OPTUM Care®

Forum for Evidence-Based Medicine

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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.
Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity participants should be able to: • Explore the educational content surrounding resistant hypertension and the high incidence of primary aldosteronism. • Review dapagliflozin for the treatment of chronic kidney disease and its effects. • Apply medical management principles grounded in evidence-based medicine for the surgical treatment of degenerative spondylolisthesis, options for treating frozen shoulder, fecal microbiota transplant and postoperative hernia pain following robotic versus laparoscopic repair.

Accreditation statement

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Credit designation statements

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

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A certificate of attendance will be provided to learners upon completion of activity requirements, enabling participants to register with licensing boards or associations that have not been pre-approved for credits. To apply for credit types not listed above, participants should use the procedure established by the specific organization with which they wish to obtain credit.

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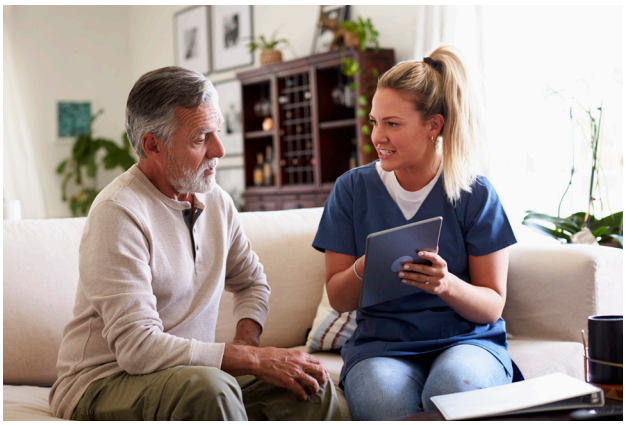
Resistant hypertension and the high incidence of primary aldosteronism

Cardiovascular disease accounts for 30% of deaths in the U.S. and hypertension (HTN) is the single most important risk factor. Suboptimally controlled HTN is one of the most commonly observed problems in medical care. Strikingly, only 43% of U.S. adults with HTN are controlled to a BP <140/90 mm Hg.[1] The reasons for this are multiple, including poor patient adherence to lifestyle and medications, clinician inertia in advancing the medical regimen, and resistant HTN. Focusing on the subset of patients with resistant HTN, one must first exclude pseudo-resistance. This is most frequently seen with alcohol excess and certain drug classes including, but not limited to, nonsteroidal anti-inflammatory drugs, sympathomimetics, oral contraceptives, and the SNRI antidepressants. Pseudo-resistance may also be seen with white coat HTN. Multiple studies have now compared the results from 24-hour ambulatory BP monitors with those blood pressure readings obtained both in the clinic and the home.[2] The studies have consistently confirmed that the mean ambulatory 24-hour BP correlates closely with the patient's home blood pressure readings and not with the readings obtained in the clinic. Therefore, in the appropriate patients, the target blood pressure should be the home BP and not the clinic BP, once the patient's home device and the BP measurement technique have been vetted for accuracy.

Assuming pseudo-resistance and white coat HTN have been excluded, about 20% of patients will be classified as having resistant HTN, defined as inadequate blood pressure control on the maximally tolerated doses of three antihypertensives. Of the various antihypertensive options, on average the greatest cardiovascular risk reduction is seen with the combination of a thiazide diuretic, an angiotensin converting enzyme inhibitor (ACE) or an angiotensin receptor blocker (ARB), and a dihydropyridine calcium channel antagonist, such as amlodipine.[3] One common therapeutic error is underdosing of the thiazide diuretic, which might require 50 mg daily of hydrochlorothiazide, or a change to the longer-acting and more potent thiazide, chlorthalidone. Potassium levels need to be watched more closely on these more potent thiazide regimens.

If adequate blood pressure control is then not established, the patient can be classified as having resistant hypertension. It had previously been thought that about 25% of patients with resistant HTN have an identifiable cause, but new research suggests that the incidence of primary aldosteronism (PA) in this population is quite high, and seriously underdiagnosed. PA is the most common cause of resistant HTN and may be etiologic in up to half of these patients. Other than PA, the major causes of resistant HTN include renal artery stenosis (RAS), progressive CKD,



and pheochromocytoma. Obstructive sleep apnea has been stated to cause resistant HTN without a strong evidence base to support this. On average, successful treatment of OSA results in only about a 4 mm drop in systolic BP, therefore OSA is not likely a cause of resistant HTN in most patients. Although RAS has been associated with resistant HTN, the treatment of atherosclerotic RAS should be medical. Randomized trials have looked at whether correction of atherosclerotic RAS could improve BP control, renal function, or overall cardiovascular mortality. These randomized trials have all been negative.[4] Therefore, MRA of the renal arteries is of limited therapeutic value, given that the optimal treatment is antihypertensive therapy and not angioplasty and stenting.

This brings us to the new science around primary aldosteronism, which is defined by renin-independent production of aldosterone. It is now recognized that there is a continuum of autonomous aldosterone secretion in the population including normotensive individuals. In 210 normotensives who had suppressed plasma renin activity, 14% were confirmed to have PA.[5] The histopathological basis for normotensive PA is thought to be aldosterone-producing cell clusters which have been discovered in otherwise normal adrenal glands.[5] These are non-neoplastic foci of autonomous aldosterone secretion, and they have shed new light on the pathogenesis of PA. These cell clusters may be a precursor for PA, however they infrequently undergo neoplastic transformation to an aldosterone-producing adenoma or adrenal hyperplasia. Another mechanism of excess aldosterone secretion is stress-related surges in adrenocorticotropic hormone (ACTH), which in addition to stimulating the release of cortisol, also stimulates aldosterone release. Chronic stress therefore is thought to increases aldosterone production. Lastly, obesity is associated with increased production of aldosterone, even among normotensive persons.[6] PA therefore, as reflected in the accompanying graph, exists as a continuum across the population.[7]

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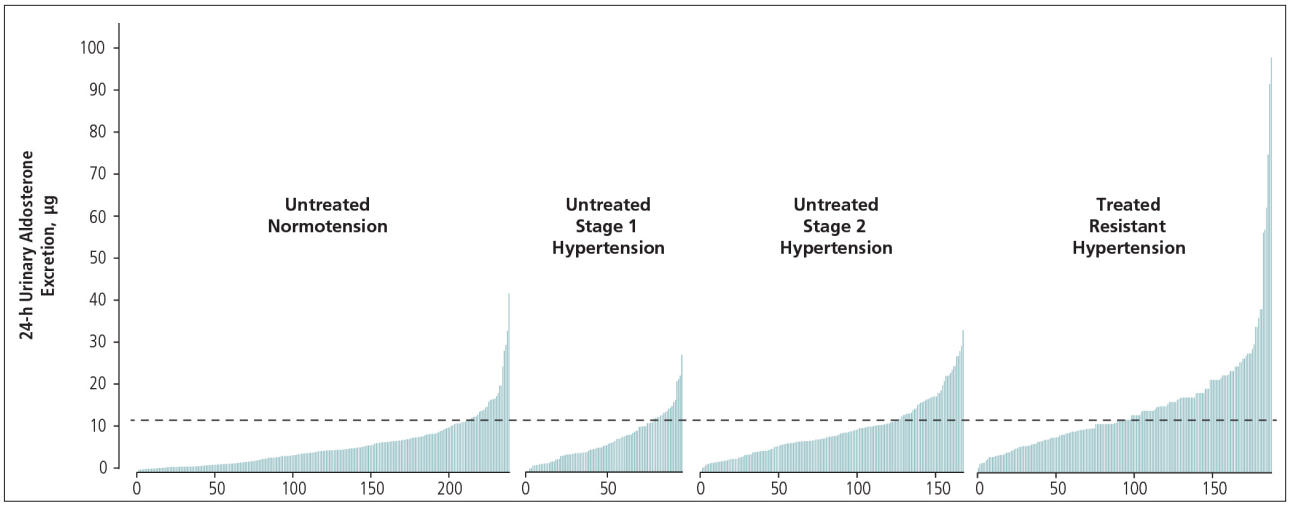

A. The unadjusted urinary aldosterone excretion rate in the context of high sodium balance and renin suppression. Vertical bars represent the unadjusted renin-independent aldosterone excretion rate (y-axis) for each individual participant, ordered from lowest to highest (x-axes). The dashed horizontal line represents the conventional 12 µg/24 h threshold for the diagnosis of biochemically overt primary aldosteronism.

Sophisticated studies of aldosterone metabolism suggest that the prevalence of PA in hypertensive patients may be on the order of 45–50%.[8] Notably, only a small fraction of these patients have an adrenal cortical adenoma.

So how best to approach the possibility of PA in these patients? Unfortunately, a single plasma aldosterone/renin ratio (ARR) is not sensitive. As part of a study looking at salt sensitivity across a broad population in the southeast U.S., over 1,800 recruits submitted data for aldosterone, renin and urinary sodium.[7] About 350 of these recruits had resistant HTN and of those that were subsequently found to have PA, the plasma ARR only identified about half of the patients. A 24-hour urine aldosterone level of >12 mcg/24 hours better defined this group, but no hard diagnostic threshold could be established since not only do these patients exist on a continuum, but their aldosterone excretion will also vary significantly day to day with their sodium intake. Lastly, PA can be frequently detected in normokalemic hypertensive persons of all BP categories.

Looking therapeutically, the PATHWAY-2 trials studied almost 300 patients with resistant HTN who were thought not to have PA by "specialist exclusion."[9,10] The studies examined the response to spironolactone or amiloride as the fourth drug, and compared this to the response to doxazosin or bisoprolol. Despite this "specialist exclusion," the average BP reduction with spironolactone or amiloride was 15–20 mm compared to 5–8 mm Hg with the other drugs. This response was felt to be consistent with underlying PA.

Based on this accumulated research, in a patient with resistant HTN, the fourth drug in the regimen should be spironolactone, eplerenone or amiloride assuming there are no contraindications.[11] It may be presumed that a patient with resistant HTN who has a brisk response to one of these three drugs has physiological PA. Often the BP-lowering effect of aldosterone blockade or amiloride is significant enough that other antihypertensives can be withdrawn. In the subset of patients who remain uncontrolled or who have persistent hypokalemia, endocrine evaluation for an adrenal adenoma may be indicated. Lastly, the primary aldosteronism diagnosis has an associated HCC and should be coded in those patients whose clinical course and response to aldosterone blockade is consistent with PA.

Dapagliflozin demonstrated to have positive effects in patients with chronic kidney disease — but at a cost

It is now well-appreciated that angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors both slow the progression of renal function deterioration. Most of this data was generated in studying patients with diabetes. Sodium-glucose cotransport 2 (SGLT2) inhibitors decrease hemoglobin A1C and improve cardiovascular and renal outcomes in patients with type 2 diabetes. The cardioprotective and renal protective effects of SGLT2 inhibitors seem to be independent of the effects on glucose. Elevated intraglomerular pressures with glomerular hyper-perfusion seems to underly the progression of most renal disease. The protective effects of this drug class may be related to natriuresis and glucose-induced osmotic diuresis with resultant decrease in intraglomerular pressure.

A multicenter, worldwide study was designed to better understand the impact the SGLT2 inhibitor, dapagliflozin, has on adverse outcomes in both diabetic and nondiabetic patients with baseline chronic renal disease.[12] The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial was recently completed. This study enrolled 4,094 patients. Patients were enrolled from 21 countries. All patients had an estimated GFR of 25–75 ml per minute and a urinary albumin to creatinine ratio of >200. All patients had to be on a stable dose of ACE or ARB (patients intolerant to an ACE or ARBs could also participate). 67% of each group had DM2. Patients received 10 mg of dapagliflozin daily or placebo.

The primary study outcomes (Table 1) were: i. decline of at least 50% in the estimated GFR; ii. the onset of end-stage kidney disease; iii. kidney transplantation; or iv. death from renal or cardiovascular causes. Secondary outcomes were: i. a composite kidney outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, death from renal causes; ii. a composite cardiovascular outcome defined as hospitalization for heart failure or death from cardiovascular causes; and iii. death from any cause.

The data safety monitoring board halted the trial early, at a median of 2.4 years, based on these positive results. The positive effects of dapagliflozin occurred in both patients with and without diabetes, and the NNT to achieve the primary outcome was 19. This is a very important trial as it shows benefit of a SGLT2 inhibitor in both diabetics and nondiabetics with CKD. This benefit extends to both cardiovascular and renal outcomes. The absolute difference in mortality between the treated and untreated groups was 0.88% per year.

Using the trial data for the primary outcome, and assuming the yearly cost of an SGLT2 inhibitor of $6,000, the yearly cost to prevent one event was approximately $256,000. Additionally, these new agents are not affordable for many patients. DeJong and coauthors modeled the costs of new diabetes therapies as recommended in current guidelines.[12] Total annual costs of new novel agents, including the SGLT2 inhibitors, are one hundred-fold more expensive than traditional drugs (metformin, sulfonylureas, thiazolidinediones). Individual out-of-pocket costs vary but are three to eight times more expensive for patients. Higher costs are known to decrease adherence and therefore these higher priced agents will differentially be "available" to patients with more economic means. The economics of drug availability and adherence will continue to increase health care disparities and must be addressed.

Table 1. Outcomes

Number of patients			
Variable	**Dapagliflozin 2152 (50%)**	**Placebo 2152 (50%)**	**Hazard ratio (95% confidence interval)**
Sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes	197 (9.2)	312 (14.5)	0.61 (0.51–0.72)
Renal disease composite outcome	142	243	0.56 (0.45–0.68)
Cardiovascular disease composite outcome	100	138	0.71 (0.55–0.92)
Death from any cause	101	146	0.69 (0.53–0.88)

Surgical treatment of degenerative spondylolisthesis: Microdecompression alone deemed noninferior to decompression with instrumented fusion

Degenerative lumbar spondylolisthesis refers to the forward slippage of one vertebra over the vertebra below it, which can cause spinal stenosis, physical disability and pain. The vertebra slippage is due to weakening of the structural tissues that maintain normal alignment of the lumbar spine.

The standard surgical treatment of spondylolisthesis has been decompression of the spinal stenosis. In the 1990s, two studies suggested that the addition of surgical fusion improved outcomes.[13,14] Two subsequent studies in the *New England Journal of Medicine* in 2016 and an accompanying editorial suggested that in most patients there was no incremental benefit to fusion over decompression alone.[15] As the overall most costly procedure performed in the United States,[16] adding a fusion procedure to spinal decompression substantially increases the costs of care compared to decompression alone. Given the controversy and added cost of surgical fusion, the Norwegian Registry for Spine Surgery (NORSpine) investigators compared patient disability scores (Oswestry Disability Index) following microdecompression alone versus decompression with instrumented fusion, using a noninferiority analysis.[17] The primary outcome was a reduction of 30% or more in disability at one year.

A total of 794 patients met eligibility criteria: 476 had microdecompression alone; 318 had decompression with instrumented fusion. Patients were then matched by propensity scores. Propensity scoring is a statistical method used to analyze observational data by estimating how certain covariates may predict the probability of a given intervention. The aim of propensity scoring in this study was to lessen the potential biases as patients were not randomized to treatments. After 1:1 matching by propensity scores, 285 patients remained in each treatment group, 570 patients total. At three months, 423 patients completed outcome measures. At one year, 434 completed outcome measures.

At one year follow-up, 150 (68%) of 219 patients who underwent microdecompression alone and 155 (72%) of 215 patients who underwent decompression with fusion achieved the primary outcome of 30% or greater improvement in disability. The difference of -4% (68%–72%) met the authors pre-analysis criterion of noninferiority (defined as an absolute difference favoring decompression with fusion no greater than 15%). There was no statistical difference in disability scores between groups. Patients in the microdecompression-alone cohort rated leg pain and back pain higher than patients in the decompression with instrumented-fusion cohort. These differences were respectively, 0.8 and 0.6 on a ten-point scale, and therefore of uncertain clinical importance.

The authors concluded that microdecompression alone is not appreciably worse than decompression with instrumented fusion for treatment of degenerative spondylolisthesis. Fusion compared to decompression alone resulted in twice the length of OR time, twice the length of hospital stays, and three times the incidence of dural tear, the most common surgical complication. Thus, given the much higher costs and increased surgical risks of added fusion, they carefully suggest that decompression alone be the primary treatment choice for most patients with lumbar degenerative spondylolisthesis. The study has limitations, including its observational (rather than randomized) design and its narrow focus on an arbitrary percent change in disability scoring as the primary outcome measure. Some patients will benefit from nonsurgical treatments such as physical therapy,[18] so physical therapy may be a reasonable first intervention for some patients.

Equivalency in surgical and nonsurgical options in the treatment of frozen shoulder

In a multi-center study, 503 patients with frozen shoulder were randomly assigned to three interventions (2:2:1): shoulder manipulation under general anesthesia, arthroscopic capsular release or early structured physical therapy (PT) to treat primary frozen shoulder.[19] Patients were followed for 12 months and assessed using the Oxford Shoulder Score (OSS). Patients were enrolled from 35 medical centers across the UK and treated by more than 200 physical therapists. Manipulation under anesthesia involved manipulation of the affected shoulder to stretch and tear the tight capsule under general anesthesia with steroid injection. Arthroscopic capsular release under general anesthesia involved surgically dividing the contracted anterior capsule, followed by manipulation; steroid injection was optional. Surgical interventions were followed by postprocedural physical therapy. Early structured PT involved mobilization techniques and a graduated home exercise program with steroid injection. All PT, including the primary intervention and post-surgical groups involved 12 sessions during up to 12 weeks.

There was a longer delay to initiation of therapy with both surgical interventions. However, importantly there were no significant clinical differences in outcomes between the three modalities at 12 months of follow-up (see table on next page).

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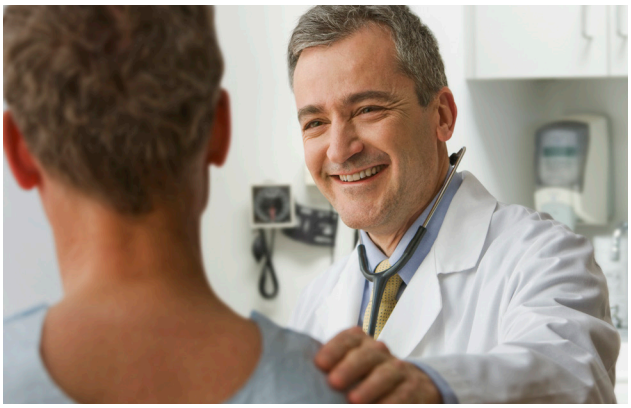
Outcomes at 12 months

Intervention	Patients (#)	Oxford Shoulder Score at 12 months	95% confidence interval
Manipulation under GA	189	38.3	36.9–39.7
Arthroscopic release	191	40.3	38.9–41.7
Early physical therapy	99	37.3	35.3–39.2

Surgical interventions had more complications, as one would expect. Manipulation under anesthesia was determined to be the most cost-effective therapy in the UK, but would be expected to be far more expensive than PT in the U.S. The study used a large number of different hospitals, surgeons and physical therapists. As a result, outcomes are felt to reflect real world outcomes in the general population. This study should be helpful in shared decision-making conversations with patients.

Fecal microbiota transplant is safe and effective in treating C. difficile infections

Previous research supports the use of fecal microbiota transplant (FMT) to treat severe or refractory C. diff infections and to prevent recurrent infections,[20,21] but prospective safety and outcome data are limited. The FMT National Registry was created to better understand FMT use and clinical outcomes across many participating sites. The registry is administered by the American Gastroenterological Association as an ongoing, prospective, observational, multicenter data collection resource. Rather than mandating a study protocol for FMT treatment, registry participants are treated at the discretion of their providers, and observational data are entered at baseline and one month, six months, one year, and two years following the FMT procedure. The current study used registry data to evaluate the real-world effectiveness of FMT in the treatment of C. diff and its safety.[22] A cure was defined as resolution of diarrhea without additional C. diff treatments. The study assessed cures at one month (window of 20–60 days) and at six months (window of 120–240 days).



From December 2017 to September 2019, 259 participants were enrolled from 20 registry sites. Most participants had moderate (44%) or mild (36%) infections at baseline, and most (91%) had received vancomycin prior to FMT. Follow-up data were available for 222 patients during the one-month window. Of these, 200 had a C. diff cure. Since some participants returned before 20 days or after 50 days and were excluded, post-hoc analysis including those patients demonstrated cure in 224 (88%) of the 256 participants. An intent-to-treat analysis had a similar cure rate of 86%. Four patients who were designated as cured at one month had a recurrence by six months, range 8–14 weeks. Of 11 participants who failed initial FMT, 7 were reported as cured at six months.

There were three procedure-related adverse events: colonoscopic perforation (n=1) and GI bleeding (n=2). Commonly-reported symptoms at one month following FMT included diarrhea (27%), abdominal pain (15%), bloating (13%) and constipation (9%). Six percent rated their symptoms as severe. Twelve percent were hospitalized within one month of FMT. Reasons for hospitalization included C. diff recurrence, continued diarrhea, abdominal pain, dehydration, and fever. At six months, 4% of those with follow-up data developed one or more new infections (other than C. diff). Four participants died, but none of the deaths were attributed to FMT.

Overall, the FMT National Registry data demonstrated excellent C. diff cure rates with few recurrences in a real-world setting. Symptoms/side effects following FMT were common, but few were considered severe.

Patients report similar levels of postoperative pain following robotic versus laparoscopic hernia repair

From 2012 to 2018 the use of robotics for general surgery has increased from 1.8% to 15.1%,[23] but high-level evidence to support its use is lacking. Since laparoscopic hernia repair with intraperitoneal mesh placement can be very painful and lead to patient dissatisfaction rates as high as 25%, investigators sought to compare postoperative pain following robotic and laparoscopic methods of ventral hernia repair as a primary outcome.[24] Pain was measured from a

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numerical rating scale, 0–10 on postoperative days 0, 1, 7 and 30. Secondary outcomes included the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Intensity short form (3a), hernia-specific quality of life, operative time, wound morbidity, hernia recurrence, length of stay and cost. Patients were blinded to the type of surgery. Two surgeons performed all hernia repairs.

Seventy-five patients were randomized: 36 underwent laparoscopic repairs and 39 had robotic repairs. There were no statistical differences in reported pain on any postoperative day. Similarly, there were no differences in secondary patient-reported measures. There were four total intraoperative complications: two in each cohort. None of the complications resulted in conversion to an open procedure. Robotic surgery operative times were 55% longer than laparoscopic surgery (median 146 minutes versus 94 minutes, both surgeons combined). Accordingly, surgical costs assessed from operating room times were higher for robotic surgeries.

This randomized, single-blinded trial demonstrated no differences in short-term patient-reported outcomes following robotic versus laparoscopic hernia repair, yet operative times and consequent costs were higher for the robotic surgeries. Given these results, the authors emphasize that there is no measurable benefit to justify the robotic approach: "… the onus remains on the robotic platform and its users to either become very efficient or provide evidence of an objective benefit to justify its use."[24] At the current time, no robotic procedures are being performed at ASCs, and the use of robotic hernia repair mandates use of the hospital outpatient department and therefore increases the facility fee for the procedure.

Update on the Optum Care shared decision-making tool

How often do you use shared decision-making (SDM) resources with your patients? Would you use them more if an SDM tool was readily available? Optum Care has created an SDM application that is ready for use. The patient information landing page can be accessed at: https://apps-stg.optumcare.com/sdm/#/sdm/questionnaire.

Mock patient data can be entered to explore current content or real patient data can be entered to use the tool. A PSA screening report is age- and sex-specific, so enter a male patient, 40 years of age or older, to review it. The reports are further grouped by topic: COVID-19, screening conditions, medical conditions and surgical conditions.

Some reports are based on a corresponding screening questionnaire. For example, the anxiety report begins with the GAD-2 screening questions. If the patient scores a 3 or higher, the remaining GAD-7 questions are provided. The generated report is based on the overall GAD-7 score. Similarly, the migraine treatment report begins with the Migraine Disability Assessment or MIDAS, and the generated report and treatment recommendations are based on the amount of migraine-related disability and headache frequency from the MIDAS score.

Fifteen reports are currently available, and four more are coming soon. Several additional reports are in various stages of development. After exploring the content or using it with a patient, please feel free to contact us with questions, comments, or recommendations for future topics. A "Help & Feedback" button can be found in the lower right corner of the webpage. Your feedback can help us to build a better product.

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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 OptumCare. He served as Chief Medical Officer from 1995 - 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for OptumCare. 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 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. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

This information is for informational purposes and should only be used by trained clinicians to aid in improving diagnosis, detection and/or clinically appropriate treatment; this information is not a substitute for clinical decision-making and should not be used to make individualized diagnostic or treatment decisions for specific patients.

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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.
Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity, participants should be able to: • Identify educational content and resources on the surveillance of papillary thyroid cancer and advanced liver fibrosis. • Review the data on triple inhaler therapy for moderate to severe asthma. • Discuss the adverse events from oral corticosteroid within the first thirty days. • Apply medical management principles grounded in evidence-based medicine regarding new-onset sciatica, nonsurgical treatment of appendicitis and the utility of nocturnal oxygen supplementation in chronic obstructive pulmonary disease (COPD).

Accreditation statement

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In support of improving patient care, this activity has been planned and implemented by OptumHealth Education. OptumHealth 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

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.
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The American Academy of Physician Assistants (AAPA) accepts credit from organizations accredited by the ACCME.

Attendance
A certificate of attendance will be provided to learners upon completion of activity requirements, enabling participants to register with licensing boards or associations that have not been pre-approved for credits. To apply for credit types not listed above, participants should use the procedure established by the specific organization with which they wish to obtain credit.

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Active surveillance of papillary thyroid cancer

Analogous to Gleason 6 prostate cancer, the prognosis of small papillary thyroid cancers is remarkably good with very infrequent progression to metastatic disease and rare mortality. The 30-year cancer-specific survival for papillary thyroid cancer is 97%.[1] In 2015, guidelines for the management of papillary thyroid cancer recommended the consideration of active surveillance; however this management option is rarely recommended or successfully adopted in the United States.[2]

Two-thirds of thyroid cancers in this country are small papillary thyroid cancers and the rate of diagnosis of these cancers has increased 380% in the past 25 years. There has not been a similar increase in mortality, suggesting a highly significant degree of overdiagnosis and overtreatment. With this as background, a Japanese study reported their experience in over 2,100 patients with newly diagnosed small papillary thyroid cancer (<1 cm).[3] A total of 1,179 patients (55%) chose active surveillance and form the study population for this report. The patients ranged in age from 15–88 and 90% were women. Patients were followed by ultrasound at six-month intervals for the fist year and then annually. The median follow-up was six years and ranged to over 12 years. 91.4% of patients adhered to the follow-up ultrasound schedule, and of those that did not adhere, the large majority were related to advanced age or concomitant life-threatening illness. Only 4.5% of patients chose to proceed to surgery for personal reasons and only 6.4% of patients had surgery due to physician concerns based on follow-up ultrasounds. Only 0.09% developed lymph node metastases requiring surgery, and no patients developed distant metastatic disease. There were no thyroid cancer related deaths.

The remarkable success of the program could be attributed to three factors:[4]

1. Delivery of information and education about papillary thyroid cancer and active surveillance before the biopsy sample is taken, at a time when anxiety over a new diagnosis of cancer was not present
2. Presentation of a choice to the patient with a clear, consistent physician recommendation for active surveillance as appropriate and safe, with the option to change to surgery if required or desired
3. Regular reassessment and reassurance about the risk at each follow-up visit and emotional support provided by the clinician to the patient for the choice taken

The University of Wisconsin in collaboration with HIPxChange has an excellent patient decision thyroid cancer treatment resource available, click **here**. Use the link provided to access the Thyroid Cancer Treatment Choice Toolkit. At the top of the page, click the View the Toolkit button to register.

This model of care should serve as a template for active surveillance discussions around not only small papillary thyroid cancers, but also for very low risk and low risk prostate cancers. Unfortunately, although the active surveillance rates of Gleason 6 prostate cancers are slowly improving, they still remain below 50%.[5] This is despite the fact that the ten-year prostate cancer specific survival in a cohort of patients followed under active surveillance is over 98%.[6] As part of the ongoing development of the OptimalCare program, there are two significant additions in 2021 specifically related to active surveillance in prostate cancer patients.

- The first is the development of a shared decision-making aid analogous to the papillary thyroid cancer version; this is also attached to the Forum. Just as in the papillary thyroid cancer example above, the discussions with the patient should begin at the time of the referral to the urologist for a PSA elevation. Waiting until the patient and the urologist have the post biopsy discussion around the new diagnosis of "prostate cancer" will significantly reduce the impact of the shared decision-making process due to anxiety around the diagnosis. This prebiopsy discussion should be a primary care priority. Click **here** to view the Localized Prostate Cancer handout, located at the end of this newsletter.
- The second OptimalCare addition is the creation of a natural language processing (NLP) engine which will review EMR data and calculate the active surveillance rates by urologist and urology practices across Optum Care. Redirection of referrals to urologists willing to employ an active surveillance strategy in the appropriate patients will improve health outcomes, and reduce both the harms of treatment and the cost of care of our patients with very low risk and low risk prostate cancer.

(continued on page 3)

DM2 and the high rate of advanced liver fibrosis

Nonalcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder worldwide, and is the most rapidly growing indication for liver transplant, ranking second in the United States behind alcoholic liver disease.[7] Twenty-eight percent of transplants in 2019 were related to NAFLD progressing to NASH and cirrhosis.[8] Because this progression is tightly linked to insulin resistance and the metabolic syndrome, it is frequently seen in patients with DM2. The best predictor of cirrhosis is early liver fibrosis, since only about 3–4% of patients with fatty liver will progress to cirrhosis. Although screening tools are now available, they are not being widely used to screen the population of patients with NAFLD to determine which are showing signs of early liver fibrosis. The available screening tests fall into the categories of blood-based testing and imaging.

The former can be more easily implemented in routine practice, but involve the use of fibrosis calculators (the NAFLD fibrosis score) which utilizes multiple clinical parameters, or specific proprietary laboratory tests which can cost as much as $500. Additionally, the performance of these tests remains suboptimal in patients with DM2.[9] Ultrasound transient elastography (TE) is an inexpensive test (~$75) that compares favorably with MRI for the detection of liver fat and fibrosis.[10] A study in *Diabetes Care*[11] looked at 825 patients with DM2 in the 2017–2018 cycle of the National Health and Nutritional Examination Survey (NHANES) who had TE performed as part of their comprehensive examination that included physical examination and lab parameters. The mean age was 60 years and 53% were male. The findings showed that 74% of patients had some degree of NAFLD with 58% having grade 3 steatosis, the highest grade. The prevalence of significant fibrosis (≥ F2) was 23.8%. The number of patients with advanced fibrosis (≥ F3) was 15.4%, and 7.7% of patients had cirrhosis (F4). No significant differences were found for sex or Hispanic ethnicity. Obese patients, as would be expected, had a higher prevalence of both steatosis and advanced fibrosis. A European study using TE evaluated 534 patients and found a prevalence of steatosis of 76.1%, with 19.6% of patients having advanced fibrosis and 8.2% with cirrhosis, findings that are highly concordant with the U.S. results.[12]

In 2016, the European Association for the Study of the Liver, the European Association for the Study of Diabetes, and the European Association for the Study of Obesity jointly published guidelines that recommended routine screening for NAFLD and advanced fibrosis in patients with T2DM.[13] To date, there are no similar guidelines in the U.S. Early detection is critical as hepatic fibrosis responds to various pharmacotherapies as well as significant weight loss including bariatric surgery when indicated. A high index of suspicion should be maintained when evaluating patients with DM2, particularly in the setting of obesity, abnormal LFT's, and concomitant alcohol excess. The NAFLD fibrosis score calculator, **nafldscore.com/** is freely available and straightforward to use. TE is available in at least some of our markets and may become the screening test of choice in this population of high-risk patients.

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Adding umeclidinium to inhaled corticosteroid plus long-acting β_2-agonist (triple inhaler therapy) slightly improves lung function but does not reduce asthma exacerbations

Asthma guidelines have recently changed and now recommend the use of a prn inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) combination for mild persistent asthma, and daily use of the combination therapy for moderate persistent asthma. Despite this therapy, a portion of patients remain symptomatic and poorly controlled. A recent study evaluated the benefit of adding a second long-acting bronchodilator, umeclidinium.[14] ICS/LABA treatments with and without the addition of umeclidinium were compared: fluticasone plus vilanterol (FF/VI) versus fluticasone plus umeclidinium plus vilanterol (FF/UMEC/VI).[14] The primary outcome was the change in lung function (trough FEV1) at 24 weeks. The key secondary outcome was the rate of moderate asthma exacerbations requiring increased need for rescue therapy and temporary change in maintenance treatment and/or severe asthma exacerbations requiring hospital admission.

In a double-blind, randomized, industry sponsored phase 3 study, 2,439 patients were recruited from 416 hospitals and primary care centers across 15 countries. Patients were at least moderately severe asthmatics with inadequately controlled symptoms despite daily ICS/LABA therapy. They had a mean predicted FEV-1 of 58% and 63% had a significant exacerbation in the prior year. Study participants were assigned control and investigational arms administered via dry powder inhaler.

Control arms (ICS/LABA therapy):

- FF/VI 100/25 µg
- FF/VI 200/25 µg

Treatment arms (triple inhaler therapy):

- FF/UMEC/VI 100/31.25/25 µg
- FF/UMEC/VI 100/62.5/25 µg
- FF/UMEC/VI 200/31.25/25 µg
- FF/UMEC/VI 200/62.5/25 µg

The addition of UMEC (62.5 and 31.25 µg) resulted in statistically significant ($p<0.001$) changes in FEV1 from baseline when compared to both the FF/VI 100/25 µg and 200/25 µg groups at 24 weeks. The mean improvements in FEV1 were small and of uncertain clinical significance, ranging from 82 mL to 110 mL. Additionally, 1,075 moderate or severe asthma exacerbation events occurred among all participants during the study period. The pooled analysis demonstrated that the addition of UMEC 62.5 µg resulted in a non-significant 13% reduction in asthma exacerbations, with no changes in the rate of severe exacerbations, and no change in the duration of moderate or severe exacerbations. Asthma symptom scores were slightly improved with triple inhaler therapy.

Overall, the addition of UMEC led to a statistically significant improvement in trough FEV1 at 24 weeks, but the degree of FEV-1 improvement likely is of little clinical relevance. The numbers of moderate and severe asthma exacerbations were not statistically different between patients treated with UMEC and those not treated with UMEC. Importantly, the cost of adding UMEC is substantial, typically in the $600–$1,000 range yearly. For patients with eosinophilia or other markers of type 2 inflammation, doubling the dose of the ICS was more effective than triple inhaler therapy in preventing severe exacerbations. For those patients failing maximum doses of ICS/LABA therapy, a trial of triple inhaler therapy may be important prior to initiating far more expensive biologic therapies.

Adverse events from oral corticosteroid bursts most common within 30 days

Adverse events from long-term corticosteroid use are well-described and include gastrointestinal bleeding and ulcers, infections, Cushing syndrome, diabetes, cataracts, glaucoma, and osteoporosis. Few studies have examined adverse events related to a single oral steroid burst of 14 or fewer days. A recent study used medical records from the National Health Insurance Research Database (2013 through 2015) in Taiwan to characterize adverse events following an oral steroid burst.[15] Adverse events were identified within 5–30 days of steroid initiation and during the subsequent 31–90 days.

Out of over 15 million medical records for adults aged 20–64 years, 2,623,327 patients received oral steroid bursts. Common adverse events included gastrointestinal bleeding, sepsis, and heart failure. The table below (modified from Yao, et al.)[15] compares incidence rates per 1,000 person-years of adverse events among patients who received burst steroids and patients who did not receive steroids.

Incidence rate ratios were used to compare study periods pretreatment, 5–30 days and 31–90 days from steroid initiation. Rates of each adverse event significantly increased in the first 30 days, followed by subsequent attenuation. The incidence rate ratios in the 5–30-day period compared to the pretreatment period were 1.8 for gastrointestinal bleeding, 1.99 for sepsis, and 2.37 for heart failure.

The study demonstrates that oral steroid bursts are associated with adverse events that usually occur within the first 30 days of treatment. This is most pronounced for GI bleeding where the overall incidence approaches 3%. These rates would be expected to be significantly higher in the elderly and underscore that fact that steroid bursts should not be used without a clear evidence base supporting a benefit that outweighs the risks.

Table. Adverse event rates for patients with and without steroid bursts

	Steroid burst	No steroids
Adverse event	**Incidence rate per 1,000 person-years [95%CI]**	**Incidence rate per 1,000 person-years [95%CI]**
GI bleeding	27.1 [26.7–27.5]	10.3 [9.9–10.7]
Sepsis	1.5 [1.4–1.6]	1.4 [1.4–1.4]
Heart failure	1.3 [1.2–1.4]	0.4 [0.4–0.4]

Patients with sciatica have similar outcomes regardless of their initial treatment

A recently published, randomized clinical study compared a stratified care approach to "usual care" for the diagnostic evaluation and treatment of new-onset sciatica.[16] The stratified care model used the overall and subscale scores from the STarT back tool and clinical features (leg pain scale score, pain present below the knee, pain interference score, and "objective" sensory deficit) to guide patient care into three groups:

- Group 1 (low risk): Brief self-management support (up to two sessions with a physiotherapist)
- Group 2 (medium risk): Physiotherapy course, up to six sessions
- Group 3 (high risk): MRI and specialist referral

An algorithm in the *Lancet* article (Figure 1)[17] delineates how scores and symptoms were used to stratify patients. Patients randomized to the control arm (usual care) were seen by a physiotherapist in clinic who determined further management. Options for further management included discharge back to the primary care provider, referral to community physiotherapy services, or referral for spinal specialty care. Physiotherapists in this study attended training workshops prior to patient recruitment. A total of 476 patients were randomized. The stratified care cohort reported minimally faster relief of symptoms (median two weeks) compared to the usual care arm, but this was not statistically different. Other outcomes — pain, function, psychological health, days lost from work, work productivity, satisfaction with healthcare, and healthcare use — did not differ between groups. The results of this trial provide validation of the OptimalCare algorithm and serve to reinforce its use in daily practice.

The OptimalCare Back Pain module is available on the shared decision-making website that incorporates the STarT back tool and stratifies treatment options according to the score.

To view the current shared decision-making modules, click **here.**

To view all the orthopedic/back pain algorithms, click **here.**

Nonsurgical treatment of appendicitis: Ready for prime time

Antibiotics are an effective alternative to surgery for uncomplicated cases of acute appendicitis. Sippola and colleagues investigated use of an oral broad, spectrum antibiotic, moxifloxacin (400mg/d), compared to initial intravenous antibiotic therapy followed by oral therapy for acute appendicitis defined by CT scan.[18] Patients were 18 to 60 years of age and had CT evidence of non-complicated appendicitis on scan. Exclusion criteria included pregnancy (or lactation), antibiotic or contrast allergy, renal insufficiency, immunosuppression of any kind, severe systemic illness or diabetes and use of metformin. Patients were randomized (1:1) to receive either oral moxifloxacin (n= 295) for seven days compared to intravenous ertapenem (1 gm/d) for two days followed by five days of oral levofloxacin (500mg/d) and oral metronidazole (500mg, 3 times/d)(n= 288). Success was defined as discharge from the hospital without surgery and no recurrence at one year. The goal was to have the two treatment arms show a success rate of greater than 65% and non-inferiority between the treatment arms of less than 6%. The mean age of the 599 randomized patients was 36 years and 44% were women. Five hundred eighty-one (99.7%) patients were available for follow-up at one year. Treatment results are summarized in Table 1.

Table 1

Treatment	Number	Appy during initial hospitalization N (%)	Appy within 1 yr of initial hospitalization N (%)	Therapeutic success % (1 side 95% CI)
PO moxifloxacin alone	295	27 (9.2)	61 (20.7)	70.2 (65.8 to ∞)
Ertapenem IV + PO levo + metro	288	22 (7.6)	53 (18.5)	73.8 (69.5 to ∞)

PO = oral, Levo = levofloxacin, Metro = metronidazole, CI = confidence interval

These results exceed the pretrial expectation of a success rate of greater than 65% and demonstrate a non-inferiority of less than the 6% threshold sought at trial onset.

This study extends earlier studies demonstrating the safety and efficacy of nonsurgical treatment of uncomplicated appendicitis. These trials are summarized in Table 2 on the next page.

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The first trial (Trial 1, Table 2), the APPAC trial compared surgical intervention to antibiotics, had a success rate of 72.7% at one year and 60.9% at five years with lower complication rates for nonsurgical treatment at both time frames.[19] The second trial (Trial 2, Table 2) of more than 1,000 children at 10 U.S. children's hospitals demonstrated a similar success rate at one year of 67.1% of antibiotic therapy alone.[20] The third trial (Trial 3, Table 2) included of over 1,500 adults and showed a success rate of antibiotic therapy alone of 71%.[21]

Table 2

Trial	Treatment	Participant number	Follow-up	Success (%)	Complication
1	Surgery	273	5 years	NA	20.5% 1 year; 24.4% 5 years
1	Antibiotics alone	256	5 years	72.7	2.8% 1 year; 6.5% 5 years
2	Surgery	698	1 year	NA	3.6% 1 year
2	Antibiotics alone	370	1 year	67.1	3.3% 1 year
3	Surgery	776	90 days	NA	3.5% at 90 days
3	Antibiotics alone	776	90 days	71	8.1% at 90 days

NA = not applicable as surgical treatment considered successful

These trials and others demonstrate the non-inferiority of antibiotics compared to surgical treatment of uncomplicated appendicitis. Sippola has shown oral antibiotics are equally effective compared to intravenous followed by oral therapy. Importantly, multiple trials also show equivalent of better patient satisfaction and less resource expenditures associated with nonsurgical treatment. Nonoperative management of uncomplicated appendicitis should be considered in appropriate patients.

The utility of nocturnal oxygen supplementation in COPD

The utility of oxygen supplementation at night in persons with COPD is not clear. A multicenter international study was designed to further define the benefit from nocturnal oxygen.[22] Patients with COPD and an oxygen saturation of less than 90% for at least 30% of the nocturnal recording time were enrolled in the trial in a 1:1 randomization to oxygen or sham concentrator (placebo). Pretrial analysis suggested the need to enroll 600 patients. The primary endpoint was death from any cause or advancement to long-term oxygen therapy as defined by the Nocturnal Oxygen Therapy Trial (NOTT) criteria. Eligible patients had COPD, did not require long-term oxygen therapy at baseline according to the NOTT criteria and did not have sleep apnea. They had not smoked in six months and did not have left heart failure, interstitial lung disease, bronchiectasis, lung cancer, severe obesity (BMI≥ 40) or any other disease known to influence survival.

The trial was stopped prematurely because of recruitment and retention difficulties after enrollment of 243 patients (123 in the oxygen group and 120 in the control group). Baseline characteristics did not differ between the groups. An intention-to-treat analysis at three years of follow-up showed no significant differences between the two groups. Thirty-nine percent of the nocturnal oxygen group and 42.0% of the placebo group met the NOTT defined criteria for long-term oxygen therapy or had died. A time-to-event analysis comparing the nocturnal oxygen and placebo groups in the composite outcome revealed no significant differences in either death or the requirement for long-term oxygen therapy.

This study was under powered, therefore the authors looked at its results in combination with other studies looking at patients with COPD and isolated nocturnal desaturation. The results of this study and two previous studies were reported in a meta-analysis which also failed to show evidence that nocturnal oxygen therapy was of benefit in COPD patients with isolated nighttime oxygen desaturation.[22] Despite the wide confidence intervals in this study, these results along with the subsequent meta-analysis suggest that it is unlikely that nocturnal oxygen therapy is of benefit in COPD patients with isolated nighttime oxygen desaturation.

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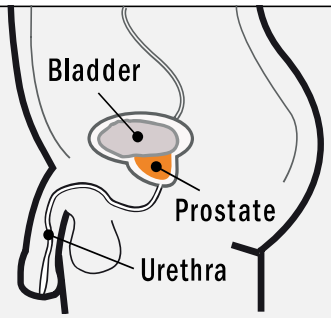
Localized Prostate Cancer

50 - Localized Prostate Cancer Adult-CLB Date of Birth: 01/01/1970

Localized prostate cancer is cancer that has not moved outside of the prostate or spread to other parts of the body. There are several ways to treat or monitor localized prostate cancer. The purpose of this guide is to inform you about treatment and monitoring options so that you and your doctor can decide which option is best for you.



What are my treatment and monitoring options?

Three common approaches to the management of localized prostate cancer are described below:

1 **Active surveillance** means that your doctor closely monitors your prostate cancer for changes, but no treatments are given. It does not mean "never treat," but rather watchful waiting to see if the cancer worsens and treatment is needed. During active surveillance your doctor will monitor a blood test called prostate-specific antigen (PSA) and perform periodic prostate exams. Repeat prostate biopsies and imaging tests are done as well. If the cancer starts to cause symptoms or there are signs that it is growing or becoming aggressive, then treatments are offered.

Active surveillance is usually offered to men with localized prostate cancer that is considered to be at low risk of worsening (or "favorable risk"), based on the biopsy and other testing results. It may seem counter-intuitive that you can be diagnosed with cancer and then be told to watch and wait. But several studies have shown that men with favorable-risk prostate cancer are at low risk of any harm from their diagnosis, including death. In these cases, the benefits of watchful waiting may outweigh the risks associated with treatment.

2 **Radiation therapy** uses radiation aimed at the prostate to kill cancer cells. There are two common types of radiation therapy: external beam radiation and brachytherapy.

External beam radiation	External beam radiation uses a machine called a linear accelerator to aim a high-energy beam of radiation at the prostate cancer, with the goal of sparing other tissues near the prostate. External beam radiation can be done as the only treatment or in combination with other treatments. The types and severity of side effects are related to the amount (or dose) of radiation given.
Brachytherapy	Brachytherapy involves the placement of radioactive material directly into the prostate. Radiation from the material kills the prostate cancer cells and has less of an effect on neighboring tissues.

3 **Surgery or radical prostatectomy** is the surgical removal of the entire prostate gland and some of the surrounding tissues.

What are the risks and benefits of each treatment and monitoring option?

The table below lists some of the potential risks and benefits associated with each treatment and monitoring option. It is important that you discuss with your doctor all of the risks and benefits that may affect you.

	Potential Risks	Potential Benefits
Active surveillance	Cancer growth and spread; Frequent medical appointments; Fewer treatment options if cancer spreads; Anxiety about having cancer and not treating it	"Favorable risk" prostate cancer may never cause harm. Since you may never need treatment, you could avoid all of the risks associated with treatment.
Radiation therapy (External beam radiation)	Erectile dysfunction (impotence); Frequent or painful urination; Rectal bleeding; Blood in urine; Rectal or urinary leakage; Fatigue; Skin reactions; New cancers near the radiation site; Frequent medical appointments	External beam radiation can successfully treat prostate cancer. It can also be used with other treatments or after surgery.
Radiation therapy (Brachytherapy)	Erectile dysfunction (impotence); Frequent or painful urination; Not being able to empty the bladder; Rectal bleeding; Blood in urine; Frequent bowel movements; New cancers near the radiation site; Narrowing of the tube that carries urine from the bladder (urethra); Abnormal opening in the wall of the rectum	Brachytherapy can successfully treat prostate cancer.
Surgery (radical prostatectomy)	Erectile dysfunction (impotence); Other sexual dysfunction (dry orgasm); Urinary incontinence; Injury to the rectum (rare); Narrowing of the tube that carries urine from the bladder (urethra); Formation of cysts containing lymph (lymphocele); Surgical complications including cardiovascular events, blood loss, and infection; Other complications from anesthesia	Surgery can successfully treat prostate cancer.

How do outcomes compare between active surveillance, radiation therapy and surgery?

10 years after diagnosis of localized prostate cancer, the rate of death caused by cancer is low irrespective of whether patients start with active surveillance, radiation therapy, or surgery. Data from a large randomized study are provided below:

	Disease progression	Total cancer deaths
Active surveillance	229 per 10,000	15 per 10,000
Radiation therapy	90 per 10,000	7 per 10,000
Surgery	89 per 10,000	9 per 10,000

About 55 out of 100 men who initially start active surveillance will eventually go on to have some form of treatment.

The following complication rates were reported by patients over the past two decades:

Complication rates may improve over time with newer technologies and advances in surgical and radiation therapies.

46 out of 100 men who underwent surgery for prostate cancer reported using absorbent pads for urinary incontinence 6 months after surgery. Urinary incontinence can improve over time. **Only 4 out of 100 men** who had active surveillance and **6 out of 100 men** who had external beam radiation reported urinary incontinence at 6 months.

Some men have sexual dysfunction at the time of their prostate cancer diagnosis. Six months after diagnosis, **48 out of 100 men** who had active surveillance reported sexual dysfunction. **78 out of 100 men** who had external beam radiation reported sexual dysfunction. **88 out of 100 men** who had surgery reported sexual dysfunction.

What treatment or monitoring option is best for you?

Although the lifetime risk of receiving a prostate cancer diagnosis is about 17%, the risk of dying from the cancer is much lower, at about 3% to 6%. You and your doctor should choose the best management approach for your cancer based on your risk of cancer progression, whether you have other medical illnesses, your baseline urinary, sexual, and bowel function, and your own treatment or monitoring preferences.

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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 Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. 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 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. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

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Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity, participants should be able to: • Identify educational content on the management of acute diverticulitis. • Review the data on high dose semaglutide for weight loss in diabetic and nondiabetic obese patients. • Discuss opioid analgesics for diabetic neuropathy pain and prescribing for uncomplicated urinary tract infections. • Apply medical management principles grounded in evidence-based medicine regarding MRI for back pain, colon cancer screening, and management of patients with patent foramen ovale and stroke.

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Management of acute diverticulitis

Annually, there are close to two million outpatient visits for acute diverticulitis (AD) and over 200,000 inpatient admissions, with a cost of over $5 billion. The incidence has increased by 130% in individuals under age 50 over the past several decades.[1] The management of AD has changed significantly over the past several years and is now most often managed as an outpatient. The American Gastroenterological Association last published a guideline on management in 2015 and thus recently updated this guideline to reflect the new research on more conservative approaches to management. This article combines recommendations from the AGA guideline as well as from additional new studies published since the guideline update.

Broadly, patients can present with either uncomplicated or complicated AD. Eighty-eight percent of patients have uncomplicated AD, presenting with the acute or subacute onset of left lower quadrant pain. Associated findings may include fever, elevated WBC count and CRP level, nausea, and change in the bowel pattern. These patients typically have peri-colonic inflammation and thickening of the bowel wall. Complicated AD is seen in the other 12% and is most often associated with abscess formation, but may also include peritonitis, stricture with obstruction, and rarely, fistula formation. Most patients fully recover, however 5% of patients will evolve to smoldering diverticulitis characterized by ongoing pain and inflammatory findings on CT.[1]

Role of imaging. Because the clinical diagnosis is only correct about half the time, CT scan with oral and IV contrast is recommended for the initial presentation of AD since it is 95% accurate for the diagnosis, and may also reveal alternative diagnoses which may mimic AD. CT is also highly accurate for differentiating uncomplicated from complicated AD. Importantly however, for patients with an established diagnosis of diverticulitis in the past, CT is not indicated for recurrences unless complicated disease is suspected, or patients fail to recover with treatment.

Role of antibiotics. This is the largest area of new research on the management of AD, with important new recommendations arising from this research. Most importantly, antibiotics are not routinely indicated, as multiple studies have shown no benefit in patients with mild, uncomplicated AD. In a meta-analysis of nine studies encompassing over 2,500 patients with uncomplicated AD who were treated with antibiotics versus placebo, there was no difference in time to resolution or risk of admission, nor were there differences in progression to complicated disease or the need for surgery.[2] Patients who should be treated with antibiotics at the outset include those that are immunocompromised, and those with suspected sepsis or complicated AD. Importantly, among patients presenting with uncomplicated AD, the risk of progression to complicated AD is only 5%, highlighting the safety of avoiding antibiotics early in the course of uncomplicated AD. Indications of a worsening clinical course which would indicate the need for antibiotic therapy are:

- Symptoms longer than five days prior to presentation
- Fever and/or vomiting
- CRP level >140 mg/dl
- WBC count >15,000/mm
- Abscess or long segment inflammation (>8 cm) on CT scan

Although not specifically discussed in the guideline, there is an important point worth noting. When patients present with LLQ abdominal pain and other nonspecific GI symptoms and diverticulitis is not present, they often have IBS or other functional GI disorders which can be significantly exacerbated by the alterations of bowel flora that follow broad spectrum antibiotic use. Additionally, both the incidence and virulence of C. diff infection is rising due to broad spectrum antibiotic use in the community.[3] Avoidance of antibiotics in mild uncomplicated AD should therefore be viewed through the lens of avoiding potentially harmful care.

When antibiotics are indicated, the recommended regimens include the combination of metronidazole and a fluoroquinolone, or amoxicillin-clavulanate, for a 4–7 day course. Note that here, as with pneumonia, UTI, and sinusitis, short course antibiotic therapy is recommended to minimize antibiotic toxicity. The fluoroquinolones in particular, are a concern due to toxicities across multiple organ systems, predominantly neurological and musculoskeletal. A recent comparative effectiveness study examined antibiotics for AD.[4] Two data bases were queried, totaling 126,000 patients, both commercial and Medicare. The study compared outcomes using these two antibiotic regimens for acute AD. Overall, 90% of patients with AD received antibiotic treatment highlighting the ongoing overuse of antibiotics for uncomplicated AD.

(continued on page 3)

Eighty-seven percent of the treated patients received the metronidazole/fluoroquinolone regimen with only 13% receiving amoxicillin-clavulanate. AD outcomes examined included the need for hospital admission, the need for urgent surgery and the need for elective surgery at three years post episode. With one exception, there were no significant differences in any outcome between the two antibiotic regimens in either the commercial or Medicare populations. The one exception was the incidence of C. diff infection which occurred with twice the frequency in the Medicare population that received metronidazole-fluoroquinolone, although the absolute incidence was low at 1.2%. Given these data, amoxicillin-clavulanate might be considered the safest initial choice.

Role of colonoscopy post recovery from AD. This stems from the concern that colon cancer can be misdiagnosed as AD. In a meta-analysis looking at over 50,000 patients diagnosed with AD, the prevalence of colon cancer was 1.3% after a diagnosis of uncomplicated AD and 7.9% following a diagnosis of complicated AD. The recommendation is therefore to perform colonoscopy 6–8 weeks after an episode of complicated AD. For uncomplicated AD, the suggestion is to perform colonoscopy if a recent screening colonoscopy has not already been performed.

Other guideline recommendations

- Because AD can transiently compromise the bowel lumen, clear liquid diet is initially recommended until clinical improvement has been documented.
- Up to 50% of the AD risk may be genetic. However, avoidance of tobacco and NSAID therapy, and improvement in diet quality with an increase in plants, grains, and fruit fibers may reduce recurrences. Avoidance of nuts, seeds, and corn is not recommended.
- Complicated AD, when present, is most often seen as the initial presentation. With subsequent episodes, the risk of complicated AD lessens. The overall risk of recurrence for AD in any given patient is only 20%, but those that recur often have multiple recurrences and the recurrence risk is higher in those with an initial episode of complicated AD. That being said, current guidelines no longer recommend surgery solely based on the number of recurrences. This should be a shared decision-making process looking at the symptom burden and the risks and benefits of the surgery.

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High dose semaglutide for weight loss in diabetic and nondiabetic obese patients

Our obesity epidemic continues to worsen with over 42% of the population now categorized as obese. Obesity related metabolic disease has eclipsed hyperlipidemia as the most important risk factor for cardiovascular disease. Pharmacotherapy for obesity has been hampered by intolerable side effects and intolerable cost of therapy, and many patients are hesitant to consider bariatric surgery. The combination of phentermine/topiramate, and liraglutide have both been approved for weight loss and have achieved weight loss in the 10% total body weight (TBW) range in many patients. Phentermine/topiramate resulted in a 10% TBW loss in 55% of patients,[5] however it is often discontinued due to intolerable side effects of fatigue, cognitive difficulties, and constipation. Liraglutide provided 10% TBW loss in 35% of patients[6] however, at ~$15,000 yearly, is unaffordable for many patients and often not covered by insurance.

Two important pharmacotherapy weight loss trials were recently published, both using the more potent GLP1-RA, semaglutide. The first study looked at 1,961 obese, nondiabetics and compared counseling on diet and exercise alone to counseling on diet and exercise plus semaglutide 2.4 mg SQ weekly.[7] The mean change in body weight from baseline to week 68 was –14.9% in the semaglutide group as compared with –2.4% with placebo, for an estimated treatment difference of –12.4% ($p<0.001$). More participants in the semaglutide group than in the placebo group achieved weight reductions of 10% or more (69.1% vs. 12.0%), and 15% or more (50.5% vs. 4.9%) at week 68 ($P<0.001$). A third of patients lost over 20% of TBW. The change in body weight from baseline to week 68 averaged –34 lbs. in the semaglutide group as compared with –6 lbs. in the placebo arm.

The second study looked at 1,210 patients with DM2, a BMI ≥ 27, and a HbA1c between 7–10%. The study design was similar to the above study, but also had a semaglutide dose arm of 1.0 mg. At 68 weeks, the average HbA1c in the 2.4 mg arm was 6.4%, compared to 7.8% in the placebo arm. Twenty-eight percent of patients had a concomitant decrease in their other medications for DM2.

Semaglutide is attractive as a weight loss drug for several reasons, including improvements in dyslipidemia, improvements in blood pressure, and reductions in cardiovascular risk. When used in the nondiabetic population, future risk of DM2 is also reduced. Side effects of treatment can be problematic. Nausea was seen in 44% of participants with about a quarter of the patients experiencing vomiting, constipation or diarrhea. We participated in both of the above phase III trials at the New West Physicians Clinical Research Center and noted that with careful slow titration, most patients were able to reach the 2.4 mg dose and in those that were not, significant weight loss was noted at the lower doses.

The highest dose of semalgutide currently available is 1.0 mg and the indication is for treatment of diabetes. It is anticipated that the 2.4 mg dose of semaglutide will be marketed for the indication of weight loss following FDA approval this spring/summer. There is also an oral formulation of semaglutide which is currently being studied for weight loss in phase III trials, but currently is indicated only for DM2. The degree of weight loss in these new trials begins to approach the weight loss seen with bariatric surgery, which is in the range of 25% TBW at one year with sleeve gastrectomy, and 28% with Roux-en-Y bypass.[8] Although the upfront costs of bariatric surgery are higher, at the current cost of liraglutide, surgery becomes cost-effective within several years. The cost-effectiveness of semaglutide will need to be addressed when the pricing becomes available. When used in patients with DM2, part of the cost may be offset if other expensive diabetes drugs can be eliminated. Overall, patient acceptance of pharmacotherapy is higher than that of bariatric surgery. As providers, we need to improve our utilization of both pharmacotherapy and bariatric surgery in the appropriate patients, as the percent of the population with obesity continues its inexorable rise.

Opioid analgesics not a recommended or appropriate treatment for diabetic neuropathy pain

Pain from diabetic neuropathy is common and can result in debility, disability, and poor life quality. To promote safe long-term pain management, clinical guidelines recommend use of anticonvulsants (pregabalin, gabapentin) and antidepressants (serotonin-norepinephrine reuptake inhibitors).[9] Additionally, topical analgesics, low dose tricyclic antidepressants, and other anticonvulsants are considered acceptable. Opioid medicines are not recommended. A retrospective cohort study examined first-line analgesic medications prescribed to patients with new diagnoses of diabetic peripheral neuropathy over a study period from 2014 to 2018.[10]

Among 3,495 patients with new diabetic neuropathy diagnoses, 1,406 were prescribed a pain medicine. Opioids were prescribed to 616 (43.8%), while recommended medicines and acceptable medicines were prescribed to 603 (42.9%) and 289 (20.6%), respectively. Men had more opioid prescriptions than women (odds ratio [OR] 1.26), and patients with fibromyalgia had less opioid prescriptions than patients without fibromyalgia (OR 0.67). Over the five-year study period, opioid prescribing decreased (OR 0.71), and prescribing of recommended medicines increased (OR 1.25).

Since the study methods did not account for other preexisting pain conditions, it is possible that not all prescribed opioids were intended to treat diabetic neuropathy. That being said, aside from palliative treatment, opioids should not be used for long-term pain management, which includes diabetic neuropathy.

Antibiotic prescribing for uncomplicated urinary tract infection: still a challenge

Uncomplicated urinary tract infection (UTI) in women results in 10.5 million health care visits annually in the United States.[11] The appropriate use of antibiotics in the treatment of uncomplicated UTI in women is outlined in national guidelines (Table 1).[12]

Table 1. Recommended antibiotics for uncomplicated UTI in women

Recommended agent	Duration
Nitrofurantoin	5 days
Trimethoprim–sulfamethoxazole	3 days
Fosfomycin	Single dose (not used frequently in U.S.)

Beta-lactams and fluoroquinolones are not considered appropriate therapy

Clinical practice frequently deviates from recommendations. Commercial insurance medical claims for uncomplicated UTI from 670,450 women ages 18–44 from 2011 to 2015 were examined to determine the choice and duration of antibiotic therapy.[13] Urinalysis was performed in 83% of cases and urine culture in one-half of cases. The incorrect antibiotic was chosen in 47% of cases and the duration of antibiotic therapy was inappropriate in 76% of cases (Table 2).

Table 2. Utilization of antibiotics in the treatment of uncomplicated UTI in women

	Recommended antibiotics		Antibiotics NOT recommended	
	Nitrofurantoin	TMP/sulfa	Fluoroquinolones	Beta-lactams
Antibiotic choice (%)	21	33	41	5
Antibiotic duration incorrect by drug (%)	81	70	78	37

TMP/sulfa = trimethoprim–sulfamethoxazole

When the correct drug was chosen the duration was incorrect in most cases. The recommended duration of antibiotic therapy is three days for fluoroquinolones and 3–7 days for beta-lactams; however, these agents are not recommended for UTI treatment; therefore, any duration is essentially inappropriate. Understanding local antibiotic susceptibility patterns is essential in determining the optimal antibiotic choice and this data is not universally available.

Inappropriate antibiotic use contributes to the development of resistant pathogens and adversely effects patient's microbial biome with multiple negative health impacts.[13] This study underscores the difficulty in translating national guidelines into practice and the urgent need for more comprehensive antimicrobial stewardship programs.

Consequences of early and unnecessary MRI for back pain far exceed the cost from imaging

Back pain is a common complaint, and many patients with uncomplicated acute back pain will recover with minimal intervention. A joint clinical practice guideline from the American College of Physicians and the American Pain Society recommends using a focused history and physical examination to categorize patients as either (1) nonspecific low back pain, (2) back pain potentially associated with radiculopathy or spinal stenosis, or (3) back pain potentially associated with another specific spinal cause.[14] There is no evidence that the routine use of imaging (plain films, CT, or MRI) improves clinical outcomes for patients with uncomplicated acute pain. Previous guidelines have recommended allowing a 4–6 week recovery period before obtaining imaging.[14,15]

A recent study examined the downstream effects of early lumbar spine imaging, defined as less than six weeks from the onset of pain when no red flags were present.[16] The retrospective study was conducted from primary care clinics in the U.S. Department of Veterans Affairs. Patients with early MRI were compared to patients with similarly uncomplicated lower back pain, but without early MRI. Several measures were evaluated including lumbar spine surgery, prescription opioid use, acute health care costs, and the last pain score within one year from the index visit.

There were 1.17 million VA primary care visits for nonspecific low back pain during the study period, 405,695 patients were included in the matched cohort for analysis. Comparing patients with early imaging to patients without early imaging the early imaging cohort characteristics included:

- Younger age
- Less likely to have an assigned PCP
- Reported higher pain levels
- Fewer chronic medical conditions

An early scan was associated with more opioid prescriptions, an over ten-fold increase in lumbar surgery rate, greater than twice the cost for acute care in the initial period, higher cost at follow-up, and more pain reported at follow-up. Since opioids are rarely indicated for prolonged pain (pain beyond 3–7 days), the number of patients prescribed opioids for longer than 3–7 days was excessive in both groups. (See Table 3.)

Table 3. Early imaging cohort outcomes vs. no early imaging cohort outcomes

Early imaging cohort	Early imaging outcomes (n=9,977)	No early imaging outcomes (n=395,718)
Need or increased prescriptions	35.1%	28.6%
Need for surgical intervention	1.48%	0.12%
Initial acute care cost	$2,254	$1,100
Follow-up care cost	$7,501	$5,112
Mean pain score at follow-up	3.87	3.28

The study results demonstrate that early MRI among patients without red flags for lower back pain led to more medical interventions and higher costs but did not improve relative pain reporting. A study limitation is that patients with early MRI may have had other confounding problems, and those variables may have influenced the study outcomes.

A similar study focused on an older population.[17] Here early imaging is often done due to concerns about a higher incidence of underlying systemic disease such as cancer or infection causing spine disease in this population. A total of 5,239 patients over age 65 presenting with new onset back pain were followed for one year following diagnosis, comparing cost and outcomes in those who had early MRI imaging with those that did not. In only one of the 1,630 patients with early imaging was a cancer found and this was an incidental abdominal lymphoma. Only 2% of the group with early imaging had a spinal fracture for which earlier diagnosis did not likely affect treatment decisions. The cost of care over one year was almost $1,500 higher in the group with early imaging and the functional back pain outcomes were not different between the two groups.

These studies once again emphasize the important point that most patients with acute, uncomplicated back pain recover on their own, early MRI rarely changes management, but has the potential to cause harm and drives excess utilization and cost of care.

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Meta-analysis supports colon cancer screening interval recommendations

Appropriate screening for colorectal cancer (CRC) remains a challenge. Initial screening is often delayed and there is continued oversurveillance of low risk adenomas, which increases both the costs and risks associated with CRC screening.[18] In a meta-analysis of 12 studies involving 510,019 patients, the correlation between findings at initial colonoscopy and colorectal cancer (CRC) were examined.[19] The incidence of CRC per 10,000 person-years was examined in those patients having no adenoma (NA), low-risk adenoma (LRA), and high-risk adenoma (HRA) as defined by the United States Multi-Society Task Force (USMSTF) guidelines.[20] Across all studies the median patient age was 59 years and 55% were male.

The incidence of CRC per 10,000 person-years based on initial colonoscopy was insignificantly higher in patients with LRA vs. NA, at one additional case of CRC for every 10,000 patient years (4.5 vs. 3.4; odds ratio [OR], 1.26; 95% CI, 1.06–1.51). However, in those patients with a HRA, the incidence of CRC was significantly higher than those without adenomas (13.8 vs. 3.4; odds ratio [OR], 2.92% CI, 2.31–3.69). The CRC-related mortality followed this pattern with no significant difference in mortality between persons with NA vs. LRA (OR, 1.15; 95% CI, 0.76–1.74) but was significantly higher in patients with HRA vs. patients with LRA (LRAs (OR, 2.48; 95% CI, 1.30–4.75) and no adenomas (OR, 2.69; 95% CI, 1.87–3.87).

This analysis lends further support to the screening intervals outlined in the USMSTF guidelines cited above. Patients should be encouraged to begin screening for CRC at age 45 years of age if at average risk, with further screening dictated by the results of initial colonoscopy. Based on the above analysis of over a half million patients, surveillance colonoscopy at an interval of less than 10 years for patients with LRA would be highly cost-ineffective and expose patients to the increased risks of screening, without significantly reducing CRC mortality. Based on the most recent AGA guideline, we are now offered the option of a 10-year screening interval in those patients with 1–2 LRA, which is by far the largest population of patients who have polyps on colonoscopy. This study supports adopting this 10-year screening interval.

American Academy of Neurology management recommendations for patients with patent foramen ovale and stroke

The prevalence of patent foramen ovale (PFO) in the general population is about 25%. Although the risk of ischemic stroke is far lower in younger adults compared to older adults, younger patients who have strokes are more likely to have PFOs, especially if the stroke is cryptogenic (meaning the cause cannot be determined).[21,22] The American Academy of Neurology recently published recommendations about the management of patients with a history of stroke or transient ischemic attack, who are found to have a PFO.[23]

A summary of the recommendations follows:

- If PFO closure is under consideration, clinicians should ensure that alternative stroke mechanisms have been ruled out (moderate recommendation).
- Clinicians should perform baseline EKG (strong recommendation) to look for atrial fibrillation and, for those patients at high risk of atrial fibrillation, prolonged monitoring should be performed for at least 28 days (moderate recommendation).
- If PFO closure is under consideration, clinicians should counsel the patient about the high prevalence of PFO, the uncertainty about whether a PFO caused a stroke, and that PFO closure probably reduces the stroke risk in select patients under 60 years of age with embolic-appearing stroke(s) (moderate recommendation).
- Among patients who opt for medical therapy (without PFO closure), clinicians may recommend an antiplatelet therapy or anticoagulation (weak recommendation).

Although robust data are available about the safety and efficacy of PFO closure in select patients with cerebral vascular disease, there are procedure-related complications including new stroke and self-limited atrial fibrillation.

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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 Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. 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 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. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

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Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity, participants should be able to: • Identify educational content on the management of heart failure with reduced EF and the role of SGLT-2 inhibitors. • Review the pharmacological considerations for prescribing SGLT-2 inhibitors and GLP1-RA therapy for diabetics to reduce cardiovascular death. • Discuss the harms versus the benefits for asymptomatic carotid screening. • Apply medical management principles grounded in evidence-based medicine regarding weight-loss surgery, knee locking and catching, elevated liver enzymes and osteoporosis screening in older men.

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New research on the role of SGLT-2 inhibitors in the management of heart failure with reduced EF (HFrEF)

Existing data suggest that the clinical course of HFrEF (EF<40%) might be significantly improved with the use of SGLT-2 inhibitors (SGLT2i) in both diabetics and non-diabetics. These clinical benefits include an improvement in performance status and a reduction in hospital admissions and cardiovascular death. It is understood that this drug class exerts a diuretic effect due to glycosuria, raising the question as to whether this might be the dominant mechanism of action. If that were to be the case, given the annual cost of ~$6,000 for these drugs, other less expensive diuretics might be of equal value. Another important consideration when thinking about adding an SGLT2i for HFrEF is that there are now five classes of drugs recommended to manage HFrEF. Since most of these patients have other comorbidities requiring additional pharmacotherapies, drug regimens could quickly become overwhelming for patients based both on their complexity and their cost. Although there have been no head-to-head trials comparing the SGLT-2i's to other diuretic agents, three studies published in the *Journal of the American College of Cardiology* (JACC) this spring add considerable knowledge to the role of this drug class in the management of HFrEF and suggest that the beneficial mechanisms of action go well beyond diuresis.

The first two studies were sub-studies of the large EMPEROR Reduced Trial (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction). The first study addressed the question of whether glycosuria and the related diuresis is the primary beneficial mechanism of action of the SGLT2i's in HFrEF.[1] It was a double-blind placebo-based trial that examined over 3,700 patients with HFrEF, both with and without diabetes. Half of the patients were randomized to receive empagliflozin 10 mg daily and the other half placebo, on a background of guideline directed medical therapy. In the four weeks prior to randomization, about 40% had volume overload. This group was sicker with more comorbidities, a higher NYHA CHF classification and higher brain natriuretic peptide (BNP) levels. The subsequent risk reduction in hospital admissions for CHF was higher in the euvolemic group at 40%, compared to 16% in the volume overload group, with results in both groups being significant. Also, irrespective of volume status, the patients on SGLT2i therapy were less likely to require diuretic intensification, had greater decreases in BNP levels, and were more likely to see improvements in their NHYA class. They also scored higher on the Kansas City Cardiomyopathy questionnaire.

The second study examined whether there was a beneficial or harmful interaction with the addition of SGLT2i's in a population of patients who were already on guideline directed medical therapy that included a mineralocorticoid receptor antagonist (MRA) with spironolactone or eplerenone.[2] The study population was the same as above, and 71% of patients were on MRA therapy and 29% were not. The beneficial effects of the SGLT2i were additive to those of aldosterone blockade. The study showed that the overall beneficial effects of the SGLT-2i were similar whether or not the patient was already receiving treatment with an MRA. Perhaps related to clinical improvements from the SGLT-2i, those patients who were not on an MRA at baseline were 35% less likely to start treatment with an MRA when on empagliflozin compared to placebo. Also, looking at the group of patients treated with an MRA, those also taking an SGLT2i were 22% less likely to discontinue it due to hyperkalemia, possible related to the SGLT2i effect of increasing sodium delivery to the distal nephron which increased urinary potassium excretion.

The third study looked at a group of patients with either ischemic or non-ischemic cardiomyopathy with reduced EF, and evaluated ventricular function and patient performance before and after the addition of a SGLT2i. It was a small double-blind trial in 84 patients without diabetes.[3] Patients were randomized to empagliflozin versus placebo on a background of guideline directed medical therapy and followed for six months. The results using cardiac MRI showed decreases in both end systolic and end diastolic volume and a significant 6% increase in ejection fraction. Treated patients walked about 120 yards further on the six-minute walk test and had about a 20% improvement in the quality of life score on the Kansas City Cardiomyopathy questionnaire. Among the potential mechanisms thought to account for the benefit include the known diuretic effects of the SGLT2i's as well as a switch in the myocardial metabolism away from glucose utilization into consumption of fatty acids, ketone bodies, and branched-chain amino acids, which enhances myocardial energetics and improve contractility in animal models. There may be other mechanisms in play that have not yet been elucidated.

It therefore appears that the mechanism of actions of the SGLT2i's in HFrEF extend beyond their diuretic effect, and they appear to exert their beneficial effect on top of other guideline directed medical therapies including MRA's. There may be an effect on ventricular remodeling that improves left ventricular function. There continue however, to be many unanswered questions. This includes understanding whether this drug class has any benefits in the larger group of CHF patients with preserved EF. Two ongoing studies will likely soon answer this question. Most importantly, we need to determine if there are incremental benefits to each of the four classes of guideline directed medical therapy for HFrEF such that the cost and complexity of a four drug regimen could be rationalized for use in daily patient care.

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With respect to broad cost effectiveness analyses of the SGLT2i's, the results are dramatically impacted by the degree of underlying risk in the patient, as well as which outcome we are attempting to prevent. The three main outcomes of interest with this drug group are reductions in major adverse cardiac event (MACE), improvements in CHF outcomes, and prevention of renal outcomes. We have data available for the first two of these. Let's first look at the cost to prevent MACE in the population of DM2 patients with either established CAD or very high CV risk. This cost is approximately ~$500k per event avoided and would therefore not be cost effective for this purpose. Data on the cost effectiveness related to CHF outcomes were just published this month.[4] The cost per QALY gained was $83,600, which would fall into the borderline cost-effective category. The authors estimated an acceptable QALY of $50,000 could be achieved if the drug cost would be reduced by 43%. Lastly, it may be cost effective to use SGLT2i's in the subset of patients with CKD and proteinuria since renal outcomes improve in this group, although formal cost-effective analyses have not yet been published for this outcome. We are working on calculating the SGLT2i cost effectiveness in each of these subgroups as well as combinations of these subgroups, using our internal data. Given the difficulty in proving robust cost effectiveness in these high-risk populations, it is doubtful that this class of drugs will be cost effective in those patients who do not fall into the above three categories of risk. See the accompanying article in the pharmacy section for further prescribing recommendations of both the SGLT2i and GLP1 RA classes of drugs.

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Evidence-based guideline for SGLT-2i and GLP1-RA use in DM2

A recent guideline in the *British Medical Journal* (BMJ) attempted to identify the subsets of patients with DM2 in whom SGLT2i and GLP1-RA therapy would be most appropriate. It used a meta-analysis of 764 trials in over 421,000 patients. This study confirmed the reduction in MACE, CV death, and progression to ESRD seen with both drug classes but precise cost effectiveness could not be studied due to marked differences in drug cost in the multiple countries involved in these studies.[4] We know that the drug costs in the U.S. for example, are over twice those in the other countries represented. In order to approximate cost in their recommendations, they considered the number needed to treat (NNT) along with the relevant clinical data in the strength of their recommendations. For example, looking at reduction in CV death, the NNT for five years to prevent one death varied from 21 (high efficacy) for patients with established CAD who were at the highest risk up to 200 (low efficacy) for those at lower risk. In this lower risk group, assuming a yearly drug cost of $6,000, the yearly cost to prevent a single MACE event would be $6 million. The authors looked at similar considerations for renal outcomes and used these data to build a guideline recommending use of these two drug classes in different clinical scenarios. This guideline is more granular, addressed both the benefits and harms of therapy, and is more cost attentive than the current U.S. guidelines from the endocrine and diabetes societies. It did not address the subset of DM2 patients who have HFrEF, but it is clear from the above three studies that these patients derive meaningful benefit from SGLT2i's. The BMJ guideline suggests:

- Not using either drug class in the absence of diabetic renal disease or at least four CV risk factors (CV risk factors are listed on the guideline).
- In patients with four or more CV risk factors, SGLT2i's are recommended.
- In patients with either established CAD or established renal disease, either drug class can be considered.
- When both diseases are present, SGLT2i's are preferred.

The link will bring you to the full article with the attached infographic guideline. https://doi.org/10.1136/bmj.n1091

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Asymptomatic carotid artery stenosis - harms outweigh benefits when screening asymptomatic populations

The U.S. Preventive Services Task Force reaffirmed in its 2021 statement that the harms of screening asymptomatic patients for carotid artery stenosis outweigh the benefits.[5] In this context, "asymptomatic" means no previous stroke, transient ischemic attack in an anterior circulation distribution, or other signs/symptoms referrable to carotid disease. Importantly, syncope, lightheadedness, vertigo and other nonspecific neurological symptoms are not referable to the carotid artery distribution. A recent editorial adds further context.[6]

With few exceptions, professional societies have recommended against the carotid artery screening among asymptotic individuals. The Choosing Wisely campaign has added carotid artery screening to its "do not do" list. The recommendation against screening is based on two principles:

- The benefits of asymptomatic carotid endarterectomy are unclear and the stroke rate in asymptomatic carotid stenosis has markedly declined due to improved medical management.[5]
- Carotid endarterectomy has substantial associated risks of stroke, CV events and death, which currently appear to be substantially higher than those in patients who are medically managed.[6]

Yet, patients continue to have carotid artery imaging for various reasons, as part of a syncope evaluation, for a carotid bruit, or because of direct-to-consumer advertising, none of which is supported by the evidence. The editorial concludes that when carotid artery stenosis is identified, mitigation of cardiovascular risk factors is the best treatment strategy. Focus on the risk factors; avoid the screening.

Weight-loss surgery significantly improves survival among adults with obesity

Projections suggest that one of every two adults in the United States will have obesity (BMI of 30 to <35 kg/m2) by the year 2030, and nearly 25% of adults will have severe obesity (BMI ≥35 kg/m2).[7] Obesity – or more specifically, visceral adiposity – is one of the components of the metabolic syndrome, which is associated with diabetes, coronary heart disease, stroke, certain cancers, and premature death. Weight-loss surgeries have been shown to facilitate improvements in metabolic complications including Type 2 diabetes, dyslipidemia, and obstructive sleep apnea, which is the reason such procedures have been termed "metabolic-bariatric surgery." However, most outcome studies of metabolic-bariatric surgery have been small.

Syn and colleagues conducted a meta-analysis of matched cohort and prospective controlled metabolic-bariatric surgeries to develop more robust outcomes data.[8] Sixteen matched cohort studies and one prospective controlled trial were included in the analysis for an overall patient population of 174,772 and 1.2 million patient-years. The procedures included gastric bypass, banding, and sleeve gastrectomy.

The study showed that metabolic-bariatric surgery was associated with a reduction in the hazard rate of death of 49.2% and an improvement in median life expectancy of 6.1 years when compared to usual care without surgery. The number needed to treat to prevent one death over a 10-year period was 8.3. When stratified by the presence or absence of Type 2 diabetes, the treatment effect was more pronounced in those with diabetes. Patients with diabetes and metabolic-bariatric surgery had a median life expectancy of 9.3 years longer than patients with diabetes but no surgery. The gain in life expectancy associated with metabolic-bariatric surgery was 5.1 years in patients without diabetes. The treatment effects did not differ between the various types of procedures. Compared to many other pharmaceutical and surgical interventions, these are very favorable NNT's.

Given the substantial improvements in life expectancy from metabolic-bariatric surgery, primary care providers should consider these procedures early in the care of patients with obesity, especially if they also have diabetes. Bariatric surgery is highly cost effective and significantly underutilized.

All that clicks, pops, grinds or locks is not a meniscal tear

The historic attribution of "knee locking or catching" to meniscal pathology is being challenged. Researchers in Boston prospectively collected patient reported knee symptoms (PRKS) pre-arthroscopy over seven years.[9] A total of 565 patients were included. The surgical teams recorded PRKS and details of any meniscal tears or damage and details of cartilage damage. The operative findings were then compared to the PRKS using regression analysis.

Importantly, a correlation between PRKS and meniscal pathology was not found. There was an association between the extent of underlying cartilage damage (i.e. DJD) but not specifically to meniscal pathology. The severity of PRKS seems to correlate well with the overall cartilage damage reflecting the overall extent of degenerative knee disease. The symptom complex previously known as "meniscal" symptoms should more accurately be termed "degenerative knee" symptoms.

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As such, mechanical knee symptoms other than trauma related in a younger patient are not an indication for arthroscopy. Treatment should be conservative, as we know the majority of these patients will have degenerative meniscal tears. Therefore, should an MRI be obtained, a "surgical indication" will most often be found in the absence of any data suggesting a benefit to meniscal surgery in this group of patients. The Optimal Care knee algorithm has been updated to reflect these new data.

Steatosis with and without elevated liver enzymes: Risk of cirrhosis and hepatocellular carcinoma

With the increased rate of obesity in the US, we are facing a potential epidemic of non-alcoholic fatty liver disease (NAFLD) related cirrhosis over the next couple of decades. The significance of liver steatosis in those patients without an increase in alanine aminotransferase (ALT) is unknown. Researchers used medical record data to follow patients selected from 130 VA hospitals over eight years with liver steatosis either with or without an elevation of ALT.[10] They compared these two groups to a control group of patients who had normal ALT levels with no known liver disease. Patients were excluded if they had any known liver disease. Records were examined for evidence of cirrhosis or hepatocellular carcinoma (HCC). Results are detailed in table one.

Table 1

Patient characteristic	Cirrhosis			Hepatocellular carcinoma		
	Case #	Person years	Incidence / 1000 PY (95% CI)	Case #	Person years	Incidence / 1000 PY (95% CI)
Steatosis normal ALT	31	25336	1.22 (0.83,1.74)	5	25441	0.2 (0.06,0.46)
Steatosis elevated ALT	435	112950	3.85 (3.5,4.2)	42	114749	0.37 (0.26,0.49
No Steatosis	61	67955	0.97 (0.74,1.24)	4	63232	0.06 (0.02,0.16)

Importantly, patients with "incidental" steatosis without an elevation in ALT had no statistically significant increase in cirrhosis or HCC over the eight years of follow-up and compared similarly to those patients with no known liver disease. The patients with steatosis with an increase in ALT were younger and more often obese than those with steatosis without an increase in ALT. Based on the data, they were at much higher risk of cirrhosis and/or HCC. There are two easy to use prediction tools (FIB4 and NAFLD calculators) that incorporate ALT along with other parameters available in the patient chart to estimate risk of advancing fibrosis. These tools should be used in any patient with known hepatic steatosis or risk factors for hepatic steatosis. If the result is intermediate or elevated, a Fibroscan (US derived transient elastography) should be performed to evaluate for NASH with accompanying early hepatic fibrosis, since treatment at an early stage can prevent the development of cirrhosis.

Screening for osteoporosis is cost-effective in older men with prior falls

The prevalence of osteoporosis increases with age, and osteoporosis affects an estimated two million men.[11] In their 2018 statement, the U.S. Preventive Services Task Force recommended screening for osteoporosis in all women 65 years and older and all postmenopausal women under 65 years at increased osteoporosis risk to prevent fractures.[12] But they found that the evidence was insufficient to recommend screening as a method of decreasing bone fractures among average-risk men without previous osteoporotic fractures.

In a recent publication, the cost-effectiveness of osteoporosis screening with dual-energy x-ray absorptiometry (DXA) and treatment of those with osteoporosis was assessed among men with previous falls.[13] A Markov model was used to develop a hypothetical population of community-dwelling men, aged 65, who had at least one fall in the previous year. Data sources were gathered from published literature about osteoporosis prevalence, fracture incidence, treatment effects, mortality, quality of life, and costs. The model demonstrated good external validity by simulating lifetime fracture risks among men aged 50 years and comparing to published estimates. Modeling of men aged 65 demonstrated an incremental cost-effectiveness ratio of $33,169 per quality-adjusted life-year gained. The number needed to screen to prevent one hip fracture was 1,876, and to prevent any fracture was 746. The findings were robust to wide variations in model assumptions. Increasing the age of the target population to 77 years improves health outcomes and overall costs. By age 70, the number needed to screen to prevent any osteoporotic fracture was 393; by age 80, the number needed to screen was 104.

Fall risk should be assessed in all older adults and preventative measures implemented when a fall risk is present. Among older men with at least one fall in the previous year, screening for osteoporosis and treating those with disease can be a cost-effective method of fracture prevention, particularly in those men aged 70 and older.

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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 Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. 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 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. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical, a medical device startup company, and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

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Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity, participants should be able to: • Review evidence on outcomes related to screening for ovarian cancer and recommended management of incidental ovarian cysts. • Identify pharmacological considerations of a new treatment for Alzheimer's disease. • Assess the cost effectiveness of SGLT-2i use in Type 2 diabetes. • Compare surgical and non-surgical treatment plans for patients with partial-thickness rotator cuff tears, and outcomes of abdominopelvic robotic surgical techniques.

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Screening for ovarian cancer

Due to the nonspecific presenting signs and symptoms of ovarian cancer, which result in 58% of women presenting with late stage disease, there has long been interest in screening for ovarian cancer to improve the prognosis. Additionally, the availability of ovarian ultrasound and CA-125 testing often drives patients to request screening in the absence of evidence supporting any benefit to this approach.

The first large contemporary screening trial of ovarian cancer was the Prostate-Lung-Colorectal-Ovary Screening trial (PLCO Trial).[1] The long-term follow-up results were published in 2011. Over 78,000 women aged 55 to 74 years were assigned to undergo either annual screening with CA-125 and ultrasound, or no screening at ten screening centers across the U.S. After 15 years, there was no reduction in ovarian cancer mortality and 9% of women had significant false positive results which necessitated surgery in about a third of that group.

Flash forward to a second large trial which was published this spring.[2] The design of the trial was similar and enrolled over 202,000 women aged 50-74 with an average risk for ovarian cancer at screening centers across the UK. The women were enrolled in a 1:1:2 ratio to either multimodal screening (MMS) which consisted of annual CA-125 with trans-vaginal ultrasound (TVUS) for any patients with CA-125 elevations, annual TVUS alone, or usual care. They were followed for a median of 16 years.

The overall incidence of ovarian and tubal cancer was not significantly different between groups at the end of the study with each group having an incidence of 0.9%. Looking at the more important outcome of ovarian/tubal cancer mortality, each of the three groups also had an identical mortality rate at 0.6%. At 9.5 years after the end of screening, when compared with the no screening group, the MMS group had a 39% higher incidence of stage I or II disease and 10% lower incidence of stage III or IV disease. There was no evidence of a shift in incidence in any stage in the TVUS group compared with the no screening group. There was therefore a disconnect between the earlier stage at presentation in the MMS compared to no screening group and the absence of an effect on subsequent mortality. This was mostly accounted for by a higher case fatality rate for stage I disease in the MMS group compared to the no screening group (14.8% vs. 9.4%), and a lower case fatality rate for stage IV disease in the no screening group compared to the MMS group (79.5% vs. 83.7%).

The changes in stage distribution in the MMS group did not translate into mortality reduction. It seems probable that the cancers shifted to an earlier stage at diagnosis had an intrinsic poorer prognosis, which was not altered by earlier detection and the available treatments for early stage disease. This therefore emphasizes the importance of having disease-specific mortality as the primary outcome in ovarian/tubal cancer screening trials. In summary, these results, added to the PLCO trial results, indicate that there is no survival benefit to screening for ovarian/tubal cancer using either CA-125 or TVUS.

Follow-up of incidentally discovered ovarian cysts

A related topic is the intensity with which incidentally discovered ovarian cysts should be followed. A large study from Kaiser Permanente Washington evaluated the likelihood of ovarian cancer being related to the presence of simple ovarian cysts in over 72,000 women who underwent transvaginal US (TVUS) and were followed for three years.[3] The incidence of simple ovarian cysts was 23.8% under age 50 and 13.4% over age 50. This older group is particularly important since most ovarian cancer occurs in women over age 50 and simple ovarian cysts in this age group are not always considered innocent. As a result, these are frequently followed regularly with an associated increase in imaging and the potential for unnecessary treatment.

In the 13,000 women under age 50 with simple cysts, there were no ovarian cancers identified on follow up. Of the 2300 women who were over age 50 and had simple cysts, 86% of the cysts were under 5 cm in diameter. Overall, in these 2300 women there was only one ovarian cancer which was felt to be unrelated to the identified 1 cm simple cyst, as the patient had a CT done for abdominal pain which revealed extensive peritoneal metastatic disease. Complex cysts or solid masses on the other hand, increased the likelihood of ovarian cancer being present by 23–37-fold in both younger and older women. Even with this markedly elevated relative risk, the likelihood of a complex cyst in a woman over age 50 being an ovarian cancer in this study was still only 6.5%. It can be helpful to remind women of this to reduce the anxiety associated with the evaluation.

This study adds to the body of evidence suggesting that simple ovarian cysts are almost universally benign, irrespective of age. Assuming a high quality TVUS with all criteria met for a simple cyst, and given the anxiety, cost, and potential for further intervention with ongoing US surveillance, the concluding sentence in this study merits attention: "Simple cysts are frequently encountered incidental and normal findings on pelvic imaging, and additional evaluation of these findings is not warranted."

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Biogen's Aduhelm (aducanumab): Unproven benefits, known harms, and substantial costs

June 7, 2021, under the accelerated approval process, the FDA approved the amyloid beta-directed antibody, Aduhelm (aducanumab), for the treatment of Alzheimer's disease. The indication for aducanumab was later changed from "Alzheimer's disease" to mild cognitive impairment and mild dementia due to Alzheimer's disease.

Biogen conducted two phase-3 studies, ENGAGE and EMERGE. Initial analyses led to a conclusion of futility in both studies. The data were later reanalyzed focusing on outcomes from the high-dose treatment arm and the surrogate marker of beta-amyloid plaque burden assessed by amyloid PET. Both studies shared identical methodologies – randomized, controlled clinical trials with 78 weeks follow-up and three study arms: low dose, high dose, and placebo. Eligible patients had mild cognitive impairment attributed to insipient Alzheimer's disease or mild dementia with presumptive Alzheimer's disease. Although the results of these analyses have not been scrutinized through the peer-review process of journal publication, select data were made available by Biogen in December 2019.[4]

ENGAGE failed to show any significant difference in clinical outcome between treatment and placebo. EMERGE did demonstrate a difference in the primary outcome, the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). Statistical significance was achieved because the comparison groups were large, but the clinical difference of -0.39 points on a scale ranging from 0-18 points does not represent clinically meaningful change. The published minimal clinically important difference for the CDR-SB is 1–2 points across the Alzheimer's disease spectrum.[5]

Both studies, however, demonstrated a decrease in beta-amyloid plaque burden on amyloid PET scan. The FDA approved aducanumab "based on reduction in amyloid beta plaques," a surrogate marker, in treated patients.[6] However, previous amyloid-targeting drugs have been able to decrease amyloid burden but failed to provide clinical benefit.[7]

Whereas the benefits of aducanumab were not clinically significant, the potentially severe adverse event were common. These include amyloid-related imaging abnormalities (ARIA) with cerebral edema, cerebral microhemorrhage, and cerebral superficial siderosis (an imaging sign of previous hemorrhage). Cerebral edema was temporary for most patients, although it was often associated with symptoms of headache, confusion, dizziness, vision changes, or nausea. The Table provides rates of adverse events compared to placebo and numbers needed to harm.

Table 1. Aducanumab adverse reactions versus placebo[6]

Adverse reaction	Aducanumab, N=1105	Placebo, N=1087	Number needed to harm[D]
Cerebral edema (ARIA-E)[A]	35%	3%	4
Headache	21%	16%	20
Cerebral microhemorrhage (ARIA-H)[B]	19%	7%	9
Cerebral siderosis (ARIA-H)	15%	2%	8
Falls	15%	12%	34
Diarrhea	9%	7%	50
Confusion/delirium/Disorientation[C]	8%	4%	25

[A]ARIA-E, Amyloid-related imaging abnormality – Edema
[B]ARIA-H, Amyloid-related imaging abnormality – Hemorrhage
[C]Also includes altered mental status
[D]Number needed to treat to produce one adverse event

The financial burden of aducanumab is also very high. The drug is currently estimated to cost $56,000 per year, not including the costs related to monthly infusion, serial MRIs, or potential downstream costs from adverse events. It is difficult to estimate the out-of-pocket costs to patients as this will vary by health plan, but it is expected to be $8,000 or more yearly.

Overall, aducanumab has not been shown to provide a clinically meaningful benefit but poses substantial risks of harm at an exorbitant financial cost. If CMS elects to cover aducanumab, the estimated spend will significantly exceed the total for all other part B drugs combined, including all chemotherapies for all cancers. An analysis by the Institute for Clinical and Economic Review (ICER) states that the evidence is insufficient to demonstrate that aducanumab benefits patients.[5] The ICER statement reads: "…[T]he FDA, in approving aducanumab (Aduhelm™, Biogen) for the treatment of Alzheimer's disease, has failed in its responsibility to protect patients and families from unproven treatments with known harms."[8]

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Unfortunately, effective treatments for Alzheimer's disease — treatments that halt progression and lead to stable improvements in cognition — do not currently exist. The lack of effective treatments can lead to desperation among patients, families, and healthcare providers. But desperation should never overwhelm a rational approach to medicine: the potential benefits of a treatment must outweigh the potential harms. Aducanumab does not appear to meet this basic standard.

SGLT-2i use in type 2 diabetes: When is it cost effective?

Metformin remains the initial guideline directed choice for treatment of type 2 diabetes. It is well appreciated that SGLT-2i agents reduce cardiovascular risk alone or in combination with metformin in patients with established CVD or at very high risk of CVD. The advantage of SGLT-2i agents over sulfonylureas (SU) has not been demonstrated and the subset of patients in which SGLT-2i agents are most cost effective is being defined.

The new use of SU or SGLT-2i in the presence of metformin was studied in 123,293 (104,423 (SU); 23870 (SGLT-2i)) patients from the VA.[9] The use of SGLT-2i resulted in a reduced overall mortality relative to SU use of 5.1 fewer deaths per 1,000 patient years. This effect was more evident in patients with Stage 3 CKD (GFR 30-59 ml/min), but not more evident in those with compared to those without CVD.

The annual out-of-pocket costs for SGLT-2i ranges from $1298 to $1615 and total cost from $5967 to $6118. Some estimates suggest that despite this high cost, the utilization of SGLT-2i is cost effective for all patients.[10] Using the above data from the VA trial, the cost to avert one death by use of an SGLT-2i over an SU would be approximately $1.2 million. A recent guideline was proposed suggesting the use of SGLT-2i only in a higher risk subset of patients with type 2 diabetes.[11] The guideline published in the British Medical Journal recommends SGLT-2i for patients with four or more cardiovascular risk factors or with established cardiovascular or renal disease. Targeting this population of patients for SGLT-2i use is likely to be cost effective.

The use of SGLT-2i agents alone or in combination with metformin should be part of a shared decision-making conversation with patients considering patients risk factors, costs and expected benefit.

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Outcomes from non-surgical and surgical treatments do not differ among patients with partial-thickness rotator cuff tears

Rotator cuff disease (RCD) is the most common cause of long-term shoulder pain and dysfunction among adults.[12] RCD comprises a spectrum of acute-to-chronic tendon damage, ranging from tendinopathy without frayed tendons to full-thickness tendon tears. Non-surgical forms of treatment are generally recommended first. Several previous studies have demonstrated equivalent outcomes from subacromial decompression and non-surgical treatments for RCD in the absence of full-thickness tears, and subacromial decompression is therefore no longer recommended.[13] Less is known about the benefits of tendon repair for RCD, especially when full-thickness tears are present.

A recent pragmatic, randomized, controlled trial sought to compare RCD outcomes from surgical and non-surgical treatments.[14] An initial cohort (n=664) underwent three months of non-surgical treatment. Of those, 377 patients continued to have pain and remained eligible for study. Ultimately, 187 patients (190 shoulders) were randomized: 95 shoulders in each study arm. Primary outcome measures included the Visual Analogue Scale (VAS) for pain and the Constant-Murley Score for shoulder function. Analyses were based on an intention to treat (ITT) principle.

At the 2-year follow-up, data from 80 shoulders were available from each study arm. Reductions in pain and improvements in function were seen in both cohorts. Among patients with partial-thickness tears, the VAS decreased by 38 in the non-surgical group and 31 in the surgery group (p=0.19). The mean Constant-Murley Score improved by 21.6 in the non-surgery group and by 20.9 in the surgery group (p=0.79). Accordingly, non-surgical and surgical treatments did not produce statistically different outcomes when patients had partial-thickness tendon tears.

In contrast, when outcomes for patients with full-thickness tears were analyzed separately, patients treated with surgery reported greater decreases in VAS compared to patients treated without surgery (37 versus 24, p=0.002) and greater increases in Constant-Murley Score (20 versus 13, p=0.008). These results suggest that surgery leads to less pain and improved function.

In summary, all patients presenting with RCD should have a period of non-surgical treatment prior to contemplation of surgery. Those who have full-thickness tears and persistent pain at 3–6 months may benefit from surgery. But surgery does not improve outcomes when a partial tear is present. This study had limitations including high attrition rates prior to and following randomization and a high rate of treatment crossover (13% of patients in the non-surgical arm had surgery and 38% in the surgical arm did not have surgery).

A related study published in *The Lancet* looked at one-year outcomes for physical therapy versus home exercise, with or without a subacromial corticosteroid injection. Patients had rotator cuff disorders that were present for a median of four months. Patients with trauma or acute full thickness tears were excluded. Over 700 patients were randomized to receive a single PT session for home exercise instruction versus six visits with a physical therapist. In both arms patients were randomized to either receive or not receive a corticosteroid injection.

At the end of one year, as measured by the Shoulder Pain and Disability Index, outcomes were equivalent with both a full course of PT and a single visit/home exercise program. With respect to the injection, there was no measurable benefit at one year. However, compared with no injection, injection provided superior outcomes at eight weeks for pain and function as well as most other patient-relevant secondary outcomes, including insomnia severity and return to desired activities.

In summary, the cost-effective approach to persistent rotator cuff pain in the absence of trauma or an acute full thickness tear should be conservative. Similar results can be achieved with a course of PT or a single visit to the physical therapist to instruct patients on a home exercise program. Out-of-pocket costs will be much lower for patients using the single visit approach. This home exercise instruction could likely also occur at the PCP level although this was not studied. For patients with significant pain and reduced function there is short term, but not long term, benefit to subacromial corticosteroid injection. For patients who fail conservative therapy, MRI is indicated. For those patients with full thickness RC tears, there is a benefit to surgical rotator cuff repair. Patients should however be counseled in a shared decision-making process, that this benefit is small, with for example a 1.3 point pain improvement on the 10 point VAS scale.

Diabetes prevalence and adequacy of risk factor control in adults in the U.S. 1999–2018

The data from the National Health and Nutrition Examination Survey spanning ten survey cycles from 1999 to 2018 was reviewed examining diabetes prevalence and control and the prevalence of risk factors for diabetes.[15] Patients were included based on a self-report of diabetes, a hemoglobin A1C of 6.5% or greater or a fasting plasma glucose 126mg/dl or greater. This resulted in an inclusion of 28,143 participants. The prevalence of diabetes was noted to increase from 9.8 % in 1999–2000 survey to 14.3% in the 2018-2019 survey. Risk factor control was improved for LDL cholesterol and blood pressure but not for A1C (Table 1). Only a minority of adults, 21% (95% CI, 15.5–26.8) achieved control of all three factors.

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Table 1. Risk factor control

Risk factor target ↓/ Time period→	1999–2002 (%)	2015–2018 (%)
Hemoglobin A1C control (A1C < target)	58.9 (95% CI, 54.4–63.3)	66.8 (95% CI, 63.2–70.4)
Blood pressure control (130/80 mg Hg)	38.5 (95% CI, 33.6–43.5)	48.2 (95% CI, 44.6–51.8)
LDL cholesterol (< 100 mg/dl)	35.4 (95% CI, 27.2–43.6)	59.7 (95% CI, 54.2–65.2)

Only non-Hispanic whites had a decrease in undiagnosed diabetes over the period. Importantly, diabetes prevalence increased among young adults (18–44 years of age). This group of patients tended to have worse diabetic and risk factor control. Obesity measured by both BMI and waist circumference increased during the survey period for both men and women.

Strikingly, less than half of the patients had controlled BP and a third did not achieve control of their diabetes. Although LDL cholesterol control showed the most improvement, control remains under 60%. This data clearly outlines the work that needs to be done to better control diabetes in adults in the U.S. Improved control will both improve survival and decrease health care costs.

Robot-assisted abdominopelvic surgeries do not have clear clinical advantages, but lead to higher costs and longer operative durations

Robot-assisted surgery was introduced about 35 years ago and has gradually increased in use since. Dhanani and colleagues recently conducted a systematic review of 50 publications (41 clinical trials) with 4,898 patients comparing robot-assisted abdominopelvic surgery to laparoscopic surgery, open surgery, or both.[16]

All included studies were randomized and placebo-controlled. Non-human, non-clinical, and pediatric studies were excluded. Trial sample size ranged from 20 to 471 (median 99). Follow up ranged from zero to 60 months. Five surgical subspecialties were included – antireflux, other gastrointestinal, colorectal, urology, and gynecology.

Operative duration: Forty-one studies reported operative durations. Robot-assisted surgeries were generally longer in duration than the conventional surgeries across each subspecialty. Data from each study were pooled to develop ranges of operative duration, but statistics for these pooled data (other than range) were not reported.

Outcomes: Long-term outcomes (≥24 months) were reported in eight studies. No differences were seen in disease-specific or overall mortality. A single study of prostate surgery demonstrated a decrease in biochemical recurrence of prostate cancer favoring robot-assisted surgery, but no differences were seen in image-based recurrences in that study. Otherwise, the other studies reporting recurrence rates did not demonstrate differences between surgery types.

Adverse events: Few studies showed differences in adverse events, but when differences were present, they favored robot-assisted surgery. The Clavien–Dindo complication reporting system consists of seven grades (I, II, IIIa, IIIb, IVa, IVb and V). Robot-assisted surgeries had slightly lower rates of Clavien–Dindo complications compared to conventional surgeries. There was also a slight benefit from robot-assisted surgeries compared to laparoscopic surgeries when evaluating conversion to open surgery. The conversion rates for robot-assisted surgeries ranged from 0% to 8% compared to conversion rates for laparoscopic surgery ranging from 0% to 12%. Pooled rates for adverse events were not reported.

Costs: The robot-assisted platform costs at least $1.5 million. In addition to the initial cost of the platform, the costs from additional training, disposable instruments, service contracts, and longer operating room times are considerable when compared to conventional surgeries. Perhaps most importantly, since ASC's do not have robotic capabilities, the use of robotics mandates the use of a HOPD facility, with costs typically at 50–100% higher than ASC costs.

Surgeon experience: No differences were seen in primary or secondary outcomes between inexperienced and experienced surgeons.

Summary: Although some studies favored robot-assisted surgery due to fewer adverse events, the overall difference in adverse events appears to be small. In contrast, costs from robot-assisted surgery and surgical times are much higher than for laparoscopic and open surgeries, yet outcomes are similar. Accordingly, based on this systematic review, robot-assisted surgeries cannot be recommended as superior to conventional forms of surgery at this time.

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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 Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. 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 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. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

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Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	At the end of this educational activity, participants should be able to: • Evaluate falls in the elderly and the interventions to help reduce morbidity, mortality and cost of care. • Review pharmacological considerations in the reduction of cardiovascular disease and progression of renal disease in Type 2 diabetes and UTI treatment in afebrile men. • Discuss studies regarding detection and treatment of atrial fibrillation and stroke risk, metabolic-bariatric surgery and glucose control in the elderly.

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Falls in the elderly–Reducing the morbidity, mortality, and cost of care

Every year, 30% of patients over age 65 will fall and 10% of falls result in serious injury or death. Falls are the leading cause of hip fracture and traumatic brain injury in seniors. From 2000 to 2016, the annual death toll from falls in seniors increased over threefold to 25,000. The annual financial toll is estimated at $50 billion.[1]

Given this burden of death and disability, there is intense interest in interventions to identify and reduce fall risk. The major risks for falls are frailty (gait and balance difficulties), drugs, cognitive decline, peripheral neuropathy, visual loss and home hazards (area rugs, power cords, oxygen tubes, etc.). The key questions are how should these patients be screened and which interventions have been demonstrated to decrease fall risk?

Screening tests

There are multiple available screening tests and none has emerged as the optimal approach.[2] An evidence-based screen can be performed quickly by the MA. It consists of two questions that should be asked of all seniors at their Annual Wellness Visit.

- Have you fallen in the past year, and if so, how many times and were you injured?
- Are you feeling unsteady when standing or walking?

If the answer to either is affirmative, patients should undergo the "Timed Up and Go Test (TUG)". The TUG, a test of functional mobility, involves timing a person standing up from a chair with armrests (using their assistive device if they normally use one), walking 10 feet at their usual pace, turning, returning to the chair, and sitting down. A TUG time greater than or equal to 12 seconds suggests a high fall risk.

Patients who fail the TUG, or fall into the category of having multiple falls or one fall with injury require a more extensive evaluation and treatment plan. The key elements of the evaluation are a risk assessment to identify factors contributing to fall risk followed by a mitigation plan to reduce future risk.

Risk assessment

The following are the major areas of focus:

Physical exam: Exam is focused on evidence of orthostasis, cognitive function, visual impairment, arthritis of the hip, knee and foot, peripheral neuropathy, or neurodegenerative disease.

Fall-Risk Increasing Drugs (FRIDs): FRIDs include antihypertensives, antiarrhythmics, anticholinergics, antihistamines, sedatives-hypnotics, antipsychotics, anticonvulsants, anti–depressants, and opioids. These drugs may increase fall risk by producing orthostatic hypotension, bradycardia, sedation, sleep disturbance, confusion, or dizziness. Contemporary trials have identified the highest fall risk with the use of antihypertensives (when orthostasis is present), anticonvulsants, and benzodiazepines.[3] Strikingly, the percent of persons who received at least one prescription for a FRID increased from 57% in 1999 to 94% in 2017.[4]

Home safety evaluation: While this may not be feasible for every patient at increased risk, those who use mobility aids or oxygen and those at very high risk will benefit.

Interventions

- Interventions based on physical exam findings can include improved vision correction (although multifocal lenses increase fall risk) or cataract surgery, corrective footwear, programs for early cognitive decline, and improved use of mobility aids.
- Fall risk specific physical therapy–Exercise interventions that focus on improving strength and balance are the most effective single intervention for reducing falls and fall-related injuries.[5] Patients should be told that on average, they must spend two hours weekly for six months to see a meaningful decrease in fall risk. These interventions can be fall risk specific physical therapy programs such as those outlined in the CDC *Stopping Elderly Accidents, Deaths and Injuries (STEADI) Toolkit*, the Matter of Balance program, or Tai Chi, among others. These are highly effective and cost effective with a NNT of 16 to prevent one fall over 12 weeks.
- Deprescribing–Deprescribing is key to reducing future fall risk, particularly with psychoactive drugs and with antihypertensives when orthostasis is present. Unfortunately, randomized trials have not shown a significant decrease in fall rates with deprescribing, not because this approach is not valid, but rather because successful discontinuation and adherence to deprescribing protocols were low in all studies.[6] PCP directed deprescribing should be able to achieve what non-physician interventions were unable to achieve in these trials. This is particularly true when the evidence base to support meaningful clinical benefit of the drug is lacking. This is the case with chronic opioid therapy, gabapentinoids, sedative-hyponotics, and anticholinergics.

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- Home interventions–There is a strong evidence base to support this approach. For example, the CAPABLE (Community Aging in Place–Advancing Better Living for Elders) Model has robust evidence showing improvements in patient outcomes as well as cost of care.[7] In the model, an interdisciplinary team is comprised of a registered nurse, an occupational therapist, and a home repair specialist. The nurse addresses pain and medication management, the occupational therapist serves both PT functions as well as provided mobility devices when needed, along with home modifications such as removing throw rugs, etc. The home repair specialist makes necessary home modifications and repairs to ensure a safe environment. Over a five-month period, in a population of dual-eligible patients, the CAPABLE intervention reduced fall-related ER visits by 26%, fall-related hospitalization by 36%, and cost by an annualized $10,000 per member per year. The savings continued for at least 24 months following completion of the five-month intervention, largely driven by reductions in hospitalizations and long-term services and supports.
- Other interventions–Bone density should be measured, and osteoporosis treated if present. There are some data suggesting a decreased fall risk with vitamin D and calcium replacement.[8]

In summary, falls and their associated injuries are common, often serious, and usually result from one or more fall risk factors, many of which may be modifiable. PCPs play a critical role in reducing fall risk factors among their older patients. A fall risk assessment and intervention program can be highly effective in improving patient outcomes and cost of care. Of the above, the three most important interventions are aimed at improving balance, deprescribing FRIDs, and improving safety in the home.

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Finerenone a new mineralocorticoid receptor antagonist: Reduction of cardiovascular disease and progression of renal disease in Type 2 diabetes

It is well appreciated that the mineralocorticoid receptor antagonists (MRA), spironolactone and eplerenone, reduce symptoms, hospitalization, and cardiovascular (CV) related mortality in patients with congestive heart failure (CHF) (Table 1) [9, 10] In these earlier trials, the effect an MRA has on progression of renal disease was not studied. Recently, finerenone, an MRA, has also been shown to decrease CV related mortality compared to placebo. Importantly, the trial was also designed to determine finerenone's effect on the progression of renal disease compared to placebo in Type 2 diabetes.[11] Patients with Type 2 diabetes and nephropathy were enrolled as two groups:

- A urinary albumin–to–creatinine of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml. per minute, and diabetic retinopathy
- A urinary albumin–to–creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml. per minute.

Patients were also treated (as in the earlier trials demonstrating reduction of CV mortality) with either an ACE (angiotensin-converting enzyme) inhibitor or ARB (angiotensin-receptor blocker). Primary outcomes included kidney failure, a sustained decrease of at least 40% in eGFR from baseline and death from renal causes. The number needed to treat to prevent a primary outcome was 29. This equates to an approximate cost to prevent one renal outcome of $232,000. The CV outcomes were secondary outcomes with a number needed to treat to prevent a CV outcome of 42. (Table 1).

Table 1. Trial outcomes

Agent	Adverse CV outcome (%)		# needed to treat	Renal disease progression (%)		# needed to treat
	Trial drug	Placebo		Trial drug	Placebo	
Spironolactone	35	46	NR	Not studied		
Eplerenone	18.3	25.9	19 (1)	Not studied		
Finerenone	13	14.8	42 (2)	17.8	21.1	29

1. Per year of follow up. 2. After 3 years. NR = not reported

Renal failure in Type 2 diabetes is frequent and significant both clinically and financially for patients. Reduction in the progression of renal failure is important. It has long been appreciated that adequate blood pressure control is essential to forestalling the progression of renal disease in diabetes. Notably the mean systolic blood pressure (sBP) at study entry was 138, well above recommended targets. It is noted that sBP decreased only 3 mm. Hg over the study.

Finerenone has both anti-inflammatory and antifibrotic effects which may have contributed to the observed improved renal outcomes. The extent to which the renal protective effects observed in this most recent trial translate to other MRAs is unknown. However, there are data from a network meta-analysis of 13 RCT's in over 13,000 patients with heart failure.[12] In that analysis, spironolactone, eplerenone and finerenone performed similarly for CHF with the exception of a mortality benefit with finerenone in one underpowered study of 160 patients. In terms of safety, it can be seen on the below table that eplerenone and finerenone have similar outcomes, with a higher rate of adverse events with spironolactone.

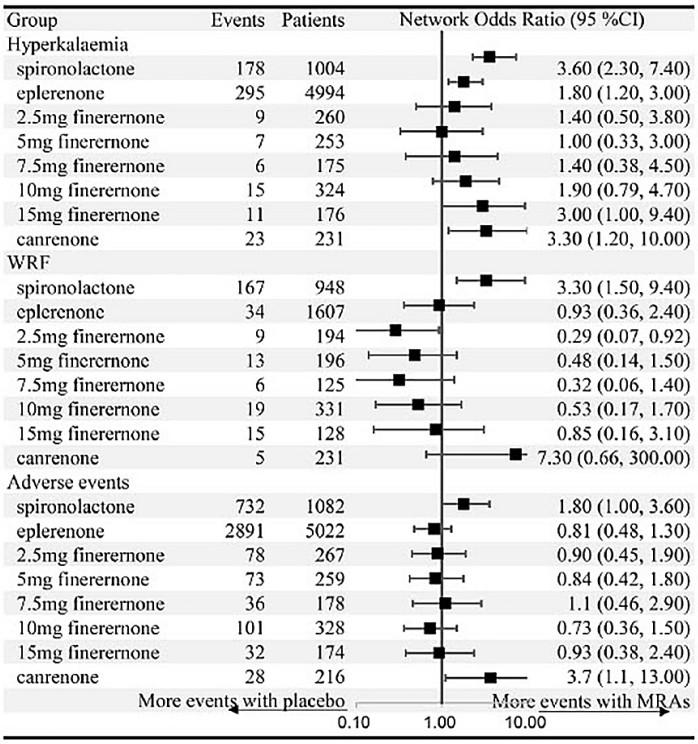

Fig. 6 Data of network comparisons with estimates for the safety outcomes of hyperkalemia, worsening renal function, and adverse events

Because of the fundamental difference in molecular structure and additional mechanisms of action, it cannot be assumed that renal preservation seen with finerenone in diabetics will be a class effect. This is an issue of substantial importance and a comparative efficacy study of renal outcomes is needed, as the yearly cost of finerenone is $8,500 and the other two MRA's are inexpensive generics. Until that data becomes available, when MRA's are needed in the presence of diabetic nephropathy, finerenone has demonstrated efficacy in retarding progression of the nephropathy.

UTI treatment in afebrile men: How long is long enough?

Increasingly, clinicians have come to realize more about the adverse effects of antibiotics. Prominent among these considerations are increasing antibiotic resistance, and the alteration of the host biome with an increasing incidence and severity of C. Diff. This has given rise to widespread antibiotic stewardship programs. Traditional courses of antibiotic treatment often were not developed as a result of trial data. For example, we now appreciate that shorter courses of antibiotics may be used for UTIs in women and pneumonia.

A recent study looked 7 vs 14 days of therapy for men with a UTI (defined as having at least one symptom of dysuria, frequency of urination, urgency of urination, hematuria, costovertebral angle (CVA) tenderness, or perineal, flank, or suprapubic pain). [13] Urine cultures were not required for enrollment, although 93% of patients had a urinalysis and 88% of the patients had a urine culture. Patients were not febrile. Patients were randomized to either ciprofloxacin (Cipro) or trimethoprim/ sulfamethoxazole (TMP/Sulfa) for a course of 7 vs 14 days. The study was designed to find a non-inferiority for the 7-day treatment course. Success was considered symptom resolution. Results are summarized in the table.

Antibiotic treatment in men 7 vs 14 days

Patient group	Symptom resolution (%)	Recurrence within 28 days
7 days Rx + 7 days placebo	122/131 (93.1)	13/131 (9.9)
14 days Rx	111/123 (90.2)	12/123 (12.9)

There was no statistical difference in outcome (symptom resolution) based on antibiotic selection or duration of therapy (7 vs 14 days). The 28-day recurrence rate was also no different.

For men with afebrile UTI a 7-day course of antibiotic therapy was equally efficacious as a 14-day course, and should be the preferred, evidence-based regimen.

Early detection and treatment of atrial fibrillation does not reduce stroke risk in the elderly

A randomized clinical trial was recently conducted to evaluate if screening for atrial fibrillation, with subsequent anticoagulation if atrial fibrillation is detected, can prevent stroke in individuals at high stroke risk.[14] Arterial embolism was also included as a primary outcome. Monitoring for atrial fibrillation was performed using an implantable loop recorder (ILR).

Researchers recruited individuals aged 70-90 years, without known atrial fibrillation, but with at least one stroke risk factor including hypertension, diabetes, previous stroke, or heart failure. ILR monitoring was done in 1,501 individuals and 4,503 individuals received usual care. During a median follow-up period of 64.5 months, atrial fibrillation was diagnosed in 477 (31.8%) of those with ILR monitoring versus 550 (12.2%) of those without monitoring, p<0.0001. Oral anticoagulation was initiated in 445 individuals in the ILR group and 591 in the usual care group, while some individuals received anticoagulation for indications other than atrial fibrillation. Although ILR monitoring improved atrial fibrillation detection compared to usual care, it did not significantly reduce the rates of stroke or arterial embolism, which occurred in 4.5% of individuals with ILR monitoring and 5.6% without monitoring, p=0.11. Major bleeding occurred in 4.3% and 3.5% of individuals with and without ILR monitoring, respectively.

A different study evaluated whether early detection and treatment of atrial fibrillation[15] reduced stroke risk and mortality among 75-76-year-olds without known atrial fibrillation. Individuals were randomized to a 14-day intermittent ECG screening (n=14,387) and control (n=14,381) groups. Whenever atrial fibrillation was diagnosed, treatment with oral anticoagulation was offered. The primary endpoint was analyzed as a composite of each of the following events: ischemic or hemorrhagic stroke, systemic embolism, bleeding requiring hospitalization, and all-cause mortality. After a median follow-up of 6.9 years, fewer primary endpoints occurred in the screening group compared to the control group (5.45 events per 100 years versus 5.68 events per 100 years). The results achieved statistical significance because the cohorts were large, but the difference between cohorts was not clinically meaningful. Ninety-one individuals would need to be invited to screen and then treated for seven years to prevent one event.

In summary, the early detection and treatment of atrial fibrillation does not appear to improve outcomes. In the first study, ILR monitoring resulted in "a three–times increase in detection of atrial fibrillation and concomitant anticoagulation, but no significant decrease in the risk of stroke or systemic arterial embolism." Given the high cost of ILR (estimated at $20,000) and potential harms, the evidence does not support the use ILR monitoring for atrial fibrillation, even among patients at high stroke risk.

Metabolic-bariatric surgery reduces all-cause mortality among adults with obesity

Previous research has shown that metabolic-bariatric surgery can lead to substantial weight loss and improvements of obesity–related complications among obese individuals. A recent meta-analysis demonstrates that the surgery also improves long–term survival when compared to standard care.[16] The survival effect was considerably greater among patients with pre–existing Type–2 diabetes.

The authors identified 16 matched cohort studies and one prospective controlled trial comparing all–cause mortality between patients with obesity and metabolic-bariatric surgery versus patients managed without surgery. The meta-analysis cohort comprised 174,772 patients with a median follow-up of 69.4 months and a total 7,712 deaths over 1,156,376 patient-years.

Among 65,785 patients (496,771 patient-years) with metabolic-bariatric surgery, 1,813 deaths occurred compared to 5,899 deaths among 108,987 matched controls (659,605 patient-years) without surgery. Metabolic-bariatric surgery led to a reduction in the hazard rate for all-cause mortality of 49.2% (p<0.0001). The number needed to treat was 25 at 10 years follow-up and 11 at 20 years follow-up. In subgroup analyses of patients with diabetes, the median life expectancy was 9.3 years longer for those with surgery compared to those without surgery. The number needed to treat was 9 at 10–year follow–up and 6 at 20–year follow–up.

With the advent of more potent GLP1-RA's such as semaglutide, we now have pharmacologic therapies that approach bariatric surgery in terms of magnitude of weight loss and have confirmed reductions in cardiovascular mortality. However, semaglutide has been priced at an egregious ~$26,000 yearly, pricing it beyond the ability of most patients to afford, and weight loss is promptly regained with discontinuation of treatment. Thus, bariatric surgery is significantly more cost effective than semaglutide at its current price.

Based on the results of this study, the authors estimated that every 1% increase in the rate of metabolic-bariatric surgery utilization would yield 5.1 million life-years globally for obese patients with diabetes and 6.6 million life–years for obese patients without diabetes. Given these clear benefits, surgical intervention should be considered early for patients with obesity who are unsuccessful at achieving weight loss goals through diet and exercise.

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Glucose control in the elderly: How tight is tight enough?

Glucose control involves a balance between control intensive enough to prevent long-term consequences from hyperglycemia and overtreatment that risks severe hypoglycemia. Insulin and sulfonylureas are associated with the highest risks of hypoglycemia, particularly when patients are treated to HbA1c targets below recommended levels. Previous studies have demonstrated that hemoglobin A1c targets should be set higher for older patients. Hypoglycemia may be less recognizable in the older patient and the long–term consequences of higher HbA1c targets are less relevant. This is important as 25% of people over 75 years of age have diabetes.

In an effort to better characterize the risk of intensive control, diabetic patients were identified using administrative data for the province of Ontario. People were included if they had HbA1c less than 8.5% and had been prescribed with the last year at least one high-risk agent (insulin, sulfonylurea) or one or more low-risk agents (metformin, dipeptidyl peptidase 4 inhibitor, acarbose thiazolidinediones). Patients treated with a high-risk and low-risk agent were placed in the high–risk group. Glycemic control was defined as intensive (HbA1c <7.0%) or conservative (HbA1c 7.1-8.5%).[17]

The primary outcome was a composite measure of diabetes-related (involving hypoglycemia) hospitalization, emergency room visits or death within 30 days of reaching glycemic control. The study included 108,620 people. These individuals had diabetes diagnosed for an average of 13.7 years. Baseline characteristics of people on high–risk agents vs. low-risk agents and those with intensive vs conservative treatment were not statistically different. Primary outcomes are summarized in the table.

Control agent	Glycemic control strategy	Number (%) of study group	People with diabetes-related primary outcome (%)	Relative risk of adverse primary outcome vs high-risk tight control
High risk	Tight control	23,484 (21.6)	217 (0.92)	NA
	Conservative	25,792 (23.7)	174 (0.67)	RR 2.22 (95% CI 1.82, 2.71)
Low risk	Tight	42,857 (39.5)	178 (0.42)	RR 1.37 (95% CI 1.12, 1.67)
	Conservative	16,488 (15.2)	68 (0.41)	RR 2.24 (95% CI 1.74, 2.94)

As noted on the table, intensive control with a high–risk agent introduced an increased risk of the composite outcome of hospitalizations, emergency room visits or death, when compared to the other three groups. This increase was related to a moderate 15 % increase in emergency department and hospital use among those people using high-risk agents to reach intensive control targets. There was no difference in all-cause mortality between any of the treatment groups.

In terms of further understanding the hypoglycemic risk and cardiovascular outcomes of the sulfonylureas, it is helpful to examine the results of the CAROLINA trial. This is the only large randomized cardiovascular outcomes trial of sulfonylurea (SU) therapy. The trial compared the SU glimepiride to the DPP-IV inhibitor linagliptin in over 6,000 patients with a mean age of 64 years. Investigators intensified medication if the HbA1c was >7.5%. The goals of the trial were to prospectively address the three potential adverse consequences of SU therapy: cardiovascular risk, severe hypoglycemia, and weight gain. At the end of six years, comparing linagliptin to glimepiride, the major cardiovascular event rate was statistically identical in both treatment arms.[18] With SU treatment, the incidence of severe hypoglycemia was 1 in 200 patient years, and the average weight gain was about three pounds. This trial, as in the above trial, highlights that sulfonylureas can be safely used when guideline directed practices are followed.

In summary, seniors with diabetes are frequently overtreated. Particularly when sulfonylureas or insulin are used in a senior population, intensive control is inappropriate and associated with adverse outcomes. HbA1c levels in the 7.5% -8% range should be the target.

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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 Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. 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 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. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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