomes in patients with coexisting atrial fibrillation (AF) and heart failure (HF). However, these studies primarily included patients with HFrEF. It is unclear whether patients with HFrEF derive the same benefit from catheter ablation as patients with HFrEF. Understanding this is important as information collected during the second 25-year period of the Framingham Heart Study reveals that the lifetime risk of HFpEF is estimated at around 19.3%. This is almost twice the approximate 11.4% lifetime risk associated with HFrEF.[28] A recent systematic review and meta-analysis examined the literature to determine the outcomes of AF ablation in the subsets of patients with HFrEF and HFpEF.[29]

The 12 randomized controlled trials included 2,465 patients and the comparators were conventional rhythm and/or rate control.

- There were 1,552 participants with HFrEF and 913 participants with HFpEF.
- The primary outcome was HF events, defined as HF hospitalization, clinically significant worsening of HF, or unscheduled visits to a clinician for treatment intensification.
- Secondary outcomes included cardiovascular and all-cause mortality.

Catheter ablation compared with conventional therapies was associated with reduced risk of cardiovascular death in patients with HFrEF (37 of 526 patients [7.0%] versus 78 of 516 patients [15.1%]; RR, 0.49) but not in patients with HFpEF (15 of 468 patients [3.2%] versus 17 of 481 patients [3.5%]; RR, 0.91). Catheter ablation compared with conventional therapies was also associated with reduced risk of all-cause mortality in patients with HFrEF (84 of 687 patients [12.2%] versus 137 of 676 patients [20.3%]; RR, 0.63) but not in patients with HFpEF (34 of 468 patients [7.3%] versus 43 of 481 patients [8.9%]; RR, 0.95). Lastly, with respect to HF hospitalizations and symptoms, the same pattern was observed. Catheter ablation was associated with a decrease in risk of HF events compared with conventional therapies in patients with HFrEF (107 of 560 patients [19.1%] versus 178 of 548 patients [32.5%]; RR, 0.59), while no benefit was observed in patients with HFpEF (51 of 468 patients [10.9%] versus 55 of 481 patients [11.4%]; RR, 0.93).

The authors conclude that “the currently available randomized evidence suggests that catheter ablation for AF was associated with reduced risk of HF events in patients with HFrEF but with no or limited efficacy in patients with HFpEF.” This includes no improvements in cardiovascular and all-cause mortality in patients with HFpEF, although the numbers of patients with these outcomes were small in these trials. There are 2 trials currently enrolling patients with HFpEF and until these results are available, catheter ablation should not be considered a standard of care for patients with HFpEF, particularly since the procedure carries risks, has a 2-year failure rate requiring a second ablation in the range of 40–50%,[30] and carries a cost of approximately $25,000.

Evidence to avoid spinal fusion, this time in the cervical region

In patients with degenerative disc disease, conservative measures, including cognitive behavioral interventions for chronic pain, are first-line therapy and often sufficient. For those in whom it is indicated, such as those with persistent neurological involvement with dysfunction, surgery may also be appropriate. Approaches to spine surgery for degenerative disc disease vary depending on the spine segment. Fusing 2 or more spinal segments together is frequently used in both the cervical and lumbar regions. In the lumbar region, spinal decompression with fusion in most patients is no better than decompression alone for most patient-centered outcomes and has been summarized in previous issues of this newsletter.[31, 32] A recent systematic review of outcomes from anterior cervical discectomy and fusion (ACDF) compared with cervical disc arthroplasty (CDA) alone also favored the non-fusion group.[33]

The meta-analysis looked at 10-year outcomes after surgery and included studies reporting on 428 patients in the ACDF group and 498 in the CDA group. At 10 years after the index surgery, the CDA group did better on the Neck Disability Index where lower is better (mean difference= -2.0; CI: -3.842 to -0.161; P= 0.033) and the Visual Analog Scale where lower is better (mean difference= -0.25, CI: -0.359 to -0.134, P<0.001). However, this group did worse on the Japanese Orthopaedic Association back and neck questionnaire where lower is worse (mean difference = -0.38; 95% CI: -0.712 to -0.047; P =0.025). None of these differences reached the minimal clinically important difference (MCID). Most importantly, the CDA group had significantly fewer secondary surgeries (OR =0.395; 95% CI: 0.252–0.620; P< 0.001) and fewer adverse events (OR =0.560; 95% CI: 0.323–0.972; P =0.039).

Taken together, these results indicate patients who undergo CDA for degenerative disc disease have fewer secondary surgeries and adverse events compared to those who undergo ACDF. Other outcomes appear to be clinically equivalent.

Surgery, needle fasciotomy or collagenase injection for dupuytren contracture

Dupuytren contracture (DC) is present in up to 30% of some populations, increasing with advancing age. There are multiple treatment options and a recent trial compared treatment by surgery, needle fasciotomy or collagenase injection.[34] Although collagenase injection and needle fasciotomy are office-based procedures, collagenase injection is expensive and the data on comparative efficacy are sparse. This study randomized about 100 patients each into the 3 treatment arms at 6 hospitals in Finland. Although participants were not blinded to their treatment allocation, the outcome assessors were. The primary outcome was > 50% tendon release along with patients reaching an acceptable symptom state.

Success rates were similar between the groups at 3 months ranging from 71% to 73%. But at 2 years, the success rates were maintained with surgery (78%), whereas they declined with both needle fasciotomy (50%) and collagenase injection (65%). Compared with surgery, both percutaneous groups had a higher rate of retreatment. Although collagenase injection was slightly more effective than needle fasciotomy, the number of treatments needed to have one patient reach the primary outcome with collagenase injection compared to needle fasciotomy was 6. With a cost of $6,400 per injection, this would equate to a cost of $38,400 to achieve a more effective outcome in one patient using collagenase injection over needle fasciotomy.

Since these patients most often present to primary care for advice on management, these results should inform the discussion that we have with our patients on the relative efficacy of the 3 procedures.

Does colonoscopy increase the risk of joint infection in those with a prior total joint arthroplasty?

There are not good data to inform whether there is a risk of periprosthetic joint infection (PJI) when having a colonoscopy within one year following a total joint arthroplasty (TJA). Periprosthetic joint infection (PJI) after TJA procedures is a rare but devastating complication that is associated with increased morbidity and mortality. The American Academy of Orthopedic Surgeons does not have a clear consensus statement for timing of colonoscopy because there is an unclear risk of PJI from transient bacteremia in accordance with the American Society for Gastrointestinal Endoscopy 2015 practice guidelines.

With this as background, a retrospective cohort study was published using the Military Data Repository (MDR).[35] The primary outcome was the incidence of PJI within one year after TJA in a cohort of patients who had a colonoscopy within 6 months prior to a TJA (preoperative colonoscopy cohort) and the incidence of PJI within one year of colonoscopy in those who had a colonoscopy following a TJA (postoperative colonoscopy cohort). In each cohort, patients were propensity matched to a control group that did not have colonoscopy. There were 11,482 patients over age 45 who had a colonoscopy within the 6 months prior to their TJA, and 7,497 patients over age 45 had a colonoscopy following a prior TJA. The risk of PJI within one year postoperatively in those in the preoperative colonoscopy cohort was 2.8% (n = 325) in patients who did have a colonoscopy versus 2.4% (n = 5504) in patients who did not have a colonoscopy within 6 months before surgery (OR 1.1, not significant). In the postoperative colonoscopy cohort, the risk of PJI within one year of the post-TJA colonoscopy date was 1.8% in the colonoscopy versus 2.1% in the control cohort, also not significant.

In the large military beneficiary cohort, no independent association was found between colonoscopy and PJI risk through the one year follow-up in patients who underwent preoperative or postoperative colonoscopy. These data can inform our recommendations to our patients and orthopedic colleagues when patients are due for colonoscopy around the time of a total joint arthroplasty.

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Learning objectives	• Examine the new peripheral artery disease practice guidelines and recognize the emphasis on avoiding screening for peripheral artery disease (PAD) in asymptomatic patients with no risk factors guideline-directed medical therapy, and revascularization surgery only for specific indications. • Identify current pharmacotherapies, the utilization of these drugs and their outcomes for chronic obstructive pulmonary disease (COPD) and nonarteritic anterior ischemic optic neuropathy (NAION). • Evaluate and compare routine functional stress testing and guideline directed medical therapy for coronary artery disease (CAD). • Determine the risk and mortality reduction with a colonoscopy screening.

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Commercial support
No commercial support was received for this activity.

Peripheral artery disease practice guideline update from American College of Cardiology (ACC) and American Heart Association (AHA)

The American College of Cardiology and American Heart Association have recently updated their 2016 practice guidelines on management of lower extremity PAD with a new 2024 version.[1] Based on the evidence of poor outcomes, these updated guidelines caution providers to not use procedural interventions for asymptomatic or below popliteal PAD except in extremely rare circumstances. The guidelines categorize lower limb PAD as asymptomatic, chronic symptomatic, chronic limb-threatening ischemia and acute limb ischemia. Limb-threatening ischemia remains the primary indication for procedural intervention, whereas asymptomatic disease and infrapopliteal disease other than limb-threatening ischemia are best managed medically. For those with chronic activity-limiting symptoms unresponsive to an adequate trial of medical management and exercise therapy, invasive procedures may also be considered. All patients with considerations for surgery should be referred to a multidisciplinary team.

Since many of the underlying pathophysiological mechanisms leading to PAD are the same as for other atherosclerotic vascular diseases, medical management follows similar principles. Anti-lipid, anti-platelet and anti-thrombotic medications, exercise and nutrition therapy, blood pressure control, diabetes management (when present) and smoking cessation are all cornerstones of treatment.

Diagnosis of PAD is based on a careful history, physical exam and ankle-brachial index (ABI) measurement. Universal screening of asymptomatic patients with no risk factors is not recommended. Those patients who have diabetes mellitus, are over age 65, or have evidence of atherosclerosis in one or more vascular beds are considered at risk. Those with symptoms of claudication, or with physical exam findings consistent with PAD, should undergo further workup with an ABI and additional physiological testing. Advanced imaging should be reserved for pre-surgery planning, but it's not typically ordered in the primary care setting.

Figure 4, below, is from the published guideline. It shows medical management of PAD. The green color represents class 1 (strong) recommendations, magenta class 2a (moderate), and purple class 2b (weak). Specific medications and dosage recommendations are available for each class in the full guideline.

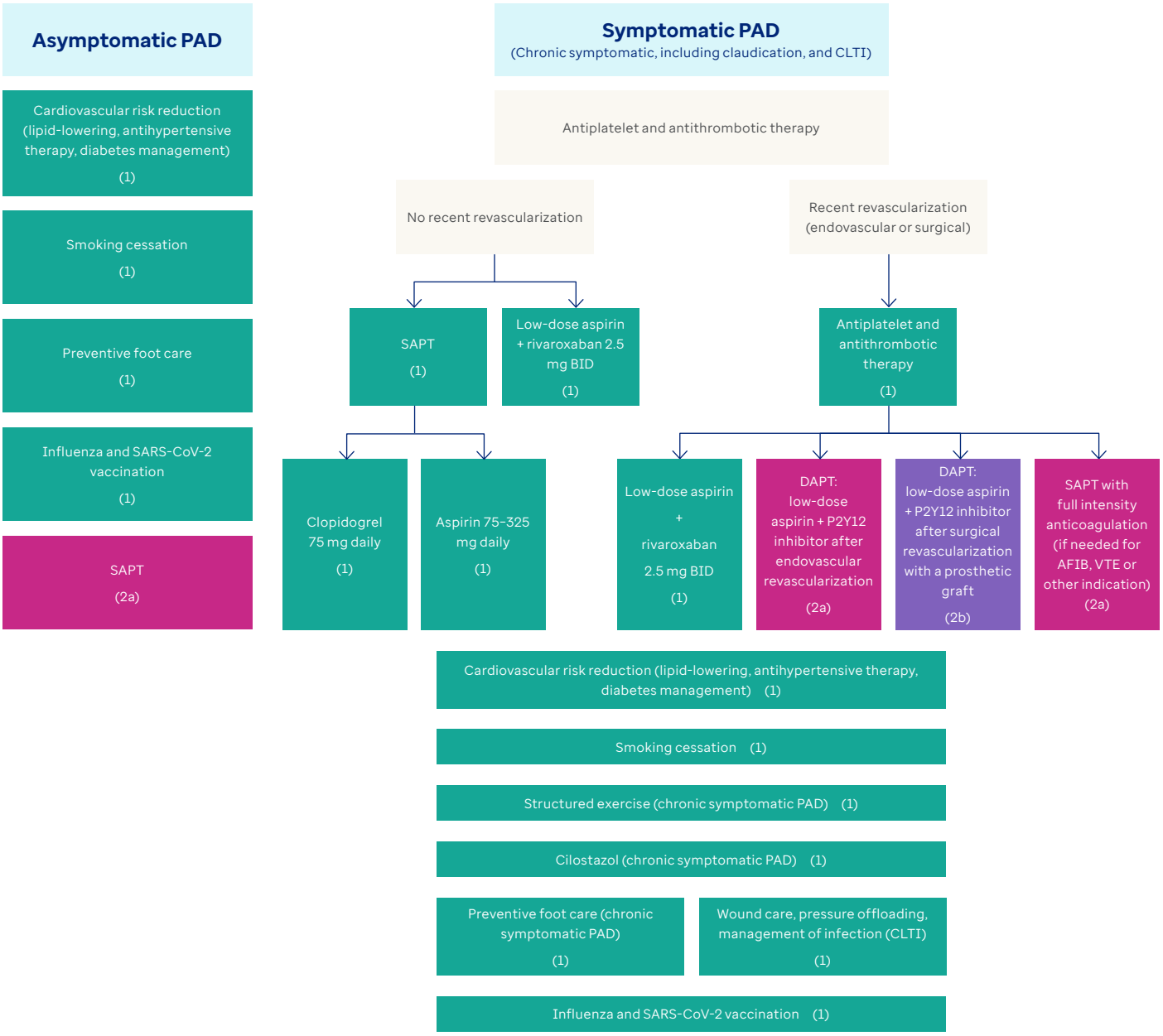

Figure 4. Medical Therapy and Foot Care for PAD.

Colors correspond to Table 3. Afib indicates atrial fibrillation; BID, 2 times daily; CLTI, chronic limb-threatening ischemia; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and VTE, venous thromboembolism.

Figure 5, below, is also from the published guideline. It shows that revascularization for chronic symptomatic PAD is a magenta class 2a (moderate), and purple class 2b (weak) recommendation when benefits outweigh risks, and an orange class 3 (no benefit, not recommended) when risks outweigh benefits.

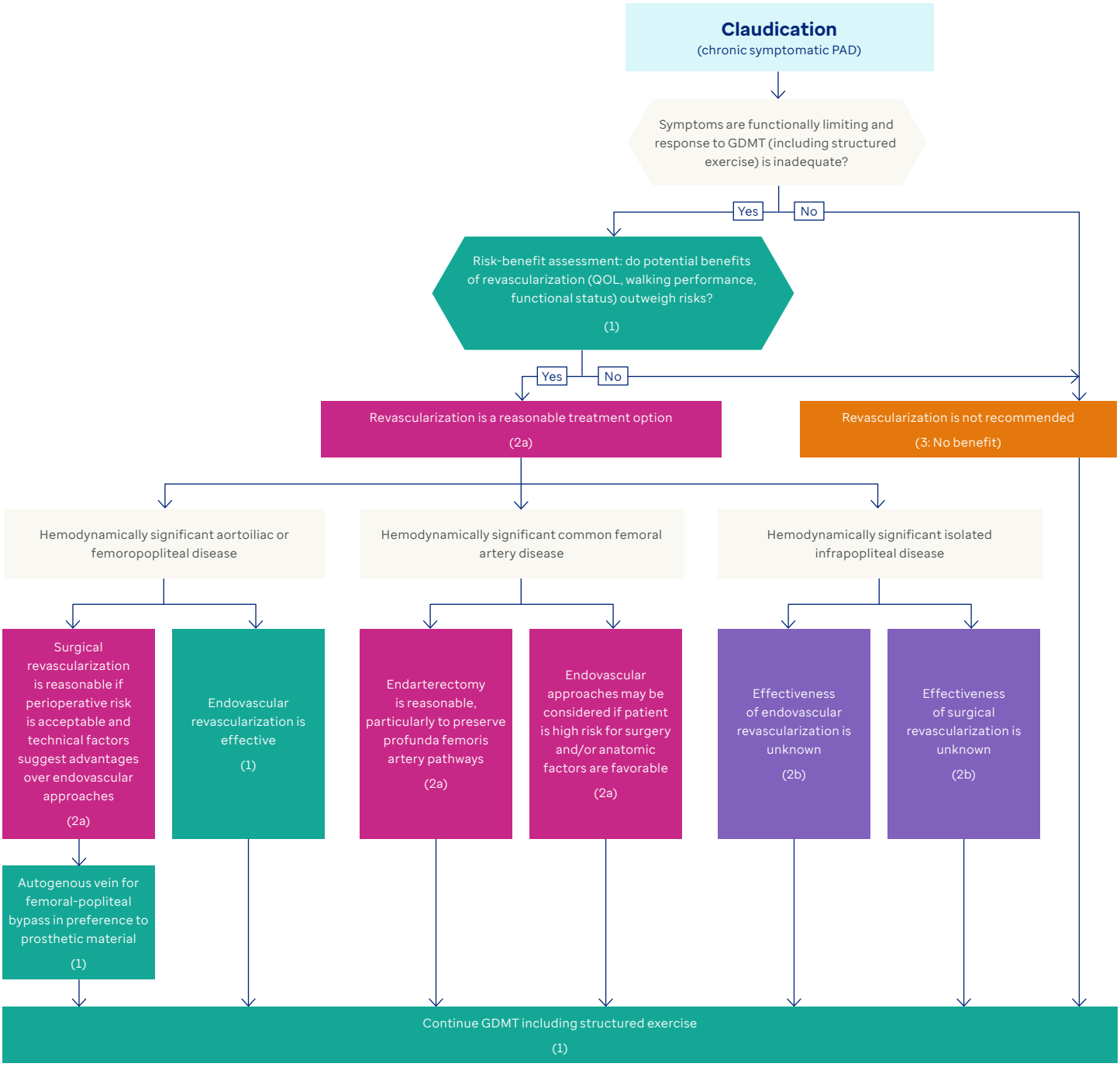

Figure 5. Algorithm for Revascularization for Claudication (Chronic Symptomatic PAD).

Colors correspond to Table 3. GDMT indicates guideline-directed management and therapy; PAD, peripheral artery disease; and COL, quality of life.

This is particularly important as studies have shown increased adverse outcomes, including increased amputation rates, with aggressive procedural management of infrapopliteal disease.[2]

In summary, the new guidelines:

- Reiterate avoiding screening for PAD in asymptomatic patients with no risk factors
- Encourage guideline-directed medical therapy for both symptomatic and asymptomatic PAD
- Endorse revascularization surgery only for specific indications

Association of sudden onset blindness with semaglutide

Nonarteritic anterior ischemic optic neuropathy (NAION) is the second most common form of optic neuropathy and is of unknown pathogenesis. The incidence is from 2–10/100,000, making it the second most common cause of blindness due to optic nerve damage, with glaucoma being the most common cause.

Based on anecdotal concerns over a relationship between the GLP1-RAs and NAION, investigators at the Massachusetts Eye and Ear Institute conducted a retrospective propensity matched cohort study. To estimate the relative risk of NAION developing in patients taking semaglutide, they examined patients referred to neuro-ophthalmology from 2017 to 2023.[3]

710 patients with myotonic dystrophy type 2 (DM2) and 979 patients with obesity who were taking semaglutide were propensity matched 2:1 to a cohort of patients not taking semaglutide.

In the diabetes population, NAION occurred in 17 patients in the semaglutide cohort versus 6 in the comparative cohort. The median age was 57 (49–63) years for the semaglutide cohort and 58 (47–66) years for the non-semaglutide cohort.

In the obese cohort, NAION occurred in 20 patients in the semaglutide cohort versus 3 in the comparative cohort. The median age was 46 (35–58) years for the semaglutide cohort and 44 (29–59) years for the non-semaglutide cohort. The hazard rate for the development of NAION in the diabetes cohort was 4.28, and for the obesity cohort was 7.64.

It is important to recognize that this relationship is not necessarily causal, but rather reflects only an association in a retrospective analysis. However, the strength of the association was strong and the sample size of 629 NAION cases over 6 years was a substantial fraction of expected cases from the Boston area. With a relatively low baseline annual incidence of NAION, the risk/benefit analysis for most patients initiating therapy would still favor the use of a GLP1-RA. However, due to the increasing utilization of these drugs and the devastating outcome of sudden blindness, further studies need to be done to confirm or refute this relationship and also to define the magnitude of the increased risk if present. The authors propose the options of a much larger, retrospective, multicenter population-based cohort study; a prospective, randomized clinical study; or a post-market analysis of all GLP-1 RA drugs.

New therapies for COPD — high cost, limited value

Over 15 million Americans are affected by COPD. It is the fourth leading cause of death and generally among the top 5 reasons for inpatient admission in the Medicare population. Available inhaler therapies have a modest effect on improving symptoms and reducing the frequency of moderate to severe exacerbations. They have a more limited effect on reduction of mortality or progressive loss of lung function. Two new drug classes of treatment will soon be added to the current armamentarium of pharmacotherapies. The first is ensifentrine, which was recently approved by the FDA. The second will be dupilumab (Dupixent), a biological therapy, which has been approved in Europe, with U.S. approval expected soon.

Ensifentrine was recently evaluated by the Institute for Clinical and Economic Review (ICER) and that information formed the basis of this review.[4] It is a novel inhaled dual inhibitor of PDE3 and PDE4 enzymes that relaxes the airway's smooth muscle and decreases inflammation. Treatment is twice daily via nebulizer. It has been evaluated in two 24-week randomized controlled trials (RCTs). About 1,500 patients were included in the combined group with a 2:1 ratio of active drug versus placebo. Since study design and participants were similar, the results have been combined. Participants had moderate to severe COPD and were on stable background therapy, including no therapy or LAMA or LABA, with or without inhaled corticosteroids (ICS). Patients on dual LAMA+LABA therapy or triple LAMA+LABA+ICS were excluded from the trials.

In terms of lung function in the 2 trials, the FEV-1 improvement was between 87 ml and 94 ml, which did not meet the minimal clinically important difference (MCID) of 100 ml. With respect to patient symptom scores, as examples, one of the studies did not show benefit in the Evaluating Respiratory Symptoms (E-RS) score and the other showed a median reduction of 1.0, with the MCID being >2.0. The scores on the dyspnea index just met the threshold for the MCID. The reduction in moderate to severe exacerbations equated to one less exacerbation every 6 years, approximately. Importantly, the subset of severe exacerbations (those requiring hospitalization) was not provided.

Ensifentrine was not found to be cost effective. At a wholesale acquisition cost of $35,400 per year, the incremental cost effectiveness ratio was $492,000 per QALY gained, or close to 5 times the accepted QALY threshold. ICER estimated that the cost was between 3- to 5-fold higher than would be needed to be cost effective. Importantly, when considering the above small benefits, it is emphasized that patients were not permitted to be on a LABA/LAMA combination or triple inhaler therapy in these 2 trials. Therefore, it is unknown whether there would be any benefit of ensifentrine for patients on these 2 regimens, which encompasses most of the patients with moderate to severe COPD.

Dupilumab (Dupixent) is a biological therapy which has been approved for asthma and atopic dermatitis. It has also been studied for use in COPD and in 2 RCTs – BOREAS and NOTUS.[5,6] These trials each enrolled approximately 1,000 patients with a 1:1 drug versus placebo ratio. Both studies evaluated the same patient population. Patients had moderate to severe COPD, blood eosinophil count ≥ 300 cells/μL, were current or former smokers, and with a history of high exacerbation risk. They were on a background of ICS+LAMA+LABA (or LAMA+LABA if ICS was contraindicated), and patients with asthma were excluded. The primary outcome was the rate of moderate to severe exacerbations per year. In BOREAS, the reduction in exacerbations equated to one less exacerbation per 3 years on therapy. For NOTUS, the reduction equated to one less exacerbation per 2.3 years. FEV1 results showed improvements of 83ml and 62 ml, once again not meeting the MCID criteria. Results were more significant for the subpopulation of patients with a baseline fractional exhaled nitric oxide (FeNO) ≥ 20 ppb. Elevated levels of FeNO are correlated with greater degrees of airways inflammation. One of three measurement scores of patient symptoms exceeded the MCID for improvement. There were no mortality improvements in either trial.

Importantly, less than 10% of exacerbations were severe, enough to require hospitalization, with the remainder being treated in the office with corticosteroids +/- antibiotics. ICER has not yet reviewed dupilumab as it is not yet FDA approved. But our Value and Therapeutics committee looked at the number needed to treat per year (NNT) to prevent one severe exacerbation and multiplied this by the yearly cost of the drug, which is approximately $50,000. The results were approximately $3 million per prevented severe exacerbation based on BOREAS results and approximately $2 million based on NOTUS results. Both results are clearly not cost effective. Whether there is a subset of patients with more severe airways inflammation, analogous to a severe asthma population, in which treatment might be cost effective is not known at this time.

Routine functional stress testing not indicated for patients after PCI following acute coronary syndrome

We now have extensive literature supporting the equivalency of guideline-directed medical therapy and invasive management of stable coronary artery disease (CAD) with respect to future major adverse coronary events.[7,8] Therefore, routine ischemia testing is no longer recommended for patients with stable CAD.

Patients who have cardiovascular disease warranting them to undergo percutaneous coronary interventions (PCI) are presumed to be at elevated risk of future major adverse coronary events (MACE). The subset of these patients who undergo PCI due to an acute coronary syndrome could be presumed to have an even higher risk. A recent study examined the effect of routine functional stress testing at 12 months after PCI compared to guideline directed medical therapy (GDMT) alone. Additional analyses were performed to examine outcomes of those patients who had a PCI following ACS versus those who underwent a PCI without a preceding ACS.[9]

The primary outcome was assessed for a 2-year period and was a composite of death, myocardial infarction or hospitalization for unstable angina. Of the 1,706 patients who underwent PCI, 526 presented with ACS. The primary outcome was similar between those who underwent routine functional testing versus those who received GDMT (functional testing: 16 of 251[6.6%]; standard care: 23 of 275 [8.5%]; HR, 0.76; 95% CI, 0.40–1.44; P = 0.39). Those who presented with ACS had higher incidence of the primary outcome compared with those who did not present with ACS (HR, 1.55; 95% CI, 1.03–2.33; P = 0.03). In other words, those who presented with ACS and underwent PCI had a higher risk of the primary outcome compared to those who did not present with ACS, but the use of routine functional stress testing in this group did not significantly change the outcomes. Those who underwent PCI without preceding ACS also did not benefit from routine functional stress testing (functional testing: 30 of 598 [5.1%]; standard care: 28 of 582 [4.9%]; HR, 1.04; 95% CI, 0.62–1.74; P = 0.88).

Patients with stable CAD do not require, nor benefit from, routine ischemia testing. For those patients who develop new stable chest pain, functional stress testing is still not preferred. Rather, coronary CT angiography (CCTA) can help guide subsequent work-up and medical versus procedural treatment.[10] The routine use of functional stress testing is of limited value in these settings.

Reduction of colorectal cancer mortality with the use of the fecal immunochemical test (FIT)

Following the publication of the NordICC trial,[11] we have a better understanding of the CRC risk reduction and mortality reduction with colonoscopy screening. Recall that using an intention-to-screen analysis, over a 10-year period, the colonoscopy group had a relative risk reduction of 18% in the incidence of colorectal cancer (CRC) compared to the control group. The risk of dying from CRC was not significantly different between the 2 groups. Since only 42% of those in the colonoscopy-invited group ultimately underwent a screening colonoscopy, additional per-protocol analyses were done looking only at patients who actually underwent colonoscopy. These showed a 31% relative risk reduction in CRC and a 50% relative reduction in death from CRC.

A recent nested, case control study evaluated whether the risk of dying from CRC was reduced with the use of FIT screening.[12] The study was conducted at Kaiser Permanente, which mails FIT kits to all eligible patients who are not otherwise up to date on CRC screening. From an underlying population of 2,127,128 members during 2011 to 2017, there were 1,279 patients identified who had died of CRC and 10,226 matched CRC-free persons.

During the 10-year period prior to the reference date, among control persons, 6,101 (63.5%) completed at least one FIT screening and 4,404 (45.8%) completed 2 or more FITs. The cumulative FIT positive rate among control persons was 12.6% (768 controls), of whom 610 (79.4%) had a colonoscopy within 12 months of the result date. In unconditional logistic regression analyses, completing FIT screening was associated with a 33% lower risk of death from overall CRC (adjusted odds ratio [aOR], 0.67; 95% CI, 0.59–0.76).

In stratified analyses, there was no statistically significant difference in CRC for right colon cancers (aOR, 0.83; 95% CI, 0.69–1.01), but there was a significant 42% lower risk of death for left colon and rectum cancers (aOR, 0.58; 95% CI, 0.48–0.71). The difference in the estimates between the right colon and left colon or rectum was statistically significant (P = .01). Interestingly, a prior study found that the mean stool hemoglobin concentration was 60.0 µg/g for left colon cancers and 12.4 µg/g for right colon cancers. More cancers in the right colon than in the left colon would be expected to generate hemoglobin concentrations below the positivity threshold.[13]

In summary, this nested case-control study found that completing one or more FIT screenings within the prior 5 years was associated with a 33% lower risk of death from colorectal adenocarcinoma. The reduction in mortality risk was significant for those with left colon or rectum cancers (42%). Although the results of this study cannot be directly compared to the colonoscopy results of the NordICC trial, it is interesting that in the invited-to-treat-cohort of NordICC, 42% of patients completed a colonoscopy and, in this study, 46% of patients completed 2 or more FIT tests. The overall reduction in CRC mortality was higher in this trial than in the invited-to-treat-cohort of NordICC. It is a reminder that FIT testing is an appropriate approach to reduce mortality from CRC.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as chief medical officer from 1995–2020. He now serves as the executive director of Translational Research for Optum Care and co-leads the Optum Center for Research and Innovation. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship, New West Physicians was awarded the AMGA Acclaim award in 2015 and the CDC Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine and School of Pharmacy. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

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With over 20 years of clinical, academic and leadership experience regionally, nationally and internationally, Dr. Jacobs currently serves as primary care engagement lead national medical director for Optimal Care within Clinical Performance at Optum Care. He is a clinical professor of Family Medicine at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

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Learning objectives	• Describe the current practice of screening for prostate cancer with elevated prostate-specific antigen (PSA) levels and recognize the distinction between systematic biopsies versus the MRI-targeted biopsies and the significance to cancer diagnosis outcomes. • Discuss the importance of including a mineralocorticoid receptor antagonist (MRA) in heart failure treatments. • Examine the use of tirzepatide and survodutide for metabolic dysfunction associated steatohepatitis (MASH) and early fibrosis. • Recognize the impact of semaglutide on individuals with myotonic dystrophy type 2 (DM2) and chronic kidney disease (CKD). • Explore the development of a blood test that could aid in the diagnosis of Alzheimer's disease and its diagnostic accuracy. • Analyze the detection rate of colorectal adenomas on colonoscopy when aided by an AI technology.

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MRI-targeted versus systematic biopsy for an elevated prostate-specific antigen (PSA)

When there is a clinical suspicion of prostate cancer based on a PSA elevation, the current practice in most of the U.S. is to perform systematic (12 core) biopsy in all patients. Previous studies have shown that when MRI is done prior to biopsy in this group of patients, many will not have a visible lesion. As summarized in the previous issue of this newsletter, when biopsy is restricted to those patients with a visible lesion on MRI, and targeted to that lesion, both the need for biopsy and the overdiagnosis of insignificant prostate cancers (GG1/Gl 6) are significantly reduced (Forum for Evidence Based Medicine July 2024).[1] The major reason this approach has not been widely adopted in the U.S. is that there are a small number of clinically significant tumors found on systematic biopsy in those individuals without a visible lesion on MRI. Because these cancers can be found and then treated on subsequent screening rounds, the pivotal question is whether delaying the diagnosis in this small number of patients risks the development of incurable prostate cancer between screening rounds.

Against this backdrop is the publication of the updated results of the Swedish GÖTEBORG-2 trial.[2] Men who were 50 to 60 years of age underwent PSA screening. Men with a PSA level of 3 ng per milliliter or higher underwent MRI of the prostate. Men were then randomly assigned to the systematic biopsy group in which they underwent systematic biopsy and, if suspicious lesions were found on MRI-targeted biopsy, versus the MRI-targeted biopsy group which underwent MRI-targeted biopsy only (6,500 men in each group). The results were presented after 4 years and 26,000 rson-years of follow-up.

Through the first 4 rounds of screening, there was a highly significant reduction in the need for biopsy in the MRI-targeted group:

- 7.2% of men in the MRI-targeted group needed biopsy, compared to 24.2% in the systematic biopsy group. This relative reduction in the need for biopsy was 70%.
- The overall rate of cancer diagnosis at 4 years was 2.8% in the MRI-targeted biopsy group versus 4.5% in the systematic biopsy group. With respect to the diagnosis of insignificant (GG1/Gl 6) cancers, there was a 57% reduction in the MRI-targeted biopsy group relative to the systematic biopsy group.
- There was also a 16% reduction in the risk of having clinically significant cancer (GG2-GG5) in the MRI-targeted biopsy group as compared with the systematic biopsy group.

Another way to look at these results is: per 1,000 enrolled men, the MRI-targeted biopsy approach led to 51 fewer men undergoing biopsy and 14 fewer men receiving a diagnosis of insignificant GG1/Gl 6 disease, but it also led to a delay in the diagnosis of GG2 or higher disease in 3 men.

What are the implications for this small group of men with delayed diagnosis of higher-grade disease in the MRI-targeted biopsy group? The authors comment that their data strongly indicate that most prostate cancers become visible on MRI before they become incurable. During approximately 26,000 person-years of follow-up in each group in their analysis, only 5 cases of cancer in the MRI-targeted biopsy group and 7 in the systematic biopsy group were very high risk (either GG 5 or advanced metastatic cancer) detected as an interval cancer. Of the 5 such cancers in the MRI-targeted biopsy group, 4 occurred in men with a PSA level of less than 3 ng per milliliter at the preceding screening visit, so would not have triggered a systematic biopsy using our current U.S. guidelines. This is also consistent with our knowledge of the benefits of cancer screening in general, where it is confined to intermediate growth cancers, with high growth rate cancers not showing improved survival through cancer screening, and low growth rate cancers generally reflecting overdiagnosis. The authors go on to state: "Therefore, diagnosis of a cancer that should be treated is delayed in some instances, but far more often, diagnosis of a cancer that is not likely to ever lead to symptoms, and that otherwise could have led to years of unnecessary active surveillance, the risk of unnecessary treatment, and the stigma of a cancer diagnosis, is prevented. These results should encourage guideline committees to update recommendations around prostate cancer diagnosis and screening."

Use of mineralocorticoid receptor antagonists in heart failure

Two recent publications highlight the importance of including a mineralocorticoid receptor antagonist (MRA) in the treatment of all types of heart failure (HF), not just for heart failure with reduced ejection fraction (HFrEF). The first was a meta-analysis of 4 previous trials including over 13,800 patients and examining the MRAs spironolactone, eplerenone and finerenone.[3] Findings confirmed previous evidence that MRAs used in patients with HFrEF reduced hospitalization (HR 0·63 [95% CI 0·55–0·72] and hospitalization, with or without cardiovascular-related death, and all-cause death (0·72 [0·63–0·82]). Additionally, evidence showed MRAs used in patients with HF with mildly reduced ejection fraction and those with preserved ejection fraction (HFmrEF; HFpEF) also had significant benefit, albeit these effects were more modest. Hospitalization was significantly reduced (0·82 [0·74–0·91]), although mortality was not.

The second publication was of 1 of the 4 studies included in the meta-analysis, above. This study reported on the effects of finerenone in patients with HF with an ejection fraction >40% (HFmrEF and HFpEF) and included about 6,000 patients evenly divided to receive finerenone or placebo.[4] The treatment and placebo groups were roughly equivalent in terms of baseline medication regiment, NYHA HF classification, comorbidities including hypertension, diabetes mellitus and others. Over the course of follow-up (median 32 months), the primary outcome of a composite of worsening HF (that is, first or recurrent unplanned hospitalization or urgent visit for HF) and death from cardiovascular causes was significantly lower in the treatment group (rate ratio, 0.84 [95% CI, 0.74–0.95; P = 0.007). Additionally, the individual outcome of worsening HF was also lower in the treatment group (rate ratio, 0.82; [95% CI, 0.71 to 0.94]; P = 0.006). As with other MRAs, finerenone was associated with increased risk of hyperkalemia. Importantly, comparing these results in the HFmrEF and HFpEF patients to those in the above meta-analysis, the overall improvements with finerenone were similar with respect to hospitalization rates, and once again there was not a significant reduction in mortality rate. Guideline-directed medical therapy for HFrEF typically includes a beta blocker, SGLT2i, ARNI and MRA. Given the high cost of some of these medications, cost-effectiveness should be considered when choosing among a drug class. In the case of MRAs, finerenone typically costs approximately $8,000 per year, whereas the others are available as generics and can cost as little as $60 per year. Use of finerenone combined with a neprilysin inhibitor and an SGLT2i would result in a heart failure drug regimen costing in excess of $20,000 yearly. As the incidence of gynecomastia is markedly increased in men taking spironolactone,[5] eplerenone may be considered for males using MRA therapy. Using MRAs in the treatment of HFrEF, and now HFmrEF and HFpEF, should strongly be considered in all patients.

Tirzepatide and survodutide for metabolic dysfunction associated steatohepatitis and early fibrosis

Metabolic dysfunction associated steatohepatitis (MASH), formerly NASH, is now the second most common cause of cirrhosis and will eclipse alcohol as the most frequent cause by the end of the decade. Metabolic-bariatric surgery has been shown to be highly effective for reversal of MASH and associated hepatic fibrosis, but patient uptake continues to be low. Resmetirom, a selective thyroid hormone receptor beta agonist, was recently approved by the Food and Drug Administration (FDA) as the first pharmacotherapy for MASH with moderate-to-advanced liver fibrosis.[6] The GLP1-RA agents and the related dual receptor agonist compounds (GLP1 receptor agonism combined with GIP or glucagon receptor agonism) have the additional benefits of significant weight reduction, improved glucose tolerance, reduced CV events including CV death, and reduced progression of diabetic nephropathy, among others. If these drugs also have efficacy in reversal of MASH and reduction in progression to cirrhosis, these may be preferred to resmetirom for treatment of MASH as the latter has not been shown to share these important off-target benefits.

Two important phase II randomized controlled trials (RCTs) were published back-to-back in the NEJM in July 2024.[7,8] They evaluated tirzepatide (glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA) and survodutide (glucagon receptor agonist and GLP1-RA) for the treatment of MASH with associated fibrosis. Although these were both placebo-based RCTs and not a direct comparison to resmetirom, it is helpful to review the results of the pivotal phase III trial of this drug in the context of these 2 new trials, as the populations studied in all 3 trials were similar (the tirzepatide study has the additional requirement of a BMI between 27 and 50, with or without diabetes). Alcohol excess was an exclusion in all 3 trials. Evidence of fibrosis was required in all 3 trials, generally in the F2-F3 range.

The tirzepatide trial enrolled 190 patients.

- The percentage of participants who met the criteria for resolution of MASH on liver biopsy without worsening of fibrosis was 10% in the placebo group, 44% in the 5 mg tirzepatide group, 56% in the 10 mg group, and 62% in the 15 mg group.
- The percentage of participants who had an improvement of at least one fibrosis stage without worsening of MASH was 30% in the placebo group, 55% in the 5 mg tirzepatide group, 51% in the 10 mg and 15 mg groups.

The survodutide trial enrolled 293 participants.

- Improvement in MASH with no worsening of fibrosis occurred in 47% of the participants in the survodutide 2.4 mg group, 62% in the 4.8 mg group, and 43% in the 6 mg group, as compared with 14% of those in the placebo group.
- Improvement in fibrosis by at least one stage occurred in 34%, 36%, 34% of the 3-dose ranges, compared with 22% in the placebo group.

Compared to the results seen in the above 2 trials, the resmetirom phase III trial submitted for FDA approval enrolled 966 patients.[9] It showed resolution of MASH with no worsening of fibrosis in 30% of the treated patients compared with 9.7% in the placebo group. Fibrosis improvement by at least one stage without worsening of MASH was seen in 26% of those on the 100 mg dose as compared with 14% in the placebo group.

Once again, these trials were not head-to-head comparisons. However, the improvements in MASH and fibrosis were at least as significant with tirzepatide and survodutide, possibly favoring tirzepatide over the other 2 drugs. In terms of the cost of therapy, the wholesale acquisition (WAC) price of resmetirom is $47,000 yearly. Survodutide has not yet been approved, and the yearly price of tirzepatide is $11,000. Given the multitude of associated benefits of tirzepatide and survodutide — and considering that the most common cause of death in those with obesity or diabetes with MASH remains CVD — if the phase III trials confirm the above benefits, tirzepatide (or metabolic bariatric surgery) should be favored over resmetirom as initial therapy for MASH and early fibrosis.

Effects of semaglutide on CKD in patients with type 2 diabetes

There is now wide recognition of the associated benefits of the SGLT2i and GLP1-RA classes of drugs for type 2 diabetes.[10] Both drug classes have demonstrated reductions in MACE with similar 1%–2% reductions in event rates at 3 years. With respect to the SGLT2is, there have been 2 benefits that have not yet been confirmed with the GLP1-RA class. The most pronounced benefit of the SGLT2is is seen in reduction in hospitalization and improvements in outcomes for patients with HFrEF, and to a much smaller extent, in patients with HFpEF. The second is the improvement in renal outcomes.[11] Although observational data have suggested improvements in renal outcomes with the GLP1-RA class, this has not been demonstrated in placebo based RCTs.

This changed with a study published in the July NEJM, which looked at the impact of semaglutide on those patients with DM2 and associated CKD, defined as eGFR between 50-75 ml/min and uACR >100.[12] Approximately 3,533 patients were randomized to semaglutide 1 mg weekly versus placebo and followed for a median of 3.4 years. Consistent with other studies examining CKD progression, the primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml/min), a 50% reduction in eGFR, or death from renal or CV causes. Primary-outcome events occurred less frequently in the semaglutide group than in the placebo group (5.8 per 100 patient-years of follow-up versus 7.5 per 100 patient-years, for an absolute risk reduction of 1.7%. Lower risk with semaglutide was also observed for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79), as well as for death from cardiovascular causes (hazard ratio, 0.71). Secondary outcomes including the rate of eGFR decline, MACE and all cause death also favored semaglutide over placebo.

The number of persons who would need to be treated over 3 years to prevent one primary renal outcome event was 20 (95% CI, 14 to 40). Given the NNT of 20 over 3 years, using the WAC pricing for semaglutide 1 mg of approximately $12,000 yearly, the cost to prevent one primary outcome event per year would be approximately $720,000, which is not considered to be cost effective.

Alzheimer's dementia blood test in the works

The timely diagnosis of Alzheimer's dementia (AD) is helpful in treatment planning including patient and caregiver preparation.[13] As it has been typically a clinical diagnosis that often evolves over time, the introduction of a novel blood test to aid in the diagnosis has the potential to streamline the process. To that end, a recent report described the performance characteristics of a blood test to aid in the diagnosis of AD.[14] The test is used to determine the ratio of plasma phosphorylated tau 217 (p-tau217) to non-p-tau217 alone, and when combined with the amyloid-beta 42 and amyloid-beta 40 plasma ratio, reported as the amyloid probability score 2 (APS2).

In the study, the blood test was compared to AD pathology as determined by abnormal cerebrospinal fluid APS2 and p-tau217 as the primary outcome, and with clinical AD as a secondary outcome. There were 208 patients evaluated from a primary care setting, and 398 from a secondary care (specialist) setting. Half of the patients had pathological findings consistent with AD.

When the plasma samples were analyzed in a single batch in the primary care cohort, the area under the curve (AUC) was 0.97 (95%CI, 0.95-0.99). When the APS2 was used, the positive predictive value (PPV) was 91% (95%CI, 87%-96%), and the negative predictive value (NPV) was 92% (95%CI, 87%-96%). In the secondary cohort, the AUC was 0.96 (95%CI, 0.94-0.98) when the APS2 was used, the PPV was 88% (95%CI, 83%-93%), and the NPV was 87% (95%CI, 82%-93%). When the plasma samples were analyzed prospectively (biweekly) in the primary care cohort, the AUC was 0.96 (95%CI, 0.94-0.98) when the APS2 was used, the PPV was 88%(95%CI, 81%-94%), and the NPV was 90% (95%CI, 84%-96%). In the secondary care cohort, the AUC was 0.97 (95%CI, 0.95-0.98) when the APS2 was used, the PPV was 91% (95%CI, 87%-95%), and the NPV was 91% (95%CI, 87%-95%).

These results are superior to the diagnostic accuracy of the clinical diagnoses by the clinicians in the study. Primary care clinicians had a diagnostic accuracy of 61% (95%CI, 53%-69%) for identifying clinical AD after clinical examination, cognitive testing, and a computed tomographic scan versus 91% (95%CI, 86%-96%) using the APS2. Dementia specialists had a diagnostic accuracy of 73% (95%CI, 68%-79%) versus 91% (95%CI, 88%-95%) using the APS2. Using the percentage of p-tau217 alone demonstrated the same diagnostic accuracy as using the APS2.

Although not yet available widely, the blood test to determine the APS2 or the p-tau217 percentage alone may be useful in confirming a suspected diagnosis of AD. Although the APS2 and p-tau217 had similar diagnostic accuracy, recent trends in AD research studies favor the use of the p-tau217 and this appears to be the clinical assay that will first become available for general use. As a recent published perspective points out, shared decision-making discussions about test interpretation and treatment options are likely to become more complex as the biomarker and monoclonal antibody treatments become more widely available.[15] It is important that these discussions begin before the lab test is drawn. Clinical outcomes and cost-effectiveness studies have yet to be conducted.

AI-enhanced endoscopy and the rising prevalence of small colorectal adenomas

The incidence of colorectal cancer (CRC) in the U.S. has been slowly declining. Currently, the lifetime risk is estimated to be approximately 4%.[16] At the same time, the detection rate of small adenomas on colonoscopy has steadily risen, currently sitting at about 35%–40% of all colonoscopies. Most of these individuals have one to two small adenomas (< 10 mm) and this is a critical point, as there are no data that the presence of these adenomas is associated with an increased risk of CRC.[17] Despite this fact, the recently revised AGA guidelines still endorse a surveillance rate of 7 to 10 years for individuals with one to 2 small adenomas,[17] rather than deferring to the 10-year interval of the average risk general population. Most gastroenterologists continue to surveille these patients at a frequency between 5 to 7 years, with few deferring to the AGA acceptable option of 10 years, and many still using a 5-year interval. This has resulted in an overuse of colonoscopy for surveillance in this average risk population.

Against this backdrop is a new study which examined the detection rate of colorectal adenomas on colonoscopy when aided by an AI technology.[18] The study looked at approximately 2,000 patients with a history of adenomas or family history of CRC (increased risk group), or patients who had a positive FIT test. However, this did not equate to the U.S. average risk screening population and would be expected to have a higher rate of adenomas. They were randomized to standard colonoscopy versus AI-assisted colonoscopy. Adenomas were detected in 57% of the AI-assisted group and 48% of the standard group and the detection rates were similar in both the FIT positive group and the high-risk group. There were no differences in the detection rate of advanced adenomas or CRC. The detection rate of sessile serrated lesions was 3% higher in the AI-assisted group, and 75% of these were in the right colon.

Where CRC screening has had less of an impact on the reduction of CRC mortality is in the detection of flat sessile serrated adenomas in the right colon. These produce less blood than left-sided polyps so are less often detected by FIT, and they are often missed by colonoscopy.[19] As this study demonstrated, detection of advanced adenomas or CRC was no different between the groups, however there was a slight 3% increase in sessile serrated adenoma detection. Interestingly, a study that looked at the detections of right-sided sessile serrated adenomas when the colonoscopist was aware of a positive stool DNA showed a detection rate of 40%, compared to 9% when the stool DNA result was not known.[20]

The question is, would the addition of AI technology simply increase the detection of low-risk adenomas, which do not increase CRC risk, or actually decrease the CRC incidence via detection of more sessile serrated adenomas? Adhering to a 10-year interval in those with one to two small adenomas while at the same time using AI to increase the detection of sessile serrated adenomas, might achieve the best balance of safety, cost and effectiveness.

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