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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.

Accreditation statement

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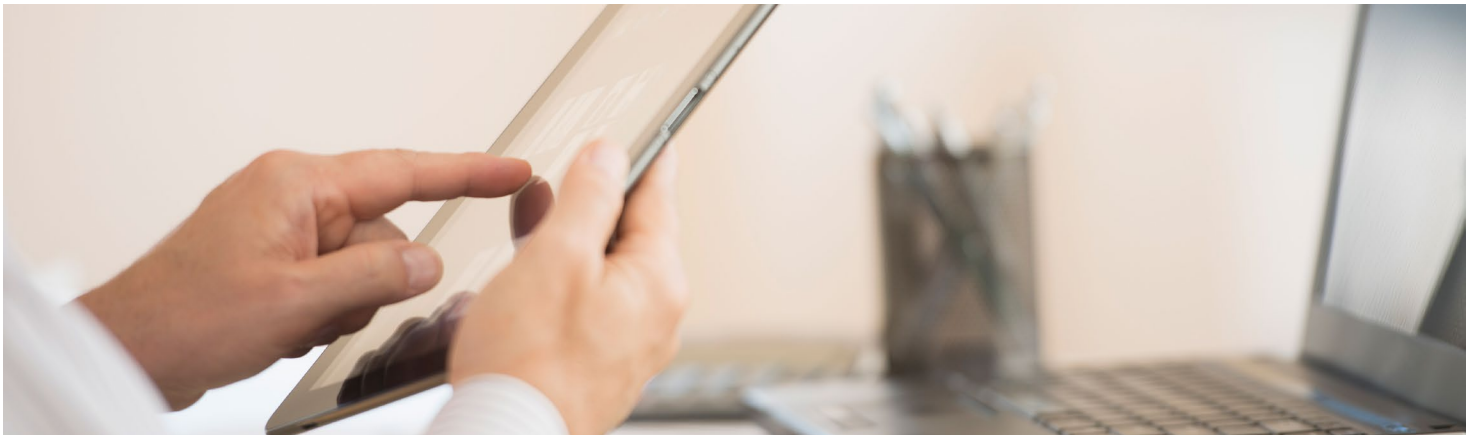
New options for colorectal cancer screening coming soon

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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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 to 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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